Review

# Could suicide be fostered through the potential antidepressant mechanism of biologic agents? A Psychodermatological approach to existing bibliography.

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**Abstract**

Bipolar Disorder is a biological condition that affects between 2 and 5% of the population, being an important cause of disability in the world. Despite this, it is often underdiagnosed as Unipolar Depression, which increases the possibility of prescribing errors, as it occurs when administering only antidepressant agents without accompanying them with mood stabilisers. This could foster episodes of inverse polarity (SWITCHING) which, in turn, raises the risk of suicide. This work reviews the existing literature for evidence that while biologic agents could improve the mood of patients with psoriasis treated with these drugs, this same favourable antidepressant effect on humour may trigger a switch into *mania*, favouring attempted and completed suicide in undiagnosed bipolar patients treated for psoriasis with the above-mentioned agents.

## Methods

### Sources and research strategy

A systematic review of the literature was performed for evidence that while biologic agents could improve the mood of patients with psoriasis treated with these drugs, this same favourable antidepressant effect on humour may trigger a switch of mood into *mania*, favouring attempted and completed suicide in undiagnosed bipolar patients treated for psoriasis with IL-17-TNF-alpha cytokine blockers. The PubMed database was systematically searched using individual or combinations of the search terms “psoriasis”, “anti-IL-17”, “interleukin-17”, “Mania”, “Bipolar Disorder”, “Hypomania”, “Depression”, “Suicide”, “Mixed episode”, “Inflammation”, and “switching”. Based on their titles and abstracts, relevant articles were selected for this review. Ongoing trials were identified from the US National Institutes of Health ongoing trials register, ClinicalTrials.gov. News briefs were also included.

### Study selection

Our review covers 48 articles in English, Spanish and French for a period of 15 years, from 2004 to 2019, with articles from Brazil, USA, UK, France, Canada, Italy, Portugal, Sweden, Turkey, Paraguay, Netherlands, Poland, Denmark, Iran, Pakistan, Japan, India and Argentina.

## Introduction

The aim of this review is to highlight the relationship between two diseases mediated by the cytokine mechanism such as Psoriasis (Ps) and Bipolar Disorder (BD) under a more integrative view of the disease.

Based on the crossing of information provided by different areas such as Psychiatry, Dermatology, Immunology and Immunopharmacology, we can refer to Inflammation as the “**Trans diagnosis”** [1] underlying these two conditions (Ps and BP) that affect around 3 percent of the general population, which are chronic, recurrent, evolving in outbreaks, highly disabling and with an important family incidence. Both diseases present a multisystem involvement with a higher rate of metabolic syndrome, dyslipidaemia, diabetes and coronary disease with a greater number of cardiovascular events and thrombotic phenomena.[2]

### *Depression*

According to the DSM-5, DEPRESSION is characterized by “the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function”. These are “discrete episodes of at least 2 weeks' duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and neurovegetative functions and inter-episode remissions”.[3]

Numerous studies have investigated the etiopathogenesis of the Major Depressive Disorder (MDD). Although monoamines play a large part in depression, evidence suggests that inflammation could have a crucial role in at least a percentage of the depressive cases.[4]

***Bipolar disorder***

Bipolar disorder is a biological disease which affects 2 to 5% of the world population, being an important cause of disability in the world. BD affects the mechanisms that regulate the mood, as well as other areas like cognitive, autonomic, endocrine and sleep. It is characterized by the appearance of episodes of depression with episodes of mania or high mood with a chronic and episodic course.[5] It has a considerable family incidence as this is a genetic-based condition with an affirmative history of the disorder in family members in up to 60-80% of cases.[6] There are positive or negative precipitating factors or none at all, this resulting from the chronic development of the disease. BP can present an associated phenomenon called SWITCHING, which is defined as "a sudden transition from a mood episode to another episode of the opposite polarity".[7]

According to the reviewed bibliography, there are multiple systemic conditions where chronic low-grade inflammation (i.e. cardiovascular disease, psoriasis, type 2 diabetes mellitus, rheumatoid arthritis (RA), inflammatory bowel disease (IBD))[8] and bipolar disorder are strongly associated, with increase pro-inflammatory cytokine levels. It is described in the literature a rise in biological markers such as high sensitivity C-reactive protein (hsCRP), CEA levels and white blood cell (WBCs) counts in manic patients. This may be caused by the bidirectional interaction of bipolar disorder with an immune dysfunction.[9] [10]

