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The Relationship Between Mental Health and Drugs used in Dermatology

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ABSTRACT:

INTRODUCTION: Dermatological diseases are a common clinical problem in medical practice. Various groups of medications are used in their treatment. Psychiatric disorders also present a significant challenge for modern medicine, some of them may have iatrogenic origins. This study analyzes drugs used in dermatological diseases and their impact on mental health.

REVIEW METHODS: This review of the literature collects data from PubMed and Google Scholar about medications used for treating dermatological conditions and their potential impact on mental health.

THE STATE OF KNOWLEDGE: Acyclovir, valacyclovir, chloroquine, hydroxychloroquine, tetracyclines, retinoids, glucocorticoids, 5-alpha-reductase inhibitors, dapsone and methotrexate are mentioned in the literature as possible, but rare causes of the onset /exacerbation of various psychiatric symptoms. Comparing to general population, patients with skin disorders suffer more often from depression and anxiety. Those two diseases are mentioned most frequently in the context of psychiatric side effect of drugs discussed in the article.

SUMMARY: Psychiatric side effects of drugs used in dermatology are not common. However, given the rising incidence of mental health disorders worldwide, it is important to be aware of them.

KEYWORDS: dermatology, psychiatry, side effects of medications, psychiatric disorders

INTRODUCTION:

Globally, there is a growing crisis in mental health. One in eight people experience mental health problems, according to the World Health Organization (WHO). [1] People are suffering from depression, the most common mental illness, at younger and younger ages. Globally, depression is expected to overtake all other diseases by 2030, according to predictions from the WHO. [2]

It is critical to understand the variables influencing the onset of mental diseases in light of this major modern mental health concern. Beyond environmental factors and genetic predispositions, it is essential to recognize that psychiatric symptoms may emerge as adverse effects of administered medications. This article explores the most commonly used drugs in dermatological diseases and their association with the occurrence of psychiatric disorders as a result of therapy.

REVIEW METHODS: This literature review gathers information available on PubMed and Google Scholar about drugs used for treating dermatological diseases and potential implications of their use.

THE STATE OF KNOWLEDGE:

Epidemiology of dermatologic diseases:

Skin diseases encompass a group of conditions with various etiologies, including infectious, autoimmune, genetic and neoplastic factors, manifesting through lesions on the skin and its appendages, such as hair and nails.

Dermatological conditions pose a significant health concern affecting nearly one-third of the global population, ranking as the fourth most diagnosed disease among people. [3] Skin disorders also represent the most frequent reason for consultations in general medical practice. [4]

Skin diseases, both acute and chronic, impact individuals of all ages and under diverse social conditions. Common dermatological issues among the younger population include acne vulgaris and skin conditions resulting from viral (e.g., viral warts) and bacterial infections. As individuals age, conditions such as psoriasis, fungal skin infections, and melanoma become more prevalent. [5] According to studies conducted by M.A. Richard (2022), the most frequently reported skin disease among the adult European population was fungal skin infection, followed by atopic dermatitis and acne. [4]

In the elderly population, skin diseases are more common as a result of age-related alterations in the structure and function of the skin. Considering the projection that by 2050, 22% of the population will be over 60 years old, it is anticipated that the prevalence of dermatological diseases will continue to rise. [6]

Dermatologic and psychiatric diseases:

Dermatological diseases are often chronic conditions with periods of exacerbation and remission, significantly impacting a patient's functioning throughout their life. The presence of noticeable skin changes can lead to psychological distress, including low self-esteem, shame, embarrassment and social isolation in patients. These conditions are recognized as predisposing factors for the development of anxiety, depression and even suicidal tendencies. [7] Additionally, symptoms such as itching, pain, and fatigue, often coexisting with skin issues, contribute to a decreased quality of life in many cases. [8] In the study Dalgard (2015), conducted across various centers in 13 European countries, it was observed that 10.1% of individuals with skin diseases exhibited clinical symptoms of depression, compared to 4.3% in the control group. Additionally, a higher prevalence of anxiety disorders was noted among patients with skin diseases (17.2% compared to 11.1%) and occurrence of suicidal ideation (12.7% compared to 8.3%). [9]

The association between psychiatric disorders and dermatological conditions is strongly pronounced. [9] Considering embryonic development, the skin and nervous tissue originate from the same germ layer, which may explain their interplay. [7]

