



# Depression in Psoriatic Arthritis: Dimensional Aspects and Link with Systemic Inflammation

Ashish J. Mathew · Vinod Chandran

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## ABSTRACT

Studying comorbidities in patients with psoriatic arthritis (PsA) provides a better understanding of the extended burden of the disease. Depression and anxiety are well recognized but understudied comorbidities in patients with

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A. J. Mathew · V. Chandran (✉)  
The Psoriatic Disease Program, Centre for Prognosis Studies in the Rheumatic Diseases, Krembil Research Institute, University Health Network, Toronto, Canada  
e-mail: vinod.chandran@uhnresearch.ca

A. J. Mathew · V. Chandran  
Division of Rheumatology, Department of Medicine, University of Toronto, Toronto, Canada

V. Chandran  
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

V. Chandran  
Institute of Medical Science, University of Toronto, Toronto, Canada

V. Chandran  
Department of Medicine, Memorial University, St. John's, Canada

A. J. Mathew  
Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, India

PsA. The prevalence of depression is significantly higher in this patient population than in the general population, with far reaching consequences in terms of long-term quality of life. Over the past few years there has been an increasing interest in the link between inflammation and depression, with several novel studies being conducted. Recent evidence suggests a significant improvement of depression in PsA patients treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs) as compared to conventional DMARDs. Depression in PsA is multidimensional, with recognized phenotypes, including cognitive disorder, alexithymia and anhedonia. The paucity of standardized, validated tools to screen these dimensional phenotypes remains an unmet need. Prevalence studies on depression in patients with PsA, mostly based on patient-reported outcomes, are only able to highlight the tip of the iceberg. A comprehensive, multi-disciplinary approach addressing the subdomains of depression is imperative for a better understanding of depression in PsA patients, as well as to find a way forward for improving their quality of life. In this scoping review, we explore existing evidence on the burden of depression in PsA patients, the link between inflammation and depression in these patients and the screening tools used to evaluate the subdomains of depression.

## PLAIN LANGUAGE SUMMARY

Psoriatic arthritis (PsA) is a chronic, deforming arthritis associated with the skin condition psoriasis. A large number of patients with PsA are known to have another co-existing chronic disease, which adds to their overall disease burden and affects their quality of life. Depression is a common illness known to co-exist in about 20% of patients with PsA. Inflammation is a common factor between psoriatic arthritis and depressive disorders and is thought to play an important role in depression occurring in these patients. Recent research in the field has revealed that different dimensions of depression, such as the inability to feel pleasure, loss of intellectual functions and difficulty identifying and expressing emotions, may contribute to the overall disease. It is important to screen for these dimensions while assessing PsA patients with depression. Most of the studies conducted to date have based the diagnosis of depression on self-reported questionnaires. In this article we describe the relation between inflammation and different dimensions of depression in patients with PsA and set out a feasible screening method for depression. A good understanding of depression in patients with PsA will be useful in designing treatment strategies.

**Keywords:** Comorbidities; Depression; Inflammation; Psoriatic arthritis

### Key Summary Points

Depression and anxiety are seen in around one third of patients with psoriatic arthritis (PsA), and have a bidirectional association with pain.

Inflammation is considered to be a core pathogenic feature of depression in PsA patients.

A renewed interest in the interaction between pain and the dimensional aspects of depression (e.g. anhedonia, cognitive dysfunction and alexythemia) has helped in understanding distinct depression phenotypes.

A comprehensive assessment of depression in PsA patients should incorporate screening tools to detect the dimensional aspects.

Use of antidepressants in PsA patients with depression may be tailored based on the distinct phenotype.

## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthritis associated with cutaneous psoriasis that can potentially affect multiple organ systems. It is seen in about 24% of patients with cutaneous psoriasis. Psoriatic disease is often restrained within the core clinical domains such as skin psoriasis, nail involvement, peripheral inflammatory arthritis, axial spondyloarthritis, enthesitis and dactylitis, while its myriad systemic effects and comorbidities are overlooked [1–3]. Over the years there has been mounting evidence on the effects of PsA extending beyond skin and joint diseases, including cardiovascular disease, diabetes, obesity, metabolic syndrome, osteoporosis, malignancy, fatty liver disease, depression and anxiety [4]. Patients with PsA tend to have a significantly higher burden of comorbidity than do patients with psoriasis alone and the non-PsA population [5, 6], and these comorbidities pose an incremental burden on their long-term quality of life [7]. Compared to the metabolic comorbidities, depression as a comorbidity in PsA has not been well studied. The psycho-social burden of PsA has been shown to bear a negative impact on the quality of life [8]. In patients with psoriasis, psychiatric disorders can both result from and contribute to disease progression, suggesting overlapping biological mechanisms [9]. The synthesis of psoriasis and destructive inflammatory arthritis in PsA patients should arguably lead to a higher point prevalence of comorbid depression and anxiety. However, the cause and effect relationship of depression and PsA is often arduous to gauge and contributes to the sparsity of data.

In this review we examine the link between depression and PsA, focusing on the different facets of depression and its long-term effects. Evaluation of depression in patients with PsA, its link with systemic inflammation and unmet needs with regards to its phenotyping and management strategies will also be discussed.

## METHODS

Databases of MEDLINE using the PubMed and Ovid platforms, Scopus and Directory of Open Access Journals were probed to review the burden of depression in patients with PsA. Searches were conducted using keywords, including “depression,” “anxiety,” “psoriatic arthritis,” “psychosocial burden” and “quality of life.” Search results were supplemented by reference citations from notable reviews on this topic and from articles identified in initial searches. A descriptive review of findings from the literature search was conducted, and the authors’ interpretation is provided.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## THE PREVALENCE OF DEPRESSION AND ANXIETY IN PATIENTS WITH PSORIATIC ARTHRITIS

The past decade has seen a rise in studies investigating the burden of mental illness comorbidities in patients with PsA. Bandinelli et al. investigated 100 early PsA patients using the Hospital Anxiety and Depression scale (HADS), comparing the scores to those of 50 healthy controls, 50 late PsA patients and 50 other SpA patients, matching for age, sex and body mass index. “Possible” anxiety and depression were reported in 29 and 26% of patients, respectively, and the “probability” of developing anxiety and depression was noted in 14 and 11% of patients, respectively [10]. Analysis of data from the University of Toronto PsA cohort in which 306 patients with PsA and 135 patients with psoriasis were compared using

HADS and the standard clinical protocol revealed a prevalence of 36.6 and 22.2% for anxiety and depression, respectively. The prevalence of both anxiety and depression in this cohort was 17.7%. The rate of depression was higher in the PsA than in the psoriasis patients [11]. Wu et al. compared the risk of depression in patients with psoriasis, patients with PsA and the general population and reported that it was 14 and 22% higher in patients with psoriasis and PsA, respectively than in the general population [12]. In a multi-center cross-sectional study in Spain. Freire et al. reported a prevalence of anxiety and depression of 29.7 and 17.6%, respectively, in 495 patients with PsA [13]. A recent systematic review reports a prevalence of depression in patients with PsA ranging from 5 to 51%, depending on the thresholds used, with 20% of patients reported as having at least mild depression and 14% reported as having at least moderate depression; the pooled prevalence of at least moderate depression was 14% [14]. Another systematic review on depression and anxiety in PsA patients from three studies included in the analysis describes a pooled prevalence of depression ranging from 9 to 22%, and of anxiety ranging from 15 to 30% [15].

