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Hot Topics: Depression in Individuals With Psoriasis and Psoriatic Arthritis

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ABSTRACT. Psoriasis and psoriatic arthritis are associated with an increased risk of mental health conditions such as depression and anxiety. People with psoriatic disease (PsD) are also more likely to die by suicide than those without. Mood disorders affect people with PsD in a multitude of ways, such as in effectiveness of care, response to treatment, remission rates, and quality of life. Although the links between PsD and mental health conditions have not been fully elucidated, this review will highlight recent studies investigating shared biologic mechanisms between depression and PsD. Since mental health disorders can be assessed and treated effectively, dermatologists and rheumatologists should be aware of the mental health burden in individuals with PsD to accomplish the following: (1) educate their patients with PsD about this association, (2) screen for mental health conditions on an ongoing basis in their clinical practice, (3) refer their patients with PsD to a mental health professional when needed, and (4) ensure selection of a safe PsD treatment in the setting of comorbid mental health disease. Finally, important treatment considerations for individuals with PsD and depression are reviewed. This topic was presented at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting.

Key Indexing Terms: comorbidity, depression, GRAPPA, psoriasis, psoriatic arthritis

Introduction

Psoriasis (PsO) is a chronic, inflammatory skin disorder with a prevalence of up to 3% of the global population.[1] Psoriatic arthritis (PsA), occurring in 30% of those with PsO, is a heterogeneous chronic inflammatory condition presenting with peripheral arthritis, skin disease, axial disease, enthesitis, and/or dactylitis.[2] PsO and PsA comprise psoriatic disease (PsD). People with PsD are at an increased risk for mental health concerns, including depression.[3] In turn, depression has been associated with greater PsD burden, including worse quality of life and increased risk of death by suicide, as well as diminished treatment adherence.[4-9] It is therefore essential that dermatologists and rheumatologists are aware of the mental health burden in individuals with PsD in order to provide comprehensive care. This article aims to provide an overview of the topic of depression in PsD, which was presented at the 2023 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

Epidemiology

From the US National Health and Nutrition Examination Survey (NHANES) 2009-2012 database, people with PsO were twice as likely to have depression (odds ratio [OR] 2.09, 95% CI 1.41-3.11) compared to those without.[10] In addition, people with PsO and PsA were nearly 3 times more likely to have depression independent of other comorbidities (OR 2.92, 95% CI 1.53-5.68) than those without PsA.[11] Among 73,447 individuals with PsO who were followed for up to 25 years in The Health Improvement Network (THIN), a primary care medical records database, those who developed major depressive disorder (MDD) were at significantly increased risk of developing PsA compared with those who did not develop MDD (hazard ratio [HR] 1.37, 95% CI 1.05-1.80).[12] Individuals with PsA also have been found to have an increased risk of depression (OR 1.68, 95% CI 1.37-2.08) compared to those without PsA.[13] In a cross-sectional study, the prevalence of depression was shown to be higher in those with PsA (22.2%) than with PsO (9.6%).[5]

With respect to suicide, a metaanalysis of 18 studies comprising 1,767,583 participants revealed that among the 330,207 who had PsO, there was a greater likelihood to attempt and to complete suicide (OR 1.32, 95% CI 1.14-1.54 and OR 1.20, 95% CI 1.04-1.39, respectively) compared to those without PsO.[8] Further, more severe PsO and younger age were associated with a greater likelihood of suicidality.[8] Though studies have not conclusively shown an increased risk of suicidal

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ideation or behavior (SIB) in those with PsA,[14,15] increased deaths by suicide in those with PsA compared to the general population were reported in a large cohort in the United Kingdom (HR 3.03, 95% CI 1.56-5.90).[9]

Although not examined in depth in the literature, available studies have shown a higher PsD burden and worse quality of life in those with depression and anxiety as well as poorer adherence to treatment.[5] In a cohort study of 306 individuals with PsA and 135 with PsO, McDonough et al showed an association of worse scores on patient-reported outcome measures evaluating function, general health, skin, and fatigue with depression and anxiety in PsA and PsO.[5] Interestingly, whereas increased inflammatory joint count was associated with depression and anxiety in PsA, worse skin disease as measured by the Psoriasis Area and Severity Index (PASI) was not associated with depression and anxiety in PsA or PsO.[5] In addition, 1 study showed that concomitant depression or anxiety can result in discrepancies between patient and physician global assessments of PsO severity, with the former more likely to rate it worse.[16] Poorer quality of life in PsO was also noted in another small cross-sectional study comprising 90 individuals with PsO in association with the presence of depression or anxiety.[3] In a longitudinal study, Kulkarni et al showed that adherence was worse in elderly adults with PsO,[6] and in a cross-sectional study, Vestergaard et al showed that adherence was worse in individuals with PsA.[7]

Proposed pathogenetic contributors

Pathophysiologic links between PsD and mental health conditions have not been fully elucidated. Depression and PsD have many pathophysiologic processes in common, including elevated proinflammatory cytokine production and a dysfunctional hypothalamic-pituitary-adrenal [HPA] axis.[17-26] Moreover, individuals with PsD experience many environmental and physical stressors, such as less social support, the economic impact of reduced productivity, and stigmatization due to visible plaques.[21,22,24,25,27,28] Stress may cause PsD to flare and influence immunomodulatory responses, including neuroendocrine responses,[26,29] and the development of neuropsychological disturbances.[20,22,29]