***Psoriasis and Depression***

This association between Psoriasis and Depression could be explained by at least two mechanisms: 1) the chronic stress caused by social isolation and stigmatization in the severe forms of psoriasis can modify the hypothalamic–pituitary-adrenal axis (HPA) generating anxiety and depression.[11] In addition, 2) the proved link between depression and the increase in pro-inflammatory [12] cytokines[4] [13] implicated in psoriasis pathogenesis: IL-1B, IL-6, TNF-alpha[14] and IL-17[15], which increase the activity of the indoleamine-2, 3-dioxygenase enzyme, resulting in depletion of serotonin levels and the production of quinolinic acid, generating depression. [16] [17]

"Although psoriasis and depression retain their own unique set of cytokines in their respective pathogenesis, interleukin (IL-17) and tumour necrosis factor (TNF) are present in both diseases."(Patel, N. et al., 2017) [15]

The IL-17 family consists of six structurally related cytokine IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F. The IL-17R family comprises five receptor subunits, being the IL-17RA the founding receptor of the family. It is necessary a balance between the pathogenic and protective/ regulative effects of IL 17. Several studies have reported elevated levels of IL-17 in psychiatric disorders like depression and anxiety, although IL-17 is expressed ubiquitously in the organism [8], maintaining the intestinal barrier integrity, driving kallikrein expression in renal cells, promoting the differentiation and activation of osteoblasts in bone observed in arthritis and periodontal disease. [12] [18]

Evidence points out that this balance between pro and anti-inflammatory cytokines in basal levels would ensure immunological stability and favour neurogenesis and neuroplasticity. IL-17A, which is a pivotal cytokine in psoriasis, may contribute to the depression pathogenesis [19] by [20] exacerbating [21] neurodegeneration through oxidative damage to lipids and proteins. By means of a double mechanism, directly and synergistically with TNF-alpha and IL-1, IL-17A promotes an abnormal neurogenesis in the hippocampus, which is in charge of maintaining the plasticity [22] in response to adaptive changes. [18] IL-17E (25) seems to produce IL-13 suppressing TH17 responses by inhibition of IL-23 IL-1B IL-6 playing an opposite role to maintain the homeostatic status.

There is a subgroup of depressed patients who would have a deregulation of the immune system that would explain the lack of response to antidepressants (up to 50% of cases). Inflammation can activate the microglia to release anti-inflammatory cytokines, acting in two ways: by activating the hypothalamic–pituitary-adrenal axis or by increasing the activity of the indoleamine-2,3-dioxygenase enzyme, resulting in depletion of serotonin levels and the rise in the production of quinolinic acid [13] [23] [24] [25]. Stress can compromise the integrity of the blood-brain barrier [14](BBB), which, faulty as it is, does not protect the brain from the infiltration of both peripheral pro-inflammatory cytokines such as TNF-alpha and IL-6 and dendritic cells. This, in turn, triggers a cascade of events in the central nervous system via the actions of the microglia, neurotransmitter metabolism, and neurogenesis [17]. There is an ongoing 12-week study that shows the presence of immune-inflammatory disturbances which may cause the depressive, manic, and euthymic periods in individuals with Bipolar Disorders (BD) and their response to Infliximab [26] in the evolution of the mood disorder.[4] [27]

***Suicide***

"Suicide is the Intentional termination of one's own life and it constitutes the 10th leading cause of death globally and the second leading cause of death among 15–29-year-olds" according to WHO. Elevated pro-inflammatory cytokines have been found in blood and cerebrospinal fluid and post-mortem brain samples from suicidal patients [25], indicating that inflammation may contribute to the pathophysiology of suicide. [28, 29]

Several studies reviewed for this paper show the existence of a high prevalence of lifetime suicidal ideation, suicidal behaviour, attempted and completed suicide in patients with psoriasis in comparison with not only normal subjects but with subjects suffering from other dermatological conditions as well. [30, 31, 32]

As the association between psoriasis and psychiatric comorbidity, including suicide and risk of self-harm, has been vastly reported in the literature, a right and early psoriasis treatment improves the mental condition, particularly depression and anxiety [19]. Some research studies show the antidepressant capacity of biologic agents. For instance, patients treated with Infliximab respond if they have a CRP (C reactive protein) blood level greater than 5, thus

inferring the usefulness of biomarkers (IL-13, IL-6 and TNF-alpha) to detect patients with suicide risk or suicidal behaviour [33]. While biologic agents improve the mood of patients with psoriasis treated with these drugs, it has been reported in the literature some cases of patients with a worsening of their depressive condition and even the emerging of suicidal ideation, attempted and completed suicide [27, 34, 35, 36, 37, 38, 39, 40, 41, 42] . Based on the evidence, two questions arise: ***If the inflammation is treated with biologic agents with its improving effect, why would the depressive condition worsen leading to suicide? Could suicide be fostered through the potential antidepressant mechanism of biologic agents?***