## THE CONSEQUENCE OF DEPRESSION/ANXIETY IN PATIENTS WITH PSORIATIC ARTHRITIS

Lewinson et al. report major depressive disorder (MDD) as a significant risk factor (hazard ratio 1.37, 95% confidence interval 1.05–1.8,  $p = 0.021$ ) for developing PsA in a longitudinal cohort of psoriasis patients followed up to 25 years until the development of PsA or the censor date [16]. Anxiety in PsA patients has an independent association with quality of life, thus accentuating the need for its proper screening and management [17]. Depression was found to have a profound effect on the health-related quality of life in patients with PsA in the Nordic Patient Survey of Psoriasis and

Psoriatic Arthritis (NORPAPP) [18]. A large study from the UK described an increase in deaths attributable to suicide in patients with PsA, as compared to the general population [19]. Although another study from the USA could not conclude any increased risk of suicidal ideation or suicide attempt in patients with PsA when compared to the general population, the authors did note a higher risk of “any suicidality”—a combined endpoint encompassing suicidal ideation and suicidal attempts [12].

## DECIPHERING THE LINK BETWEEN DEPRESSION AND PSORIATIC ARTHRITIS

The cause–effect relationship between depression and PsA is difficult to decrypt. There is compelling evidence suggesting the role of inflammatory responses in the pathophysiology of depression, as manifested by the overexpression of proinflammatory cytokines, acute phase reactants and chemokines in patients with major depression who are otherwise medically healthy [20]. Inflammation has been increasingly explored as an important factor linking the complex relationship between depression and chronic medical illness [21]. Levels of proinflammatory cytokines involved in the pathogenesis of PsA, such as interleukin (IL)-6, IL-17 and tumor necrosis factor-alpha (TNF $\alpha$ ), are raised in patients with depression and anxiety [8]. Patients with autoimmune diseases are, when treated with inflammation-based therapies such as interferon or certain vaccinations, at a higher risk of developing mood disorders [22]. However, much as inflammation is considered to be central to the pathogenesis of depression in PsA, inflammation in itself cannot explain the complete link, with some studies failing to find an association between depression and inflammation [23, 24]. Kim et al. studied the effect of the IL-23 and IL-17 axis on major depression by measuring the levels of these cytokines in 26 patients with MDD and in 28 age- and sex-matched normal controls both before and after 6 weeks of treatment with antidepressants [25]. These authors reported that the baseline levels of these cytokines in the

MDD patient group were not significantly different from those of the normal controls and that there was also no difference in the levels after 6 weeks of therapy, results which conflict with the cytokine theory of MDD [25]. This study is important in the context of anti-IL-17 therapies being used in the treatment of PsA. A meta-analysis by Hannestad et al. in which all available data on changes in serum levels of TNF- $\alpha$ , IL-6 and/or IL-1 $\beta$  during antidepressant therapy were pooled did not show a reduction in the levels of TNF- $\alpha$ , but did show reduced levels of IL-1 $\beta$  and possibly IL-6. Serotonin uptake inhibitors were shown to reduce the levels of IL-6 and TNF $\alpha$ ; other antidepressants did not [26].

The role of hypothalamic–pituitary–adrenal (HPA) axis hyperactivity has been proposed in the context of a link between psychiatric stress and an inflammatory immune response activating cell-mediated autoimmunity and triggering chronic inflammation, as seen in psoriasis patients [27]. HPA hyperactivity, commonly seen in depression, leads to the release of high levels of corticotropin-releasing hormone (CRH) and cortisol [28]. CRH signaling has been suggested to play a role in pathologic mechanisms associated with joint inflammation in arthritis [29]. Although the exact mechanism is still unknown, there seems to be a bidirectional relationship between PsA and depression.

## DEPRESSION HAS A BIDIRECTIONAL ASSOCIATION WITH PAIN IN PATIENTS WITH PSORIATIC ARTHRITIS

The interaction between depression and pain, often labeled as the depression–pain syndrome, has been the nucleus of a growing body of literature [30]. The bidirectional hypothesis suggesting a common pathophysiology for both these disorders has been tested in rheumatic diseases, with conflicting results [31, 32]. Husted et al. evaluated the relationship of depressive symptoms and pain with the changes in inflammatory joint activity in 394 patients with PsA and noted a small but consequential

bidirectional relationship between depressive symptoms and pain [33]. These results indicate that pain from PsA and depressive symptoms are inter-connected and point to a common inflammatory etiology for both. Pro-inflammatory cytokines associated with PsA are associated with symptoms of depression and anxiety [34, 35]. Previous studies have drawn attention to the higher morbidity and mortality in patients with comorbid pain and depression compared to those with either condition alone [36–38]. Depression leads to sensitization and plays a pivotal role in the shaping of pain responses and outcomes [39].