Gut dysbiosis including less richness and diversity of the microbiome may contribute to both depression and PsD.[23,30] As a result, it is postulated that local inflammation results in disruption of the gut epithelial barrier and subsequent translocation of bacteria.[23,30] These bacteria, metabolites, or endotoxins (such as lipopolysaccharide) in turn stimulate toll-like receptors, resulting in the production of many proinflammatory cytokines.[23,30]

Although there are inconsistent results between various studies, generally, elevated levels of proinflammatory cytokines such as interleukin (IL)-6, IL-17, IL-23, and tumor necrosis factor (TNF) have been measured in the blood of individuals with depression, and the latter 3 are known therapeutic targets for the treatment of PsD.[18,25,31,32] Increased cytokine levels can contribute to both peripheral and central neuroinflammation by crossing a permeable blood-brain barrier (BBB) induced by activated mast cells and central cytokine production by astrocytes, neurons, and microglia.[31] Peripherally activated T helper 17 cells also contribute to disrupted BBB integrity and activation of astrocytes and microglia via the IL-17A receptor; downstream events include synaptic dysfunction and neuronal cell death.[31] Inflammatory cytokines can also activate a key enzyme, indoleamine 2,3-dioxygenase (IDO), which converts tryptophan into kynurenine, resulting in a partial depletion of serotonin in the brain, a known factor in depression pathogenesis. IDO also shifts kynurenine metabolism toward microglial byproducts such as 3-hydroxykynurenine and quinolinic acid, resulting in elevated oxidative stress and glutamate, all which can contribute to neurotoxicity.[31]

Elevated proinflammatory cytokines (eg, TNF) also activate the HPA axis, increasing levels of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol, as well as decreasing the effects of glucocorticoid receptors.[17] However, the effect of cortisol to reduce inflammation is likely blunted as a result of the decreased activity of the glucocorticoid receptors.[17] Cortisol also increases hepatic tryptophan 2,3-dioxygenase activity and like IDO, results in tryptophan depletion, decreased serotonin synthesis, and shifts to kynurenine and quinolonic acid production.[17] Cortisol and increased proinflammatory cytokines can also contribute to amygdala dysfunction and decreased release of neurotropic growth factors, resulting in decreased neurogenesis and hippocampal volume loss.[29] Hippocampal loss, a well-documented feature of the brain associated with depression, may also occur in part due to the production of neurotoxins.[29]

Considerations for clinical practice

Patient voice. At the annual meeting, a patient research partner (PRP) provided a patient perspective on the topic recognizing that depression, anxiety, and mood disorders are complicated, especially in the setting of PsD. She acknowledged that inflammation could drive depression and vice versa. More importantly, she stated that the overall effect of mood disorders on PsD is multidimensional and that we do not yet fully understand the interplay between inflammatory disease and mood. However, because these disorders affect people with PsD in many ways (eg, effectiveness of care, adherence, response to treatment, remission rates, and quality of life[2,4,5,16,33-36]), they should be assessed and treated effectively. The PRP indicated that their PsD specialist need not be a therapist or prescribe medications for mood disorders. However, she requested that this topic be discussed with the patients at their visits related to PsD and that healthcare providers (HCPs) understand that anxiety and depression may be a result of still-active disease and/or affect PsD outcomes. Referrals to a care team partner or other HCPs who understand how to screen/diagnose and treat anxiety and depression should be offered.[37] She requested that HCPs treating PsD build a plan within their institution or office setting to address mood disorders, allowing affected individuals to get the care they need for these issues. Ultimately, it was felt that instituting such measures would help people with PsD achieve better outcomes and potentially positively change the trajectory of treatment responses.

Education and screening. Dermatologists and rheumatologists play a critical role in educating individuals with PsD about asso-

ciated mental health conditions. When sharing with patients that people with PsD are more likely to be depressed, anxious, and have higher rates of suicide, it can be helpful for HCPs to provide supporting data and rationale for why identification of these mood disorders plays a role in PsD management and treatment outcomes to assist in shared decision making.

Dermatologists and rheumatologists are encouraged to routinely screen their patients with PsD for depression and anxiety, which can be accomplished through self-reported questionnaires.[2,35,38] In 1 study, screening for depression led to better outcomes for people with PsO at 1 year.[39] However, screening rates are reportedly low. In 1 cross-sectional survey study of 74 dermatologists, although almost 60% of participants agreed or strongly agreed that people with PsO require regular monitoring for depression and SIB, only about a quarter said they asked about mood in the majority of visits with individuals with PsD.[40] Further, only 7% reported using a depression screening tool, and only 30% were familiar with the 2-item Patient Health Questionnaire (PHQ-2; see below). On a scale of 1 (not at all comfortable) to 10 (very comfortable), dermatologists scored approximately 7-8 for asking their patients about mood, discussing depression, and referring for mental health services, but only 6.3 for asking about SIB. Use of a screening tool, frequency of screening, and belief that regular monitoring is required were associated with more comfort in talking about depression and SIB. Regular monitoring was also associated with more comfort in talking about depression, whereas awareness of the PHQ-2 was associated with more comfort in asking about SIB. Therefore, normalizing conversations between HCPs and patients around mental health is crucial.[40]