***Discussion***

In most of the revised bibliography, there is not enough data so as to infer the kind of depression, if any, present in the patients included in drug trials. In this respect, it should be pointed out the need for a differential diagnosis between UNIPOLAR depression (UPD) and BIPOLAR Depression (BP). There is a high incidence of under-diagnosis of Bipolar Disorder since it often appears as a long, sustained depressive episode with isolated episodes of hypomania in the past that may go unnoticed if the patient is not properly questioned. In most cases (30-50% of the patients, resistant to treatment with common antidepressants), the patients are diagnosed as unipolar depressions, needing around 8 years to reach a correct diagnosis. [43]

As mentioned before, bipolar disorder is characterized by the appearance of cycles of depression with episodes of mania or high mood. It could also appear as **an episode with mixed features**, defined by depressive symptoms associated with impulsivity, aggression and dysphoria. The presence of only three symptoms of opposite mood polarity is sufficient for a patient to qualify for the specifier "with mixed features" (DSM-5), this condition being even more frequent than manic episodes. "As opposed to previous editions, in DSM-5 the specifier "with mixed features" is used for manic, hypomanic or depressive episodes in bipolar spectrum and major depressive disorders. The term "mixed episode" used in the context of bipolar disorder type I has been discontinued in DSM-5"(Muneer, A., 2017) [6] These episodes with mixed features would present a genetic vulnerability for the dopaminergic neurotransmission [7, 44]. The usefulness of knowing the neurobiological and inflammatory phenomena that surround the change of polarity in the course of BD lies in the power of sub classifying, in the future, patients according to individual vulnerability and the exogenous factors capable of triggering the switch, either spontaneous or iatrogenic. Reported in the reviewed literature, the most frequent exogenous factors are circadian disturbances such as the ones produced by shift work or transmeridian travel, stress caused by life events or chaotic lifestyle, high levels of catecholamines and HPA axis hyperactivity. [7]

At this point, it would be necessary to clarify the difference between CYCLING and SWITCHING. While the former refers to a pattern of frequent, distinct periodic episodes that extend throughout the patient's life, the latter is an intra-episodic change from the depressive to the

manic pole often with a iatrogenic connotation. Although iatrogenesis is usually related to switching (trans-polar switching), there are reports in the literature that show that drugs could also affect cycling. This is important since patients with a higher frequency of switching have a greater number of comorbidities, a higher incidence of substance abuse and a greater risk of committing suicide. [44] The drugs capable of causing an iatrogenic change in polarity in patients with BP include systemic steroids, dopamine agonists, amphetamines and tricyclic antidepressants (TCAs). Intrinsically, all antidepressants can be associated with TEAS (treatment-emergent affective switch), their ranges varying according to the methodological study design, concomitant treatments and type of statistical analyses applied. Compared to other antidepressants, TCAs are associated up to 70% of the incidents of polarity change since modification of TWO monoaminergic systems more likely induce TEAS than a single SSRI (Selective serotonin re-uptake inhibitor) [7] In the case of Venlafaxine (selective norepinephrine reuptake inhibitor), its connection to switching ranges from 13 to 29% while Bupropion (a dual norepinephrine/dopamine re-uptake blocker) up to 20%. Cases of a mania episode following the exposure to SSRI appear to be more common among patients with a certain genetic make-up. Their agitation is associated with the long allele (LL-genotype) of the promoter region of the serotonin transporter. [44]

A noteworthy fact is that Escitalopram (SSRI) is described in the literature as an antidepressant among those least likely to cause manic switch and those with the greatest anti-inflammatory effect. This correlates to the fact that this drug would decrease IL-17 levels in patients with depression, posing the possibility of theorizing about an inflammatory trigger in the polarity change. [6, 21, 45]

Alternatively, inflammatory phenomena mediated by cytokines could precipitate a polarity change explained by the elevation of IL-17, which has been described as elevated in patients with BD and psoriasis. [1]

It should be made clear that suicide is always a multi-causal phenomenon. It may depend on three factors. First, the genetics of the patient and the expression of indoleamine-2,3-dioxygenase enzyme (IDO) and amino-*ß-carboxymuconate-semialdehyde-decarboxylase enzyme* (ACMSD) that transforms picolinic acid into quinolinic acid. Second, the inflammatory status of the patient based on the balance between pro and anti-inflammatory cytokines. Whereas cytokines foster inflammation, it should be required a basal level of them to maintain neurogenesis and neuroplasticity. Last, the administered drug which will act and trigger the previous two factors, especially those drugs that act on IL-17 and its receptor as they are involved in neurogenesis and neurodegeneration.