## EFFECT OF TREATMENT ON PSA PATIENTS WITH COMORBID DEPRESSION

Response to therapy in PsA patients with comorbid depression is poor. The cause for this is often multi-factorial. Michelsen et al. reviewed the Norwegian Disease-Modifying Anti-Rheumatic Drugs (NOR-DMARD) registry with the aim to investigate the predictive value of baseline depression on the probability of achieving joint remission in rheumatoid arthritis and PsA patients [40]. Based on scores of  $\leq 56$  on the Medical Outcomes Study Short Form-36 (SF-36) mental health (MH) domain and  $\leq 38$  on the SF-36 mental health component (MHC) summary, baseline depression and anxiety were negative predictors at 3 and 6 months for achieving a Disease Activity in Psoriatic Arthritis (DAPSA) score of  $\leq 4$ . Depression and anxiety were not associated with inflammatory markers and swollen joint count during follow-up [40]. Adherence to treatment is more difficult in PsA patients with comorbid depression, which interferes with treat-to-target strategies and the achievement of a minimal disease activity state [41]. A study using data from the Danish Biological Registry (DANBIO), which included 1750 patients with PsA, noted that patients with depression and/or anxiety showed shorter persistence on TNF inhibitors (TNFi) than did those without comorbidities [42]. In a British cohort study of 566 PsA patients, the presence of pre-specified

comorbidities, including depression, at baseline was associated with significantly higher TNFi discontinuation rates [43]. Physicians should also remain cognizant of the close link between chronic widespread pain and depression while planning treatment strategies in patients with PsA. Composite disease activity measures include tender joint count and patient global visual analogue scales that may be high despite the absence of joint inflammation in patients with comorbid depression. Setting sight on tight control of PsA activity using such measures in these situations risks inappropriate escalation of therapy, which may lead to more adverse events. Clinical judgement of the degree of disease activity is always important.

The reported increased rate of depression and suicidal ideations with some of the newer biologic and targeted DMARDs used for treating psoriatic disease needs to be evaluated. Brodalumab, a fully human anti-IL17 receptor A inhibitor, is approved for the treatment of moderate to severe plaque psoriasis. However, concerns regarding suicidal ideation and behavior during phase III clinical trials in PsA led to early termination of all studies and a boxed warning being added to the monograph of the drug [44]. This concern was explored in great detail, as similar adverse events were not reported in any of the other IL-17 inhibitors, including secukinumab or ixekizumab. Patients with a history of psychiatric disorders or substance abuse were included in the brodalumab trial, in contrast with trials on IL-17 inhibitors, which had excluded them [45]. Similar concerns were raised with apremilast, a selective phosphodiesterase-4 inhibitor approved for the treatment of psoriasis and PsA [46]. However, a long-term experience study with apremilast in PsA patients did not observe any safety signals pertaining to suicidal risks [47]. Nevertheless, given the increased risk of depression in patients with psoriatic disease it is important for treating physicians to be appraised of these observations and engage in a candid and ongoing conversation with patients that leads to an informed and shared decision on therapy. The labels of both brodalumab (black box warning) and apremilast carry a warning about suicidal ideation and depression.



## BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS IN THE TREATMENT OF DEPRESSION

Psoriatic arthritis patients with depression are often prescribed antidepressants along with DMARDs. The effect of these medications on depression either in combination or separately may be worth exploring. A recent study from a Swedish registry evaluated the use of antidepressants and benzodiazepine-related hypnotics in patients with rheumatoid arthritis (RA), PsA and ankylosing spondylitis. Prior to starting treatment with DMARDs, the rates of psychotropic substance medicines had increased among the patients, comparable to the rates among the matched population control subjects. However, after initiation of DMARDs, the rates of antidepressant medicines diminished, or leveled out, while the increase among the control group continued [48]. This reduction in the use of antidepressants could be due to a direct or indirect treatment effect. Mitigation of pain and disease activity with DMARDs, which in turn leads to enhancement of mood and sleep cycle could be another explanation. In patients with RA, blockade of the TNF pathway has been shown to modulate serotonin transporter expression, a key target of conventional antidepressant therapy [49]. The synergistic effect of DMARDs and antidepressants needs to be studied further. In this context it is also important to be mindful of the placebo effects in the treatment of depression and anxiety, as analyses of the majority of published clinical trial data on antidepressants demonstrate that the difference in improvement between drug and placebo is not clinically meaningful [50].

The cytokine theory of depression, greeted with much enthusiasm, has led to biomarker-guided anti-inflammatory therapies being investigated in MDD patients. Two clinical trials in this regard are noteworthy. Raison et al. studied the effect of infliximab on depressed mood in patients with treatment-resistant depression. Although the study failed to achieve its primary outcome, findings suggestive of a favorable outcome in patients with raised

baseline C-reactive protein were noted [51]. This was followed by another clinical trial on infliximab in which patients had to meet certain biochemical or phenotypic inclusion criteria that indicated a state of inflammatory activation at baseline. Infliximab did not reduce symptoms of depression compared to placebo in the 60 patients with bipolar depression included in the study [52]. As attractive as this theory appears, realization of the promise of precision medicine for treating MDD has been dismal to date.

On the contrary, the effect of biologics on depression in patients with psoriasis has been encouraging. Randomized controlled trials on adalimumab, etanercept and ustekinumab are associated with a statistically significant reduction in depressive symptom scores using different scales in patients with moderate to severe psoriasis [53]. In a nationwide cohort study from Taiwan consisting of 980 patients with PsA or psoriasis, Wu et al. examined the effects of biologic therapy on reducing depression and insomnia rates and attempted to identify the subgroups of patients who would benefit from biologic therapy. The prevalence of patients on antidepressants before biologic therapy was 20%. The authors noted a reduction of more than 40% in this prevalence rate 2 years after biologic therapy. The stratified analysis revealed a more rapid and significant reduction in depression in patients aged < 45 years who took continuous biologics and in those who did not have PsA [54].

In summary, the pain and higher inflammation in PsA patients, which are interlinked with depression, seem to be intractable constructs in the treatment of PsA with biologic therapies. This may also explain the differential outcomes in patients with PsA and psoriasis being treated with biologic therapy.

## DEPRESSION IN PSORIATIC ARTHRITIS IS MULTI-DIMENSIONAL WITH DISTINCT PHENOTYPES

With a better understanding of MDD, there has been a renewed interest in the interaction of pain with other subdomains of depression, such

as anhedonia, cognitive deficits and alexithymia. Depression is multi-dimensional, and it is often challenging to obtain a snapshot of the entire spectrum. Most of the assessment tools of these subdomains are self-reported questionnaires, and it is important to include these tools in the overall assessment of depression in PsA patients in order to understand the bigger picture (Table 1).

There is a growing body of evidence on the broad cognitive deficits associated with impaired daily and psychosocial functioning in MDD [67]. Di Carlo et al. assessed the prevalence of mild cognitive impairment in 96 patients with PsA and reported that short-term memory was the most prevalent affected domain, present in the patient population at a rate of 48.9% [66]. TNF $\alpha$  has been shown to play a critical role in cognitive dysfunction associated with MDD [68]. Cognitive dysfunctions can be used to prognosticate at-risk individuals and monitor progression. However, a comprehensive tool to assess cognitive deficits is lacking. The THINC-integrated tool (THINC-it) is a validated, computerized cognitive assessment system that screens both objective and subjective cognitive deficits in MDD [69]. Other validated tools used to assess objective and subjective cognitive impairment in MDD include the Screen for Cognitive Impairment in Psychiatry (SCIP-D) and the Cognitive Complaints in Bipolar Disorder Assessment (COBRA) [70]. Assessment of cognitive impairment should be an integral part of the assessment and treatment of MDD [71, 72].