The PHQ2 is suitable for busy dermatology and rheumatology clinics as it takes less than 2 minutes to complete. It was developed and validated to screen for depression with follow-up using the PHQ-9 (a 9-item questionnaire with a score range of 0-27, taking up to 5 minutes to complete) if the PHQ-2 score is suggestive of depression.[41] The 2 questions in the PHQ-2 tool ask about the frequency of depressed mood and lack of enjoyment of daily activities, scoring each as 0 (not at all) to 3 (nearly every day) with a total possible score ranging from 0 to 6. A PHQ-2 score ≥ 3 was shown to have a sensitivity of 83% and a specificity of 92% for detecting major depression; a PHQ-9 score ≥ 10 had a sensitivity of 88% and a specificity of 88% for major depression with scores of 5, 10, 15, and 20 representing mild, moderate, moderately severe, and severe depression, respectively.[41,42] Other potential screening tools include the Hospital Anxiety and Depression Scale, a 14-item self-report questionnaire (questions scored 0-3), with 7 questions assessing depression and 7 assessing anxiety. A score ≥ 8 for anxiety has a specificity of 0.78 and a sensitivity of 0.9, and for depression, it has a specificity of 0.79 and a sensitivity of 0.83. It also takes 2 to 5 minutes to complete.[43] Other scales exist, such as the Goldberg Anxiety and Depression Scale comprising 18-items, which may also be used.

Individuals with a positive screening result using any tool should be referred to a mental health professional for further evaluation. Since these screening tools were developed for the general population and have not been fully validated in PsD, they may not capture all those with PsD who are affected with anxiety or depression. These individuals may require the application of different cut-offs to optimize sensitivity and specificity in PsD.[44] Mathew and Chandran also caution that these screening tools do not delve into the multifaceted nature of depression; for example, they are missing constructs of cognitive dysfunction.[20] Therefore, even if the screening results are negative, referral should still be considered if mental health concerns are suspected.

Optimize PsD treatment. Successful treatment of PsD can reduce depression[35] and vice versa.[45] There has been a call to use PsD treatments to improve associated anxiety and depression.[38] Data support that this is best accomplished with targeted therapies.[46] Though most randomized placebo-controlled trials leading to the approval of targeted therapeutics for PsD tend to exclude individuals with severe psychiatric disorders, depression in PsO was shown to statistically significantly improve on treatment with multiple targeted therapies as assessed by various mental health measures (Table). In randomized placebo-controlled studies of PsA, the most reported measure of mental health appears to be the 36-item Short Form Health Survey (SF-36) mental component summary (MCS). Baseline SF-36 MCS scores were similar for enrolled participants with PsO and PsA, and were slightly below the US norm. Treatment of PsA improved symptoms of depression compared to placebo, similar to treatment of PsO, but the results were only statistically significantly different in some studies[47-52] and not others.[48,53-58] Reasons for the variance in these results and results compared to PsO are largely unknown, but they might reflect drug dosage differences used for PsO compared to PsA, different pathophysiological mechanisms of depression in PsA, and/or the relative insensitivity of the SF-36 MCS (or the SF-36 domains evaluating emotional or mental health) to detect improvement of depressive symptoms in PsA.

One consideration in individualizing treatment for PsD is that 2 systemic treatments, which include (1) apremilast, a phosphodiesterase-4 inhibitor (approved for both the treatment of plaque PsO and PsA in the US and European Union [EU]), and (2) brodalumab, an IL-17A receptor antagonist (approved for the treatment of moderate-to-severe plaque PsO in the US), contain warnings in their prescribing/product information related to depression and/or suicidality.[59-62] Specifically, brodalumab has a black box warning in the US for SIB, including completed suicides. Prescribers are required to undergo certification through the company's Risk Evaluation and Mitigation Strategy to prescribe brodalumab, and patients must register to be able to receive brodalumab when prescribed.[61] Follow-up studies are indicated in the EU to evaluate SIB as part of the risk management plan for brodalumab.[63]

For apremilast specifically, across 3 16-week randomized placebo-controlled trials in moderate-to-severe plaque PsO, there were more reports of depression and depressed mood for those treated with apremilast (1.3% [12/920]) compared to placebo (0.4% [2/506]), but there was no apparent imbalance in SIB.[60,64-66] Similarly, across 3 16-week randomized

Table. Depression data from phase III randomized placebo-controlled trials of approved targeted therapeutics at licensed doses for psoriasis.