The field of Psychodermatology has been established with the purpose to investigate the mutual connection between psychiatric and dermatological disorders. Four groups of psychodermatology disorders have been identified:

1. Psychophysiologic disorders: These are dermatological conditions precipitated or exacerbated by psychological stress, e.g., urticaria, psoriasis.
2. Psychiatric disorders with dermatologic symptoms, e.g., trichotillomania.
3. Dermatologic disorders with psychiatric symptoms, e.g., alopecia areata, vitiligo.
4. Miscellaneous: This category describes conditions that cannot be classified into the above groups, e.g., Cutaneous Sensory Syndromes plus medication-related adverse effects of both psychiatric and dermatological medications. [10]

Antiviral drugs

Antiviral drugs used in dermatology include acyclovir and valacyclovir. They are prescribed in the treatment of infection and recurrence of herpes simplex caused by HSV types 1 and 2, as well as chickenpox and shingles caused by the VZV virus. The mechanism of action of acyclovir is to block the viral DNA polymerase and to incorporate its derivative, acyclovir triphosphate, into the viral DNA chain, which ultimately inhibits the virus replication process. [11] Valacyclovir is a prodrug of acyclovir, with a better absorption profile, and when converted to acyclovir, it has the same action profile. [12]

Psychiatric side effects of acyclovir are rare, occurring in 1:1000-1:10000 patients and include agitation, confusion, hallucination, and signs of psychosis. [13] It is vital to remember the fact that those antivirals are eliminated through the urinary system and incorrectly adjusted dose during kidney diseases may cause development of side effects.

A case of Cotard syndrome was described as a result of taking an unadjusted dose of valaciclovir for shingles treatment in a patient with bilateral renal cell carcinoma. Cotard syndrome manifests as nihilistic delusions ranging from denial of the existence of body parts to denial of self-existence. [14] The patient's previous history of psychiatric illnesses included only anxiety disorders. On the first day of symptoms, the patient was hospitalized. At the reception, she claimed that she had died and was in heaven. The decision was made to implement hemodialysis. On the second day of treatment, improvement was noted, and on the third day, the nihilistic delusions disappeared. [15]

Antimalarial drugs

Antimalarial drugs used in dermatology include quinine derivatives - chloroquine and hydroxychloroquine, which is obtained by hydroxylation of the former. Beside their primary indication for treating the infectious disease- malaria, they are also used in the treatment of dermatological diseases. These encompass lupus erythematosus, photodermatoses and off-label uses such as: dermatomyositis, sarcoidosis, disseminated granuloma annulare and porphyria cutanea tarda. [16]

In addition to their antiprotozoal activity, quinine derivatives have immunomodulatory, anti-inflammatory, antiproliferative and photoprotective properties. At the cellular level, they accumulate in lysosomes. As weak bases, they disturb the acidic environment in lysosomes. This inhibits the processes of proteolysis, chemotaxis, and antigen presentation, which results in a reduction in the production of cytokines, T lymphocytes and presenting cells. [16] [17]

In the literature, chloroquine and hydroxychloroquine are less frequently associated with mental disorders compared to other antimalarial drugs. However, these may still cause a diverse range of psychiatric manifestations including insomnia, catatonia, anxiety disorders, psychosis, persecutory delusions, hallucinations, depression, mania, suicide attempts and the exacerbation of existing mental illnesses. A case was described of a young female patient suffering from systemic lupus erythematosus. At a certain point of the skin lesions treatment, she was prescribed an oral therapy with 250 mg of chloroquine daily. At that time, it was the only systemic drug used by the patient. After 3 days of therapy, headache and dizziness appeared. Few days later the patient experienced derealization and persecutory delusions. Additionally, anxiety and visual illusions followed. It was decided to discontinue the drug, 2 days after the last dose symptoms disappeared. [18]

Tetracyclines

Tetracyclines constitute a group of broad-spectrum antibiotics with potent bacteriostatic activity. These antibiotics demonstrate efficacy against gram-positive bacteria (including Staphylococcus, Streptococcus, Pneumococcus, Enterococcus) and gram-negative bacteria (such as Neisseria gonorrhoea, Vibrio cholerae, Shigella dysenteriae, Brucela). [19]

The mechanism of action involves inhibiting the biosynthesis of bacterial proteins (blocking the 30S ribosomal subunit) and disrupting the energetic processes in bacterial cells. Representative members of this class of antibiotics include tetracycline, doxycycline, minocycline and tigecycline.