Anhedonia, defined as the diminished ability to experience pleasure or enjoy previously pleasurable activities, is a diagnostic feature of depression and shown to be a predictor of antidepressant nonresponse [73, 74]. Validated self-reported measures for anhedonia used in clinical research include the Snaith–Hamilton Pleasure Scale (SHAPS), the Fawcett–Clark Pleasure Capacity Scale (FCPS), the Revised Chapman Physical Anhedonia Scale (CPAS) and the Chapman Social Anhedonia Scale (CSAS) [75].

Alexithymia is a disorder of emotion regulation mechanisms that presents as a dissociation of emotional and physical responses to life events and bodily sensations [76]. Li et al.

performed a meta-analysis of studies including 3572 subjects and highlighted a moderate correlation of alexithymia scores with the severity of depression [77]. In a more recent study, Chimenti et al. assessed the prevalence of alexithymia in 50 patients with RA and 51 with PsA using the Toronto Alexithymia Scale (TAS-20), a self-reported questionnaire. Alexithymia was noted in 33.3% of patients with PsA [78]. Other tools used to determine alexithymia include the Bermond–Vorst Alexithymia Questionnaire (BVAQ), the Toronto Structured Interview for Alexithymia (TSIA) and the modified Beth Israel Hospital Questionnaire (BIHQ) [79].

## SCREENING TOOLS FOR DETECTING DEPRESSION IN PSA STUDIES MISS THE BIG PICTURE

The diagnosis of depression in prevalence studies among PsA patients is mostly based on self-reported questionnaires. These questionnaires do not delve into the multifaceted nature of depression. The dynamic nature of depression adds to this conundrum. The common screening tools used to report depression and anxiety include HADS, Patient Health Questionnaire 9-item scale (PHQ-9), Generalized Anxiety Disorder scale (GAD-7) and the SF-36 MCS and SF-36 MH [14]. A systematic screening method encompassing crucial constructs like cognitive dysfunction and anhedonia in PsA patients may be able to capture depression more comprehensively. This will guide therapeutic decisions as the subdomains of depression may respond differentially to treatment [80, 81].

## NEUROIMAGING AUGMENTS THE SCREENING TOOLS IN DEFINING DEPRESSION

The field of brain imaging over the last decade has enhanced our understanding of depression in general. Neuroimaging, mostly using magnetic resonance imaging (MRI) can aid in phenotyping comorbid depression, the discovery of

**Table 1** Comprehensive screening tools for depression in psoriatic arthritis

Dimensional phenotype	Screening tool	PsA studies using the tool				
		First Author	Year	Study type	References	
Overall depression	Medical Outcomes Study Short Form-36 (SF-36) Mental Component Summary (MCS) and Mental Health (MH) domains	Strand	2012	RCT	[55]	
		Rosen	2012	CS	[56]	
		Michelsen	2017	CS	[40]	
		Gladman	2014	RCT	[57]	
		Gniadecki	2011	RCT	[58]	
		Freire	2011	CS	[13]	
		Bandinelli	2013	CS	[10]	
		McDonough	2014	CS	[11]	
		Meesters	2014	CS	[59]	
		Howells	2018	CS	[60]	
	Strober	2018	CS	[61]		
	Hospital Anxiety and Depression scale (HADS)	Patient Health Questionnaire 9-item scale (PHQ-9)	Kotsis	2012	CS	[62]
			Lamb	2017	CS	[63]
			Wu	2017	CS	[12]
	Generalized Anxiety Disorder scale (GAD-7)	Beck's depression inventory (BDI)	Lamb	2017	CS	[63]
			Milutinovic	2019	CS	[64]
	World Health Organization International Classification of Diseases (ICD), 9th revision, 10 codes		Wu	2016	CS	[54]
Ballegaard			2017	CS	[42]	
Löfvendahl			2018	CS	[65]	
Kaine			2019	CS	[6]	
Di Carlo			2019	CS	[66]	
Cognitive disorder	Montreal Cognitive Assessment (MoCA)	Di Carlo	2019	CS	[66]	
	THINC-Integrated Tool (THINC-it)	No studies in PsA				
	Mini-Cog	No studies in PsA				
	Screen for Cognitive Impairment in Psychiatry (SCIP-D)	No studies in PsA				
	Cognitive Complaints in Bipolar Disorder Assessment (COBRA)	No studies in PsA				
Anhedonia	Snaith–Hamilton Pleasure Scale (SHAPS)	No studies in PsA				
	Fawcett–Clark Pleasure Capacity Scale (FCPS)	No studies in PsA				
	Revised Chapman Physical Anhedonia Scale (CPAS)	No studies in PsA				
	Chapman Social Anhedonia Scale (CSAS)	No studies in PsA				