Active Drug Study, Acronym(s) (if applicable)	Drug, n	PBO, n	Drug Dose and Regimen	EP	Measure	Depressive Symptoms at BL Drug, n (%)	Depressive Symptoms at BL PBO, n (%)	BL Measure Scores, range	CFB in Measure Drug, mean (SD)[a]	CFB in Measure PBO, mean (SD)[a]	*P*
ADA,[72,73] VOYAGE 2	248	248	80 mg W0, 40 mg W1, 2, then Q2W	W16	HADS-D (0-21)	74 (30.1)	66 (26.6)	5.1-5.3	−1.2 (3.4)[b]	−0.1 (2.9)[b]	< 0.001
						HADS-D ≥ 8	HADS-D ≥ 8				
					SF-36 MCS (0-100)	NR	NR	NR	4.57 (9.36)[b]	0.57 (8.76)[b]	< 0.001
APR,[74] ESTEEM 1	562	282	30 mg BID	W16	SF-36 MCS (0-100)	N = 246 (19.6%) of ESTEEM 1 and ESTEEM 2 populations with PHQ-8 ≥ 10		45.8-47.0	2.4 (9.5)[b]	−1.0 (9.6)[c]	< 0.0001
					PHQ-8 (0-24)			5.2-5.4	−0.6 (4.3)[b]	0.3 (4.2)[c]	0.01
APR,[74] ESTEEM 2	274	137	30 mg BID	W16	SF-36 MCS (0-100)			45.3-45.4	2.6 (10.1)[b]	0.0 (10.5)[b]	0.01
					PHQ-8 (0-24)			5.3-5.4	−0.8 (4.5)[b]	0.2 (4.5)[c]	0.01
Bimekizumab[75] (SF-36 collected in phase III program but results not reported)											
BRO,[70] AMAGINE 1	221	216	210 mg W0, 1, 2, then Q2W	W12	HADS-D (0-21)	30 (13.6) HADS-D ≥ 11	22 (10.2) HADS-D ≥ 11	5.3-5.5	3.4 (0.2)[b,d]	5.5 (0.3)[c,d]	0.001
CZP,[76] CIMPASI-1, CIMPASI-2	173	97	400 mg Q2W	W16	SF-36 MCS (0-100)	NR	NR	45.3-45.5	50.1 (10.2)[b,d]	45.9 (12.3)[b,d]	NR
Deucravacitinib[77,78] (PHQ-8 and SF-36 MCS collected in phase III program but results not reported)											
ETN,[79]	193	194	50 mg BIW	W12	SF-36 MCS (0-100)	NR	NR	~46.1-47.2	51.0 (NR)[b,d]	46.5 (NR)[b,d]	< 0.01
ETN,[80,81]	311	307	50 mg BIW	W12	Ham-D (0-53)	77 (25) Ham-D > 6	80 (26) Ham-D > 6	4.5-4.5	−1.5 (NR)[b]	−0.4 (NR)[b]	0.001 0.001
					BDI (0-63)	102 (33) BDI > 9	106 (35) BDI > 9	8.1-8.4	−3.9 (NR)[b]	−2.1 (NR)[b]	< 0.001
ETN,[82] UNCOVER 2, UNCOVER 3	739	361	50 mg BIW	W12	QIDS-SR16 (0-27)	66 (8.9) QIDS-SR16 ≥ 11	47 (13.0) QIDS-SR16 ≥ 11	NR	−4.1 (0.57)[b,e,f]	−3.7 (0.68)[b,e,f]	NR
GUS,[72,73] VOYAGE 2	496	248	100 mg W0, 4, 12	W16	HADS-D (0-21)	134 (27.1) HADS-D ≥ 8	66 (26.6) HADS-D ≥ 8	5.1-5.3	−1.6 (3.6)[b]	−0.1 (2.9)[b]	< 0.001
					SF-36 MCS (0-100)	NR	NR	NR	5.66 (9.51)[b]	0.57 (8.76)[b]	< 0.001
IFX[83] EXPRESS	301	77	5 mg/kg W0, 2, 6	W10	SF-36 MCS (0-100)	NR	NR	45.4-45.8	6.3 (11.0)[b]	−0.8 (9.7)[c]	< 0.001
IXE,[82] UNCOVER 1, UNCOVER 2, UNCOVER 3,	1165	792	80 mg Q4W	W12	QIDS-SR16 (0-27)	120 (10.3) with QIDS-SR16 ≥ 11	93 (11.7) with QIDS-SR16 ≥ 11	14.0-14.2	-6.1 (0.41)[b,e,f]	−3.4 (0.48)[b,e,f]	< 0.001
RZB,[84] UltIMMa-1, UltIMMa-2	598	200	150 mg W0, 4, then Q12W	W16	HADS-D (0-21)	150 (25.1) HADS-D ≥ 8	54 (27.0) HADS-D ≥ 8	5.3-5.3	NR[g]	NR[g]	NR
SEC,[85] OASIS-2[h]	448	112	300 mg W0, 1, 2, 3, 4, then Q4W	W16	SF-36 MCS (0-100)	NR	NR	NR	4.21 (0.398)[b,f]	0.50 (0.701)[b,f]	NR
TIL,[86] reSURFACE 1	301	149	100 mg W0, 4	W12	SF-36 MCS (0-100)	NR	NR	46.4-46.8	3.9 (9.39)[b]	−0.7 (7.52)[c]	NR

Table. Continued.