In dermatology, tetracyclines are most used in the treatment of common acne, rosacea and skin and subcutaneous tissue infections. They can be administered orally or topically. [20]

While psychiatric symptoms are not among the most frequently mentioned side effects of tetracyclines, literature describes cases of psychiatric manifestations during therapy with these drugs. It is important to note that various antibiotics may induce neuropsychiatric symptoms such as depression, anxiety or psychosis. The mechanism of this phenomenon is not precisely understood. One possible psychiatric symptom is psychosis, which can occur in 0.3-3.8% of patients treated with antibiotics. However, tetracyclines are associated with a lower risk of psychosis compared to other antibiotics. Studies have shown that minocycline, in fact, contributes to reducing the risk of psychotic symptoms. [21]

Doxycycline, used in the therapy of various inflammatory skin conditions, has been mentioned in the literature in the context of inducing suicidal tendencies in patients. Described patients were young adults taking the drug orally for adolescent acne and perioral dermatitis. [22]

The previously mentioned minocycline appears to be a tetracycline that does not induce psychiatric manifestations. It is an anti-inflammatory drug that crosses the blood-brain barrier, making it a promising therapeutic option for depression resistant to drugs with coexisting elevated neuroinflammatory markers. Unfortunately, recent studies have shown that the efficacy of minocycline in managing treatment-resistant depression does not yield the expected results and does not constitute a significant competitor for currently employed methods. [23]

Retinoids

The term "Retinoids" refers to natural or synthetic substances that are derivatives of vitamin A. They were discovered in 1913 and the first applications in dermatology for treating acne vulgaris date back to the 1940s. [24] [25]

Despite being widely known for treating acne vulgaris, their use is not limited to this condition alone, and they are also applied in the following conditions: rosacea, hidradenitis suppurativa, psoriasis, pityriasis rubra pilaris, chronic hand eczema, lichen planus, ichthyosis, Darier’s disease, aging/photoaging, actinic keratosis, cutaneous T-cell lymphoma, basal cell carcinomas and squamous cell carcinoma.

Retinoids are classified into three generations due to structural changes in their domains. The first generation comprises non-aromatic retinoids such as retinol, isotretinoin and tretinoin. Second-generation retinoids, like etretinate and acitretin are monoaromatic compounds with

increased lipophilicity. Third-generation retinoids, including adapalene and tazarotene are polyaromatic with more rigid structures. Each generation possesses distinct properties that influence their interactions with cellular receptors, contributing to their unique therapeutic profiles.

Retinoids play a crucial role in cellular functions by binding to retinoid nuclear receptors, specifically retinoic acid receptors (RARs) and retinoid X receptors (RXRs), forming heterodimers. This binding regulates gene expression by interacting with retinoic acid response elements (RARE) in the DNA promoter region, influencing processes like cell growth, differentiation, and apoptosis. [26]

In literature, particularly in the context of mental health, isotretinoin is frequently mentioned. The impact of this substance on the occurrence of conditions such as depression, suicide, anxiety, bipolar disorder, and psychosis is being described. Controversies regarding its impact on depression and suicidal tendencies have persisted for many years. Given its common use in treating acne vulgaris, a condition prevalent among adolescents, it is crucial to exercise caution. There is ongoing debate about whether the negative influence on mental health stems more from the often-low self-esteem and previous psychiatric disorders in individuals with acne vulgaris or if it is an effect of isotretinoin therapy. [27] [28]

The results of the meta-analyses by Li in 2019 and Yu-Chen Huang in 2017 did not demonstrate an exacerbation of depressive symptoms due to isotretinoin. Instead, they indicated a contrary effect, showing an alleviation of depressive symptoms in patients undergoing isotretinoin treatment. [28] [29] A similar trend in alleviating symptoms is observed in anxiety. [30]

It is worth noting that the severe course of acne vulgaris is a risk factor for suicide alone. Therefore, reports of suicides and suicide attempts during isotretinoin treatment cannot be solely attributed to the influence of this medication. However, there is a lack of definitive data that could unequivocally speak to the impact of isotretinoin on the risk of suicide.