**Table 1** continued

Dimensional phenotype	Screening tool	PsA studies using the tool			
		First Author	Year	Study type	References
Alexithymia	Toronto Alexithymia Scale (TAS-20) Bermond–Vorst Alexithymia Questionnaire (BVAQ) Toronto Structured Interview for Alexithymia (TSIA) Modified Beth Israel Hospital Questionnaire (BIHQ)	Chimenti	2019	CS	[78]
Neuroimaging	Structural magnetic resonance imaging (MR)I Functional MRI MR spectroscopy Positron emission tomography (PET) scan	No studies in PsA			

*PsA* Psoriatic arthritis

<sup>a</sup> Study type: CS, Cohort study; RCT, randomized controlled trial

diagnostic and prognostic biomarkers, and eventually translate to precision medicine. Structural MRI (sMRI), functional MRI (fMRI) and positron emission tomography are the various neuroimaging modalities described [82]. fMRI has shown activity changes and increased connectivity over brain regions implicated in self-relation and cognitive tasks, respectively [83, 84]. sMRI helps in identifying hippocampal volume, which has been shown to be reduced in patients with MDD [85]. The cognitive decline seen in MDD has been proposed to be due to reduction in hippocampal volume [86]. Magnetic resonance spectroscopy has demonstrated reduced levels of glutamate, glutamine and gamma-aminobutyric acid in depressed patients [87]. Utility of these modalities in a clinical setting, however, may be limited.

## FUTURE PERSPECTIVES

Given the renewed interest in pathogenesis, assessment and therapeutic options, the future of treating comorbid depression in patients with PsA looks promising. While novel hypotheses for pathogenesis are being identified, a comprehensive assessment of depression

in PsA patients is pivotal in planning treatment. A well-designed study in patients with PsA that incorporates an assessment of various constructs of depression is yet to be done. We propose a comprehensive study in three phases to identify the associations between disease severity, dimensional disturbances of depression and brain imaging abnormalities in patients with PsA. In the first phase, data on outcomes of depression and anxiety symptomatology should be collected through self-reported questionnaires, including the SHAPS, Generalized Anxiety Disorder (GAD-7) scale and the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR). These data should be augmented in the second phase by structured interviews applying the Montgomery-Asberg Depression Rating Scale (MADRS) and assessment of cognitive function using the THINC-it tool [88–91]. The third phase should comprise neuroimaging by structural and functional magnetic resonance imaging modalities to assess central nervous system volume and functional connectivity alterations.

The results from this study should inform a well-designed clinical trial of biologic therapy, targeting different constructs of depression.

## CONCLUSIONS

The intricate relationship between comorbid depression and systemic inflammation and disease manifestations in patients with PsA is still being deciphered. Novel mechanisms tying the loose threads of depression, psoriatic disease, pain and inflammation together need to be evaluated, potentially translating to drug discovery. Physicians should be conversant with the comprehensive assessment of the subdomains of depression as this knowledge will effectively enhance remission rates and the quality of life in patients with PsA.

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