Active Drug Study, Acronym(s) (if applicable)	Drug, n	PBO, n	Drug Dose and Regimen	EP	Measure	Depressive Symptoms at BL Drug, n (%)	Depressive Symptoms at BL PBO, n (%)	BL Measure Scores, range	CFB in Measure Drug, mean (SD)[a]	CFB in Measure PBO, mean (SD)[a]	*P*
UST;[87] PHOENIX 2	409	405	90 mg W0, 4, 12	W12	HADS-D (0-21)	144 (31.5) HADS-D ≥ 8	98 (24.2) HADS-D ≥ 8	4.9-5.4	−2.1 (3.4)[b]	0.21 (2.8)[c]	< 0.001
	405	405	45 mg W0, 4, 12		HADS-D (0-21)	100 (24.7) HADS-D ≥ 8	98 (24.2) HADS-D ≥ 8	4.9-4.9	−1.7 (3.1)[b]	0.21 (2.8)[c]	< 0.001
UST;[84] UltIMMa-1, UltIMMa-2	199	200	45 mg or 90 mg W0, 4, 12	W16	HADS-D (0-21)	56 (28.1) HADS-D ≥ 8	54 (27.0) HADS-D ≥ 8	5.3-5.3	NR[g]	NR[g]	NR

[a] Unless otherwise specified. [b] Improvement. [c] Worsening. [d] Absolute mean (SE); CZP and ETN are reported as absolute mean (SD). [e] Only in those with QIDS-SR16 ≥ 11 at BL. [f] LSMC (SE) [g] Only a responder analysis was presented in this study. [h] QIDS-SR16 also collected but not reported.[88] ADA: adalimumab; APR: apremilast; BDI: Beck Depression Inventory; BID: twice a day; BIW: twice weekly; BL: baseline; BRO: brodalumab; CFB: change from baseline; CZP: certolizumab pegol; EP: time of endpoint measurement; ESTEEM: Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; ETN: etanercept; EXPRESS: European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study; GUS: guselkumab; HADS-D: Hospital Anxiety and Depression Scale-Depression; Ham-D: Hamilton Depression Rating Scale; IFX: infliximab; IXE: ixekizumab; LSMC: least squares mean change; NR: not reported; PBO: placebo; PHQ-8: 8-item Patient Health Questionnaire; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; QIDS-SR16:16-item Quick Inventory of Depressive Symptomatology; RZB: risankizumab; SE: standard error; SEC: secukinumab; SF-36 MCS: 36-Item Short Form Health Survey mental component summary; TIL: tildrakizumab; UltIMMa-1: BI 655066/ABBV-066 (risankizumab) Versus Ustekinumab and Placebo Comparators in a Randomized Double Blind Trial for Maintenance Use in Moderate to Severe Plaque Type Psoriasis; UST: ustekinumab; W: week.

placebo-controlled PsA trials, slightly more participants on apremilast (1% [10/998]) reported depression or depressed mood than those receiving placebo (0.8% [4/495]). Slightly higher rates of SIB were also seen in individuals with PsA on apremilast (0.2%, 3/1441) compared to placebo (0/495), though no individuals on apremilast attempted suicide and 2 on placebo committed suicide.[60,67]

In the pooled trials with brodalumab during the 12-week randomized treatment period,[68-70] 1 of 3066 individuals on brodalumab attempted suicide and none attempted suicide in the placebo (n = 879) or ustekinumab (n = 613) groups. From initiation through week 52 of the trials, SIB occurred in 7 of 4019 individuals (0.2/100 patient-years [PY]) treated with brodalumab and in 2 of 613 individuals (0.4/100 PY) treated with ustekinumab. During the course of the PsO clinical trials, SIB occurred in 34 of 4464 participants treated with brodalumab (0.37/100 PY). Overall, there were 4 completed suicides on brodalumab in the PsO development program.[61] Subsequent analyses demonstrated that brodalumab users with a history of depression or suicidality had an approximately 7-fold and 12- to 18-fold increased SIB incidence, respectively, compared to users without this history. Additional analyses demonstrated that the rate of SIB observed in the brodalumab development program was 3 to 4 times higher than in pooled trials of other biologics for PsO based on publicly available data. The proportion of all deaths due to suicide in brodalumab clinical trials (19%) was roughly twice the proportion in PsO trials of other biologics (9%). In the same comparison, brodalumab was associated with a 3-fold higher than expected suicide rate (58 suicides/100,000 PY vs 19 suicides/100,000 PY).[71]

It is important to understand that no formal link has been established between these medications and depression or suicide. Further, mechanistically, the reason for these imbalances in depression and SIB incidence are not well understood, especially as both therapies in PsO have shown a benefit in depressive symptoms with treatment vs placebo (Table). However, due to the warnings on these drugs and the increased risk of depression and SIB in individuals with PsD, it is imperative that companies with drugs in development or approved for PsD treatment (Table) evaluate depression in their phase III clinical trials using various measures aside from reporting adverse events of depression and SIB. Ultimately, these data need to be reported in the literature, since not having these data diminishes the ability of treating clinicians to offer information about risks and benefits of various PsD treatments to their patients.

Clinicians must be aware of these warnings and supporting data when considering prescribing one of these systemic therapies to individuals with PsD. A discussion of the risk-benefit analysis regarding the use of these therapies is necessary to have with individuals with PsD. Alternative therapies for individuals with PsD should be considered for those either with a suggestive screening evaluation for depression or with PsD and a history of depression (eg, through PHQ-2 with follow-up using PHQ-9) and/or SIB. HCPs must conduct a careful reevaluation of need for continued treatment with these systemic therapies should depressive or SIB events occur. Regardless of therapeutic options

used, patients should be thoroughly counseled on what steps to take if depressive or SIB events occur during treatment, including contacting their HCP.

