Depression: How should psoriasis patients with a history of depression and/or suicidal ideation be managed?

This chapter is based on the corresponding chapter in the previous versions of the guideline [1,2]. A search was conducted, details of which can be found below**.**

Results/Recommendations:

Psoriasis is associated with a higher risk for psychiatric comorbidities including anxiety and depression while results on suicide ideation and suicide are more unclear [3-7]. In general, interventions that are effective for psoriasis correspondingly also improve symptoms of depression. Clinical studies using adalimumab, etanercept, ustekinumab, ixekizumab, guselkumab, risankizumab or fumarates for the treatment of psoriasis have shown that all these anti-inflammatory drugs not only improve psoriatic manifestations, but also symptoms of depression [6,8-14]. In head-to-head studies, guselkumab was associated with greater improvements in symptoms of depression compared with adalimumab [10], and risankizumab greater improvements compared to ustekinumab [14]. In a prospective, longitudinal registry study, biologic therapy was found to have the greatest improvement on symptoms of depression followed by conventional systemic therapy and phototherapy [5,15]. Taken together, these data suggest that the more effective the intervention for psoriasis, the greater the benefit to the mood. However, whether the overall beneficial effect on depressive symptoms is direct, or indirect (through improvement in psoriasis and therefore mood) is not clear. No treatment related emergent risk of depression or suicidality has been reported in phase III trials with deucravacitinib compared to apremilast or placebo [16,17].

Systemic treatments for psoriasis with special attention to a possible increased risk of depression, suicide ideation and completed suicide are discussed below:

Acitretin: Acitretin has been reported to be associated with depression in some case reports [18,19]. However, more recent reviews of the literature conclude that except for very few cases of depression and suicidal ideation there are no convincing evidence-based data to support an association between acitretin and depression/suicidality [20,21]. A formal review of retinoids (including acitretin and isotretionin) carried out by EMA's Pharmacovigilance Risk Assessment Committee in 2018 [22] concluded that it was not possible to identify a clear increase in the risk of neuropsychiatric disorders in people taking oral retinoids compared to those that did not. However, the EMA decided to include a warning about the possible risk in the product information for oral retinoids, since PRAC noticed that severe skin disorders themselves increase the risk of psychiatric disorders [23]. Based on the above, the

guideline group did not consider there to be sufficient evidence to specifically counsel against use of acitretin in those patients with mood disorders but, in common with all systemic therapies, clinicians should monitor for mood changes given that people with psoriasis are at increased risk of anxiety and depression.

Brodalumab: In two out of three phase III studies of efficacy and safety of brodalumab in patients with plaque psoriasis (AMAGINE 1-3) cases of suicide were reported (two patients in each of studies 1 and 2) [24,25]. An expert opinion (2019) discussing these observed cases of suicide highlighted the following aspects [26]: Further review of the suicides by the Columbia Classification Algorithm of Suicide Assessment Review Board confirmed only three of the cases as suicides. All of them had underlying psychiatric disorders or stressors and all three suicides occurred at one center. Both symptoms of depression and anxiety decreased during treatment with brodalumab [25].

In the European SmPC, the reported Suicidal ideation and behaviour, including completed suicide in patients treated with brodalumab was mentioned. However, it was also stated that a causal association between treatment with brodalumab and increased risk of suicidal ideation and behaviour has not been established. In the SmPC, it is recommended that risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behavior is identified, it was recommended to discontinue treatment with brodalumab [27].

Apremilast: Results from two phase III studies including patients with moderate-to-severe psoriasis (ESTEEM 1 and ESTEEM 2) with open-label extension for up to four years, showed that patient reported depression occurred in 1.4% of patients treated with apremilast and in 0.5% of receiving placebo. The incidence of depression did not increase over time. There was one suicide attempt, and no completed suicides with apremilast [28]. Similar results were achieved in an open-label extension study (for up to additional four years) of three phase III studies of patients with psoriatic arthritis (PsA); 1.2% in patients treated with apremilast and 0.8% in patients receiving placebo. There were two suicide attempts, and no completed suicides with apremilast [29]. Postmarketing experience, including five cases of completed suicides, was reported and a new safety information was published for apremilast provided by Celgene in agreement with the European Medicines Agency and the Health Products Regulatory Authority in 2016 [30] and last updated in 2022 [31]. In here it was stated that evidence from clinical trials and

postmarketing experience describe the risk of depression and suicidal ideation as important and identified risk (i.e. sufficient proof of link with apremilast). The SmPC and patient leaflet for apremilast was updated to add a warning about depression (common adverse reaction (≥1/100 to <1/10)) and suicidal behavior and ideation (uncommon adverse reaction (≥1/1,000 to <1/100)) [32].