Biologic agents may modify the neurotransmitter levels either improving or worsening the mood. Based on all the above described, a plausible hypothesis arises on the double-edged nature of biologic agents. With their ability to block the action of pro-inflammatory cytokines, they would have an antidepressant effect that would be beneficial to treat the psychiatric

comorbidity of the patient with psoriasis.[8] However, this same antidepressant effect, in a patient with genetic vulnerability for depression with a concomitant inflammatory disease, could trigger a mood alteration. This alteration could range from a slight mood change to a polarity switch in an underdiagnosed bipolar disorder that could lead to a suicide attempt when receiving a biologic agent. Thus, the biological agent would only be the triggering factor of a series of underdiagnosed predisposing factors. [46]

As referred in the reviewed literature, there are cases of patients with psoriasis, depression and attempted suicide during treatment with different biologic agents that could be interpreted as depressive episodes within the context of an underdiagnosed bipolar disorder. Adding this to their inflammatory status, (their high levels of pro-inflammatory cytokines in blood and Cerebrospinal fluid) and the use of a biologic agent that modifies the balance of pro and anti-inflammatory cytokines, an episode with mixed features could be triggered. In this scenario, the biologic agent would worsen the depressive symptoms, accelerate the cycling, and favour the switching (polarity change) or even precipitate a suicide attempt. It should also be considered that the suicide attempt or suicide completion described in the bibliography can be expected in the chronic course of bipolar disorder associated with the psoriasis, independently of the received treatment.

***Conclusions***

Considering both bipolar disorder and psoriasis as a multi-system entity should help us understand the common physiopathology of this comorbidity so as not to see them as separated disorders. Consequently, it is vital to emphasize **the importance of the initial psychiatric evaluation** for a correct psychiatric/ clinical diagnosis for patients with psoriasis to be admitted to clinical studies as well as for therapeutic purposes. This would imply: 1) Questioning for depression symptoms. Currently, there are no scales that are reliable enough when assessing the risk of suicide. [47] Screening for the early detection of patients with risk of suicide should be improved after the consultation with the psychiatrist. In case of suicidal ideation or attempted suicide, the professional should be able to perform a differential diagnosis between a) switching and cycling secondary to the chronic course of the BP disease and b) Iatrogenic switching and modification of the cycling. A suggested diagnostic triad would be: the use of the Columbia test [47], the assessment of the extent of psoriasis to evaluate the patient's inflammatory status (PASI) and biomarkers (CRP) [38, 48] 2) Making a differential diagnosis of unipolar depression or bipolar depression, looking for a short period in the past (few days) where the patient has had hypomanic symptoms. That being the case, a specific treatment with mood stabilizers may be initiated prior to the use of biologic agents. 3) In the event of an episode with mixed features, we should consider if these patients can receive biologic agents or if they should be stabilized first and once compensated, they can be administered the biologic treatment. 4) Intra study and post study follow-up by a

psychodermatologist is suggested since the treatment could cause mood alterations which, whereas not as extreme as a suicidal ideation or attempt, may as well deteriorate the patient's quality of life. 5) Prescription of antidepressants to patients with psoriasis and accompanying depression should be cautious, supervised by a psychiatrist who would rule out BD. In case of prescription and according to all the above-mentioned references in the literature, Escitalopram would be a good therapeutic option for its possible anti-inflammatory effect. 6) Due to their capacity to cause iatrogenic switching, it would be sensible to avoid the combination of tricyclic antidepressants (TCAs), Venlafaxine or Bupropion with biologic agents.

To conclude, we would suggest that more research should be conducted a) to evaluate Incidence rates of Bipolar Disease in patients with psoriasis, b) to attempt to stratify patients based on their inflammatory profile, c) to deepen the current knowledge on the pivotal role of IL-17 and its receptor IL-17R in mood stability, by maintaining a balance between its pro–inflammatory properties and its host-protective capacities, d) to assess the risk of combining tricyclic antidepressants (TCAs), Venlafaxine or Bupropion with biologic agents and e) to validate the anti-inflammatory effect of Escitalopram on account of its action on the IL-17 levels. The result of such studies along with articulated multidisciplinary work may contribute to an integrative understanding of a patient with an inflammatory condition that is expressed ubiquitously in the organism.

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