Conclusions

PsO and PsA are associated with an increased risk of mental health conditions, including depression. Further research is needed to better characterize shared biologic mechanisms between depression and PsO. In the clinical setting, dermatologists and rheumatologists can provide education on this association, implement screening tools during patient visits, provide referrals to a mental health professional when necessary, and optimize PsD treatment in order to provide comprehensive and exceptional care.

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REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377-85.
2. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 2022;18:465-79.
3. Lukmanji A, Basmadjian RB, Vallerand IA, Patten SB, Tang KL. Risk of depression in patients with psoriatic disease: a systematic review and meta-analysis. J Cutan Med Surg 2021;25:257-70.
4. Lakshmy S, Balasundaram S, Sarkar S, Audhya M, Subramaniam E. A cross-sectional study of prevalence and implications of depression and anxiety in psoriasis. Indian J Psychol Med 2015;37:434-40.
5. McDonough E, Ayearst R, Eder L, et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. J Rheumatol 2014;41:887-96.
6. Kulkarni AS, Balkrishnan R, Camacho FT, Anderson RT, Feldman SR. Medication and health care service utilization related to depressive symptoms in older adults with psoriasis. J Drugs Dermatol 2004;3:661-6.
7. Vestergaard SB, Esbensen BA, Klausen JM, et al. Prevalence of anxiety and depression and the association with self-management behaviour in >12 000 patients with inflammatory rheumatic disease: a cross-sectional nationwide study. RMD Open 2024;10:e003412.
8. Singh S, Taylor C, Kornmehl H, Armstrong AW. Psoriasis and suicidality: a systematic review and meta-analysis. J Am Acad Dermatol 2017;77:425-440.e2.
9. Ogdie A, Maliha S, Shin D, et al. Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology 2017;56:907-11.
10. Cohen BE, Martires KJ, Ho RS. Psoriasis and the risk of depression in the US population: National Health and Nutrition Examination Survey 2009-2012. JAMA Dermatol 2016;152:73-9.
11. Lada G, Chinoy H, Heal C, Warren RB, Talbot PS, Kleyn CE. Depression and suicidality in patients with psoriasis and the role of psoriatic arthritis: a cross-sectional study in a tertiary setting. J Acad Consult Liaison Psychiatry 2022;63:372-83.
12. Lewinson RT, Vallerand IA, Lowerison MW, et al. Depression is associated with an increased risk of psoriatic arthritis among patients with psoriasis: a population-based study. J Invest Dermatol 2017;137:828-35.
13. Zusman EZ, Howren AM, Park JYE, Dutz J, De Vera MA. Epidemiology of depression and anxiety in patients with psoriatic arthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2020;50:1481-8.
14. Hagberg KW, Li L, Peng M, Shah K, Paris M, Jick S. Incidence rates of suicidal behaviors and treated depression in patients with and without psoriatic arthritis using the Clinical Practice Research Datalink. Mod Rheumatol 2016;26:774-9.
15. Wu JJ, Penfold RB, Primatesta P, et al. The risk of depression, suicidal ideation and suicide attempt in patients with psoriasis, psoriatic arthritis or ankylosing spondylitis. J Eur Acad Dermatol Venereol 2017;31:1168-75.
16. Carr E, Mahil SK, Brailean A, et al. Association of patient mental health status with the level of agreement between patient and physician ratings of psoriasis severity. JAMA Dermatol 2021;157:413-20.
17. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 2014;53:23-34.
18. Ganança L, Oquendo MA, Tyrka AR, Cisneros-Trujillo S, Mann JJ, Sublette ME. The role of cytokines in the pathophysiology of suicidal behavior. Psychoneuroendocrinology 2016;63:296-310.
19. Patel N, Nadkarni A, Cardwell LA, et al. Psoriasis, depression, and inflammatory overlap: a review. Am J Clin Dermatol 2017;18:613-20.
20. Mathew AJ, Chandran V. Depression in psoriatic arthritis: dimensional aspects and link with systemic inflammation. Rheumatol Ther 2020;7:287-300.
21. Sahi FM, Masood A, Danawar NA, Mekaiel A, Malik BH. Association between psoriasis and depression: a traditional review. Cureus 2020;12:e9708.
22. Hölsken S, Krefting F, Schedlowski M, Sondermann W. Common fundamentals of psoriasis and depression. Acta Derm Venereol 2021;101:adv00609.
23. Wang X, Li Y, Wu L, et al. Dysregulation of the gut-brain-skin axis and key overlapping inflammatory and immune mechanisms of psoriasis and depression. Biomed Pharmacother 2021;137:111065.
24. Marek-Jozefowicz L, Czajkowski R, Borkowska A, et al. The brain-skin axis in psoriasis-psychological, psychiatric, hormonal, and dermatological aspects. Int J Mol Sci 2022;23:669.
25. Tabra SA, Abd Elghany SE, Amer RA, Fouda MH, Abu-Zaid MH. Serum interleukin-23 levels: relation to depression, anxiety, and disease activity in psoriatic arthritis patients. Clin Rheumatol 2022;41:3391-9.
26. Mrowietz U, Sümbül M, Gerdes S. Depression, a major comorbidity of psoriatic disease, is caused by metabolic inflammation. J Eur Acad Dermatol Venereol 2023;37:1731-8.
27. Picardi A, Mazzotti E, Gaetano P, et al. Stress, social support, emotional regulation, and exacerbation of diffuse plaque psoriasis. Psychosomatics 2005;46:556-64.
28. Chan B, Hales B, Shear N, et al. Work-related lost productivity and its economic impact on Canadian patients with moderate to severe psoriasis. J Cutan Med Surg 2009;13:192-7.
29. Kleyn CE, Talbot PS, Mehta NN, et al. Psoriasis and mental health workshop report: exploring the links between psychosocial factors, psoriasis, neuroinflammation and cardiovascular disease risk. Acta Derm Venereol 2020;100:adv00020.
30. Myers B, Brownstone N, Reddy V, et al. The gut microbiome in psoriasis and psoriatic arthritis. Best Pract Res Clin Rheumatol 2019;33:101494.
31. Bliźniewska-Kowalska K, Halaris A, Gałecki P, Gałecka M. Role of

