



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 isotretinoin) 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 ($\geq 1/100$ to $< 1/10$)) and suicidal behavior and ideation (uncommon adverse reaction ($\geq 1/1,000$ 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.

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| <p>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.</p> | <p>↑↑</p> | <p>STRONG CONSENSUS¹</p> <div style="text-align: center;">  <p>100% Agreement</p> </div> |
| <p>We suggest using alternatives to brodalumab and apremilast in patients with a history of depression and/or suicidal ideation.</p> | <p>↑</p> | <p>EXPERT CONSENSUS</p> |

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

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|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patients | Inclusion: adult patients with a clinical diagnosis of psoriasis and depression |
| Intervention | Conventional systemic treatment (acitretin, apremilast, ciclosporin, fumarates, methotrexate) and biologicals (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 | <ul style="list-style-type: none"> ▪ risk to develop depression ▪ risk of suicide ideation and completed suicide |
| Study Design | <p>Inclusion:</p> <p>Primary: Systematic reviews</p> <p>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</p> <p>Exclusion:</p> <p>non-systematic reviews, letter, comments</p> |

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 |
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| 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 |
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| 36 | (tnf antibod\$ or tnf alpha antibod\$.mp. | 2387 |
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| 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 |



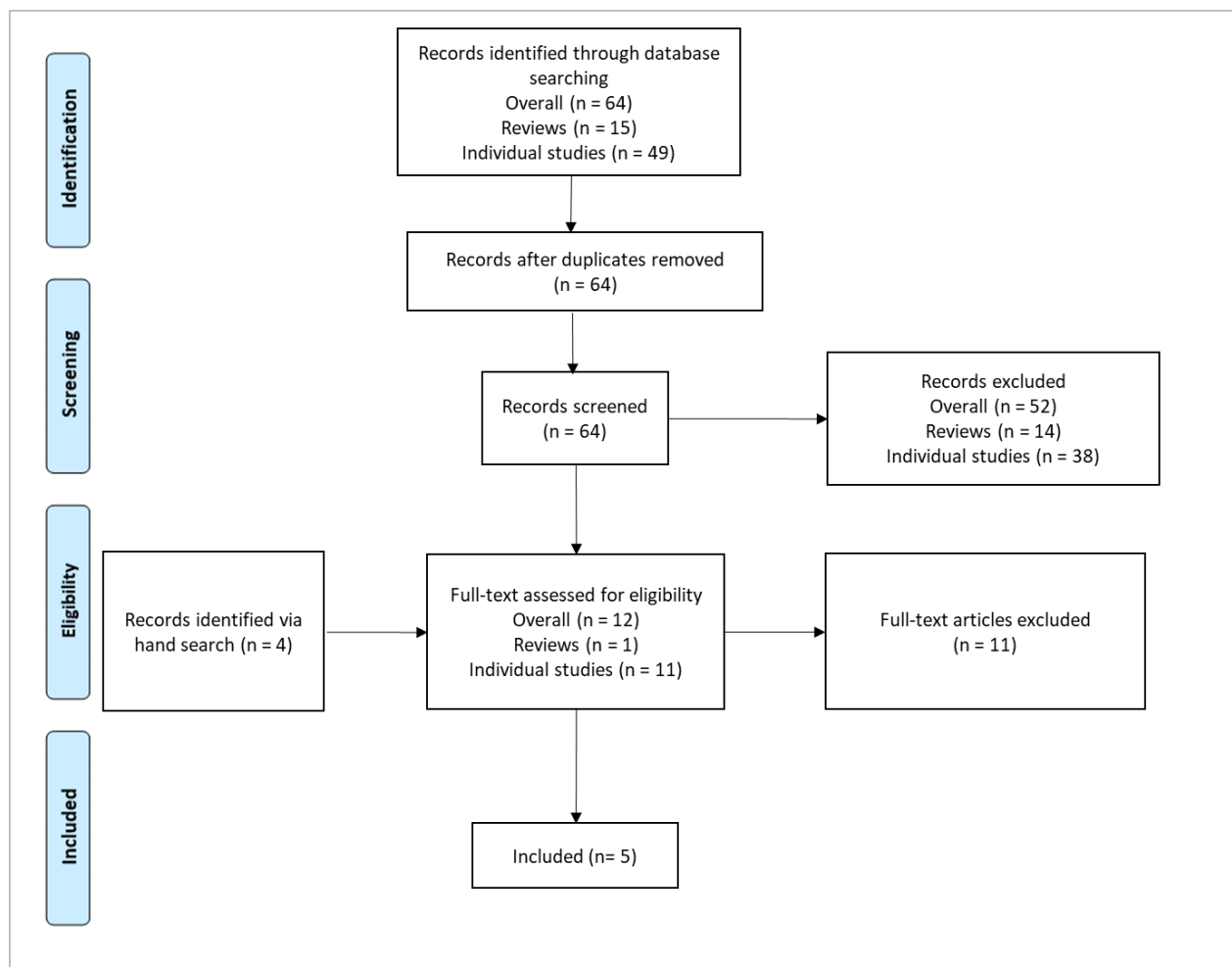
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| 49 | tildrakizumab.mp. | 243 |
| 50 | bimekizumab.mp. | 105 |
| 51 | risankizumab.mp. | 336 |
| 52 | or/6-51 | 777987 |
| 53 | exp Psoriasis/ | 46876 |
| 54 | psoria*.ti,ab. | 57249 |
| 55 | palmoplantar\$ pustulosis.ti,ab. | 664 |
| 56 | pustulosis 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



EUROGUIDERM GUIDELINE FOR THE
TREATMENT OF PSORIASIS
VULGARIS. SYSTEMIC TREATMENT

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