

# Depression and Anxiety in Patients with Bullous Pemphigoid: Impact and Management Challenges

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**Abstract:** Bullous pemphigoid is the most common autoimmune subepidermal blistering disease of the skin and mucous membranes. It is also associated with high mortality and poor prognosis due to advanced age of the patients and coexisting comorbidities. There is a dearth of data in the literature regarding depression and anxiety among those patients. The objective of this brief review is to discuss the intertwining relationship between depression and anxiety with bullous pemphigoid.

**Keywords:** anxiety, bullous pemphigoid, corticosteroids, depression, drug-induced bullous pemphigoid, quality of life

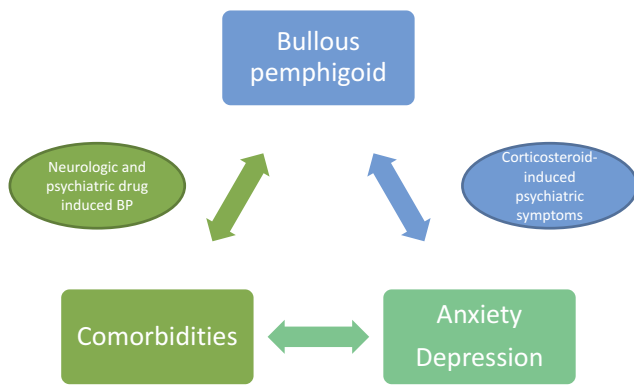
## Introduction

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin and mucous membranes.<sup>1</sup> It affects mainly the elderly patients aged  $\geq 65$  years and displays its highest incidence after the age of 90.<sup>2,3</sup> In Europe, its incidence ranges from 2.5 to 42.8 per 10,000,000 person-years.<sup>4</sup> BP presents as tense blisters leaving erosions and crusts and erythema, associated with urticarial plaques and itch.<sup>1-3</sup> BP is also associated with high mortality and poor prognosis due to advanced age of the patients and comorbidities.<sup>5-10</sup> In this brief review, we discuss the relationships between depression and anxiety with BP (Figure 1).

## Quality of Life in Patients with Bullous Pemphigoid

The morbidity of BP and its impact on the quality of life (QoL) are significant.<sup>1</sup> BP causes significant physical discomfort (itchy patches, blisters, erosions) and physical limitations. Besides time spent on treatment, financial burden (high number of corticosteroid tubes, nurse at home) and social misconceptions should not be forgotten. For a patient treated with the recommended 30 g/day clobetasol propionate cream protocol,<sup>5</sup> the costs for the treatment of one patient with potent topical corticosteroids during 4 months will be €174.80 (\$224.57) in the Netherlands.<sup>11</sup> However, this pharmaco-economic evaluation does not include body application by home care nurses that can substantially increase the total costs.<sup>11</sup> Studies have shown the impact on the QoL of patients with autoimmune bullous diseases (AIBD).<sup>12,13</sup> However, most of these studies have focused on pemphigus<sup>12,13</sup> or BP patients are analyzed along with other AIBD.<sup>14</sup> To the best of our knowledge, only Kouris et al have specifically reported on BP's impact on QoL. In their series of 57 patients with BP, they found that patients had higher scores for depression compared to sex- and gender-matched healthy controls, but did not find any difference for anxiety. The

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**Figure 1** Intertwining between depression and anxiety with bullous pemphigoid and associated comorbidities. Pemphigoid and any associated comorbidities may be responsible for anxiety or depression. Drugs given to treat anxiety or depression might be a potential trigger of BP. Additionally, cross-reactive immune responses between neural and cutaneous antigens may also have an influence. On the other hand, systemic corticosteroids to treat bullous pemphigoid may induce psychiatric complications.

patients had a higher perception of loneliness and social isolation compared to the controls. There was a positive correlation between depression and loneliness scores.<sup>15</sup> BP may result in restrictions on work and daily activities, patients may be concerned about their appearance, the BP treatment and its probable recurrence.<sup>15</sup> It is however important to stress that the series of patients in the report by Kouris et al was small and included quite young people. The mean age was 59 years, which is far from being representative of the typical population of BP patients ( $\geq 70$  years-old). In another small comparative study, DeGrazia et al found that patients with atopic dermatitis and BP shared similar experience and QoL impact in relation to chronic itch.<sup>16</sup>

A questionnaire specific to AIBD was recently developed: the Autoimmune Bullous Disease Quality of Life (ABQOL). It was found to be more sensitive than the Dermatology Life Quality Index (DQLI). It explores 17 items including depression, anxiety, relationships, social life, etc.<sup>17</sup> However, we did not find any publication about its use in “real life” with large cohort of BP patients.