interleukin 17 (IL-17) in the inflammatory hypothesis of depression. J Affect Disord Rep 2023;14:100610.
32. Yao L, Pan L, Qian M, et al. Tumor necrosis factor-alpha variations in patients with major depressive disorder before and after antidepressant treatment. Front Psychiatry 2020;11:518837.
33. Jin W, Zhang S, Duan Y. Depression symptoms predict worse clinical response to etanercept treatment in psoriasis patients. Dermatology 2019;235:55-64.
34. Michelsen B, Kristianslund EK, Sexton J, et al. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. Ann Rheum Dis 2017;76:1906-10.
35. Korman AM, Hill D, Alikhan A, Feldman SR. Impact and management of depression in psoriasis patients. Expert Opin Pharmacother 2016;17:147-52.
36. Zhao SS, Miller N, Harrison N, Duffield SJ, Dey M, Goodson NJ. Systematic review of mental health comorbidities in psoriatic arthritis. Clin Rheumatol 2020;39:217-25.
37. Betteridge N, Boehncke WH, Bundy C, Gossec L, Gratacós J, Augustin M. Promoting patient-centred care in psoriatic arthritis: a multidisciplinary European perspective on improving the patient experience. J Eur Acad Dermatol Venereol 2016;30:576-85.
38. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA 2020;323:1945-60.
39. Kromer C, Mohr J, Celis D, et al. Screening for depression in psoriasis patients during a dermatological consultation: a first step towards treatment. J Deutsche Derma Gesell 2021;19:1451-61.
40. Liang SE, Cohen JM, Ho RS. Screening for depression and suicidality in psoriasis patients: a survey of US dermatologists. J Am Acad Dermatol 2019;80:1460-2.
41. Siniscalchi KA, Broome ME, Fish J, et al. Depression screening and measurement-based care in primary care. J Prim Care Community Health 2020;11:2150132720931261.
42. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
43. Stern AF. The hospital anxiety and depression scale. Occup Med 2014;64:393-4.
44. Kiely KM, Butterworth P. Validation of four measures of mental health against depression and generalized anxiety in a community based sample. Psychiatry Res 2015;225:291-8.
45. Xiao Y, Zhang X, Luo D, et al. The efficacy of psychological interventions on psoriasis treatment: a systematic review and meta-analysis of randomized controlled trials. Psychol Res Behav Manag 2019;12:97-106.
46. Strober B, Gooderham M, de Jong EMGJ, et al. Depressive symptoms, depression, and the effect of biologic therapy among patients in Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Am Acad Dermatol 2018;78:70-80.
47. Strand V, Van den Bosch F, Ranza R, et al. Patient-reported outcomes in psoriatic arthritis patients with an inadequate response to biologic disease-modifying antirheumatic drugs: SELECT-PsA 2. Rheumatol Ther 2021;8:1827-44.
48. Kristensen LE, Soliman AM, Papp K, Barcomb L, Eldred A, Östör A. The effect of risankizumab on achieving minimal clinically important differences in patient-reported outcomes in patients with psoriatic arthritis: results from KEEPsAKE 1 and 2. J Eur Acad Dermatol Venereol 2022;36:2120-9.
49. Orbai AM, McInnes IB, Coates LC, et al. Effect of secukinumab on the different GRAPPA-OMERACT core domains in psoriatic arthritis: a pooled analysis of 2049 patients. J Rheumatol 2020;47:854-64.
50. Gladman D, Fleischmann R, Coteur G, Woltering F, Mease PJ. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. Arthritis Care Res 2014;66:1085-92.
51. Husni ME, Kavanaugh A, Chan EKH, et al. Effects of intravenous golimumab on health-related quality of life in patients with psoriatic arthritis: 24-week results of the GO-VIBRANT trial. Value Health 2020;23:1286-91.
52. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317-27.
53. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1126-36.
54. Strand V, de Vlam K, Covarrubias-Cobos JA, et al. Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond. RMD Open 2019;5:e000808.
55. Strand V, de Vlam K, Covarrubias-Cobos JA, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. RMD Open 2019;5:e000806.
56. Strand V, Alemao E, Lehman T, et al. Improved patient-reported outcomes in patients with psoriatic arthritis treated with abatacept: results from a phase 3 trial. Arthritis Res Ther 2018;20:269.
57. Mease PJ, Woolley JM, Singh A, Tsuji W, Dunn M, Chiou CF. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. J Rheumatol 2010;37:1221-7.
58. Gottlieb AB, Strand V, Kishimoto M, et al. Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naive patients with active psoriatic arthritis (SPIRIT-P1). Rheumatology 2018;57:1777-88.
59. European Medicines Agency. Otezla (apremilast): European public assessment report – product information. [Internet. Accessed April 12, 2024.] Available from: https://www.ema.europa.eu/en/documents/product-information/otezla-epar-product-information_en.pdf
60. Amgen, Inc. Apremilast (US prescribing information). [Internet. Accessed April 12, 2024.] Available from: https://www.pi.amgen.com/united_states/otezla/otezla_pi_english.pdf
61. Bausch Health USA, LLC. Brodalumab (US prescribing information). [Internet. Accessed April 12, 2024.] Available from: https://www.bauschhealth.com/Portals/25/Pdf/PI/Siliq-pi.pdf
62. European Medicines Agency. Kyntheum (Brodalumab): European public assessment report – product information. [Internet. Accessed April 12, 2024.] Available from: https://www.ema.europa.eu/en/documents/product-information/kyntheum-epar-product-information_en.pdf
63. European Medicines Agency. Part VI: summary of the risk management plan. Summary of risk management plan for Kyntheum® (brodalumab). [Internet. Accessed April 12, 2024.] Available from: https://www.ema.europa.eu/en/documents/rmp-summary/kyntheum-epar-risk-management-plan-summary_en.pdf
64. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of apremilast in psoriasis [ESTEEM] 1). J Am Acad Dermatol 2015;73:37-49.
65. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol 2015;173:1387-99.

66. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol 2017;31:507-17.
67. Kavanaugh A, Gladman DD, Edwards CJ, et al. Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1-3 pooled analysis. Arthritis Res Ther 2019;21:118.
68. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing Brodalumab with ustekinumab in psoriasis. N Engl J Med 2015;373:1318-28.
69. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med 2012;366:1181-9.
70. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of Brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol 2016;175:273-86.
71. US Food and Drug Administration. Summary Review: BLA 761032 Siliq (Brodalumab), 210-mg single dose prefilled syringe. [Internet. Accessed April 12, 2024.] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761032Orig1s000SumR.pdf
72. Gordon KB, Armstrong AW, Han C, et al. Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study. J Eur Acad Dermatol Venereol 2018;32:1940-9.
73. Clinical review report: guselkumab (Tremfya): (Janssen Inc.). [Internet. Accessed April 12, 2024.] Available from: https://pubmed.ncbi.nlm.nih.gov/30480924/
74. Thaçi D, Kimball A, Foley P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials. J Eur Acad Dermatol Venereol 2017;31:498-506.
75. Canadian Agency for Drugs and Technologies in Health. Bimekizumab (Bimzelz). [Internet. Accessed April 12, 2024.] Available from: https://www.cadth.ca/sites/default/files/DRR/2022/SR0698%20Bimzelx%20-%20CADTH%20Final%20Rec%20Final.pdf
76. Gisondi P, Gottlieb AB, Elewski B, et al. Long-term health-related quality of life in patients with plaque psoriasis treated with certolizumab pegol: three-year results from two randomised phase 3 studies (CIMPASI-1 and CIMPASI-2). Dermatol Ther 2023;13:315-28.
77. US Food and Drug Administration. Multidisciplinary Review and Evaluation: NDA 214958 Sotyktu (deucravacitinib) tablets, 6 mg. [Internet. Accessed April 12, 2024.] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214958Orig1s000MultidisciplineR.pdf
78. Canadian Agency for Drugs and Technologies in Health. Deucravacitinib (Sotyktu). [Internet. Accessed April 12, 2024.] Available from: https://canjhealthtechnol.ca/index.php/cjht/article/view/SR0756r/SR0756r
79. Krueger GG, Langley RG, Finlay AY, et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. Br J Dermatol 2005;153:1192-9.
80. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367:29-35.
81. Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol Psychiatry 2018;23:335-43.
82. Griffiths CEM, Fava M, Miller AH, et al. Impact of ixekizumab treatment on depressive symptoms and systemic inflammation in patients with moderate-to-severe psoriasis: an integrated analysis of three phase 3 clinical studies. Psychother Psychosom 2017;86:260-7.
83. Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. Br J Dermatol 2006;154:1161-8.
84. Augustin M, Lambert J, Zema C, et al. Effect of risankizumab on patient-reported outcomes in moderate to severe psoriasis: the UltIMMa-1 and UltIMMa-2 randomized clinical trials. JAMA Dermatol 2020;156:1344-53.
85. Papp K, Warren RB, Green L, et al. Safety and efficacy of mirikizumab versus secukinumab and placebo in the treatment of moderate-to-severe plaque psoriasis (OASIS-2): a phase 3, multicentre, randomised, double-blind study. Lancet Rheumatol 2023;5:e542-52.
86. Clinical review report: tildrakizumab (Ilumya). [Internet. Accessed February 28, 2024.] Available from: https://www.ncbi.nlm.nih.gov/books/NBK583939/
87. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. J Am Acad Dermatol 2010;63:457-65.
88. Eli Lilly and Company. A multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of mirikizumab to secukinumab and placebo in patients with moderate to severe plaque psoriasis (OASIS-2). [Internet. Accessed April 12, 2024.] Available from: https://storage.googleapis.com/ctgov2-large-docs/94/NCT03535194/Prot_000.pdf