It was recommended that risks and benefits of starting or continuing treatment with apremilast should be carefully assessed in patients with previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events are in use or intended. Additionally, it was recommended to discontinue treatment with apremilast in patients suffering from new or worsening psychiatric symptoms, or if suicidal ideation or suicidal attempt is identified.

We **recommend** to be aware of signs and symptoms of anxiety and depression in patients with psoriasis and monitor for symptoms of depression and/or suicidal ideation or anxiety during systemic treatments for psoriasis especially in those with a history of any of the above.	↑↑	STRONG CONSENSUS[1] 100 % Agreement
We **suggest** using alternatives to brodalumab and apremilast in patients with a history of depression and/or suicidal ideation.	↑	EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

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Review of the evidence on psoriasis and depression

Methods

Inclusion criteria

Patients	Inclusion: adult patients with a clinical diagnosis of psoriasis and depression
Intervention	acitretin, apremilast, ciclosporin, fumarates, methotrexate) TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new)
Comparator	Comparisons with another included drug and/or placebo
Outcomes	▪ risk to develop depression ▪ risk of suicide ideation and completed suicide
Study Design	Inclusion: Primary: Systematic reviews Secondary: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies Exclusion: non-systematic reviews, letter, comments

Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for the period October 2019 to 17 January 2023. One methodologist conducted a topic specific but non-systematic screening. The authors of the chapter then screened included full texts based on the above listed eligibility criteria.

Search strategy

Filter for detecting systematic reviews: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. https://pubmed.ncbi.nlm.nih.gov/17082841/ (Strategies minimizing difference between sensitivity and specificity)

Ressource: Ovid MEDLINE(R) ALL <1946 to January 17, 2023>

ID	Search term	Result
1	depression*.ti,ab.	403831
2	depress*.ti,ab.	541248
3	Depression/	146458
4	exp Depressive Disorder/	120214
5	**or/1-4**	**585928**

ID	Search term	Result
6	exp Methotrexate/	40879
7	methotrexate$.mp.	59566
8	amethopterin.mp.	401
9	mtx.ti,ab.	14592
10	exp Fumarates/	5316
11	(fumar$ and esters).mp.	468
12	dimethylfumarate.mp.	205
13	fae.ti,ab.	1021
14	dmf.ti,ab.	9700
15	fumarate$1.mp.	20781
16	Etretinate/	1352
17	Acitretin/	1286
18	((oral or orally or systemic) and retinoid$).ti,ab.	2931
19	Isotretinoin/	3942
20	isotretinoin.ti,ab.	3695
21	etretin$.mp.	1745
22	acitretin.mp.	2023
23	Retinoids/	6308
24	Ustekinumab.mp.	2952
25	secukinumab.mp.	1851
26	apremilast.mp.	1027
27	guselkumab.mp.	524
28	exp antibodies, monoclonal/	271864
29	monoclonal antibod$.mp.	204408
30	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30052
31	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1901
32	exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/	196082
33	(anti tumour necrosis factor or anti tumor necrosis factor).mp.	6177
34	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.	189039
35	anti tnf.mp.	12449
36	(tnf antibod$ or tnf alpha antibod$).mp.	2387
37	(tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp.	161
38	(antitumor necrosis factor or antitumour necrosis factor).mp.	918
39	exp Immunoglobulin Fab Fragments/	29391
40	(infliximab$ or monoclonal antibody cA2).mp.	17256
41	etanercept$.mp.	9583
42	adalimumab$.mp.	10560
43	Cyclosporine/	30456
44	(Ciclosporin or cyclosporine or cyclosporin).mp.	59498

ID	Search term	Result
45	brodalumab.mp.	498
46	ixekizumab.mp.	934
47	certolizumab.mp.	1554
48	Certolizumab Pegol/	726
49	tildrakizumab.mp.	243
50	bimekizumab.mp.	105
51	risankizumab.mp.	336
52	**or/6-51**	**777987**
53	exp Psoriasis/	46876
54	psoria*.ti,ab.	57249
55	palmoplantar$ pustulosis.ti,ab.	664
56	pustulosis palmaris et plantaris.ti,ab.	173
57	(pustulosis and palms and soles).ti,ab.	107
58	**or/53-57**	**63986**
59	deucravacitinib.mp.	45
60	TYK2 Kinase/	609
61	(TYK2 or tyrosine kinase 2).ti,ab.	2131
62	**or/59-61**	**2252**
63	5 and 52 and 58	206
64	5 and 58 and 62	0
65	("201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5035956
66	63 and 65	64
67	meta analysis.mp,pt. or review.pt. or search:.tw.	3569837
68	**66 and 67**	**15**
69	**66 not 68**	**49**

Link:
https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=3AH4CbgUZGpBhGUPKx2y5JHOOpaB3S1Y2ar6NNuZ8bZXg8KPVHHHc4Zzk1MLymi9p

Results