## Bullous Pemphigoid and Neurological and Psychiatric Disorders

BP is associated with various comorbidities including neurological and psychiatric disorders. In Finland, Försti et al found patients with various central nervous system disorders were at higher risk of developing BP. They included multiple sclerosis, various forms of dementia, cerebral

strokes, and hemorrhages as well as epilepsy. They also found various psychiatric conditions, mostly schizophrenia, and personality disorders, but also bipolar disorders and major depression as risk factors.<sup>18</sup> Association with neurological conditions and psychiatric disorders have been observed also in other epidemiological studies.<sup>19–21</sup> Link with psychiatric conditions is not consistently found in every series.<sup>19,22</sup> Bastuji-Garin et al observed that patients with BP were more likely to have bipolar disorder (4%) compared with controls.<sup>23</sup> Conversely, a large US study showed that patients with BP that were hospitalized were more likely to have psychoses or depression (among others) but no bipolar disorder.<sup>24</sup> One appealing hypothesis is that neurodegeneration or neuroinflammation could lead to a cross-reactive immune response between neural and cutaneous antigens and the failure of self-tolerance. Indeed, BP autoantigens BP180 and BP230 are expressed in the central nervous system.<sup>25</sup> Circulating BP antibodies have been found in some patients with neurological diseases such as dementia and Parkinson’s disease but is not known for patients with psychiatric conditions.<sup>25</sup>

## Drug-Induced Bullous Pemphigoid

Drug-induced BP is a well-known subset of BP.<sup>26</sup> Medications to treat any associated comorbidities should be investigated. Until recently, the list of culprit drugs is rather small regarding psychiatric disorders. Neuroleptics have been reported to be associated,<sup>27</sup> and anecdotal case reports have been published with risperidone<sup>28</sup> or with fluoxetine.<sup>29</sup> Varpuluoma et al published recently a study from the Finnish Care Register of Health.<sup>30</sup> They found that a very large number of drugs intended from neurologic or psychiatric conditions were associated with an increased risk of BP.<sup>30</sup> Drugs that particularly elevated the risk for BP included periciazine, melperone, haloperidol, biperiden, and risperidone. However, adjusted odd ratio for antidepressants such as escitalopram, venlafaxine or duloxetine were also significantly associated with BP.<sup>30</sup>

## Corticosteroids-Induced Mood Changes

Superpotent topical corticosteroids are currently the gold standard treatment.<sup>1</sup> However, they may be difficult to initiate because of the necessity of help at home (partner or other family members; home nurses). Different national health-care systems may not be always supportive enough in terms of costs. Oral corticosteroid can be the first choice of treatment in

case of generalized disease.<sup>1</sup> Nevertheless, psychiatric side effects from corticosteroids include mood disorders (mania, mixed states, depression), anxiety, panic disorders, delirium, agitation, insomnia or suicidal behaviour.<sup>31</sup> Symptoms usually occur within the first 1 to 2 weeks after initiation and are dose related.<sup>31,32</sup> The risk of depression may increase with prolonged or chronic exposure.<sup>31</sup> The first step of treatment in case of psychiatric corticosteroid-induced symptoms is corticosteroid dose reduction or withdrawal.<sup>31</sup> In a spirit of completeness, we wish to remind that both adrenal insufficiency<sup>33</sup> and Cushing syndrome may present as depression.<sup>34</sup>

In conclusion, BP may impact the QoL of the patients with possible direct effect on anxiety or depression. However, the review of the literature shows a dearth in terms of publications on the topic. Depression and anxiety may be related to other comorbidities, such as dementia.<sup>35,36</sup> BP induced by medications given to treat depression or anxiety should be kept in mind. Corticosteroids may be associated with acute psychiatric symptoms, including depression or anxiety.

## Disclosure

The authors report no conflicts of interest in this work.

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