In the context of bipolar disorder, cases have been documented where the course of pre-existing conditions was exacerbated. There are also reports of psychoses induced by isotretinoin. [30] An intriguing case report describes a 24-year-old patient with no prior psychiatric history or family history, who experienced delusions after an increase in the daily dose of isotretinoin from 40 mg to 80 mg. [31]

Glucocorticoids (GCS)

Glucocorticoids (GCS) are a class of drugs commonly used in dermatology, administered topically, which is often the preferred method, orally and intravenously. They exhibit anti-inflammatory, antiproliferative and immunosuppressive properties. Their broad spectrum of action makes them applicable in autoimmune, inflammatory and hyperproliferative dermatoses. Dermatological conditions in which glucocorticoids find application include atopic dermatitis (AD), alopecia areata, and blistering diseases.

The prolonged use of GCS is associated with various side effects, such as diabetes, osteoporosis, hypertension and weight gain. Psychiatric manifestations resulting from GCS use also occur among patients, although they are less commonly associated with these medications. [32] Side effects are more noticeable during systemic glucocorticoid therapy, but they can also occur with topical application. [33]

GCS can induce behavioral or psychiatric adverse events (BPAE) and cognitive function disorders. Both chronic and short-term use can lead to acute symptoms such as psychotic symptoms or mania, as well as slower-developing symptoms such as depression, insomnia, cognitive disturbances or anxiety. [34]

Research on neuropsychiatric effects of glucocorticoids indicates that over half of patients treated with GCS experienced mood changes. Patients most commonly reported irritability, euphoric hyperactivity, anxiety and depression.

The mechanism underlying the occurrence of psychiatric disorders during glucocorticoid therapy is not fully understood. However, in the case of depression, it has been observed that high cortisol levels inhibit brain-derived neurotrophic factor (BDNF). Low levels of BDNF in the hippocampus and prefrontal cortex may contribute to the development of depression and anxiety. [35]

5a-Reductase inhibitors

The 5-alpha-reductase inhibitors, which include finasteride and dutasteride are antiandrogenic medications initially used in the treatment of benign prostate hyperplasia and later in dermatology for androgenic alopecia. Their mechanism of action involves blocking the activity of the enzyme 5-alpha-reductase, which converts testosterone into dihydrotestosterone (DHT). This reduction in the concentration of the more potent hormone DHT, clinically contributes to decreasing pattern hair loss. [36] [37]

Adverse effects such as suicide, self-harm and depression have been reported to the US Food and Drug Administration in connection with patients taking finasteride. This led to the inclusion of depression and suicidal ideation as recognized side effects of the drug in the USA

in 2011, later in other countries. The article, Irwig (2020) describes the following correlation: "Men under the age of 40 who use finasteride for alopecia are at risk for suicide if they experience persistent sexual adverse effects and insomnia." [38] [39]

Reports on the side effects of 5-alpha-reductase inhibitors have raised clinical vigilance, giving rise to the concept of post-finasteride syndrome. This term describes groups of sexual, physical and psychological symptoms that emerge during or after exposure to finasteride and persist after discontinuation. Sexual symptoms include libido loss, erectile dysfunction and ejaculatory disorders. Physical symptoms encompass skin rash, gynecomastia, fatigue, muscle weakness, hearing defects and metabolic anomalies. Psychological disorders may manifest as self-harm, memory impairment, slow cognition, depression, suicidal ideation, anxiety, changes in emotional affect and insomnia. [37]

Dapsone

Dapsone, also known as 4,4'-sulfonyldianiline, belongs to the sulfone group of drugs and has the simplest structure within this category. Structurally, it can be classified as an aniline derivative. It is primarily administered orally, less frequently topically. [40]

Dapsone is used in various dermatological and non-dermatological conditions. Its mechanism of action in dermatological disorders is not fully understood. Due to its anti-inflammatory properties, it is utilized in the prevention and treatment of leprosy and other infectious diseases such as malaria. In treating leprosy, dapsone exhibits a bacteriostatic mechanism against Mycobacterium leprae bacteria.

Dapsone is also used in the treatment of diseases characterized by the presence of neutrophilic or eosinophilic infiltrates, such as linear IgA bullous dermatosis and dermatitis herpetiformis. Additionally, dapsone is among the therapeutic options for blistering diseases such as bullous systemic lupus erythematosus and bullous pemphigoid. [40][41]

The most mentioned side effects of dapsone therapy include methemoglobinemia, hepatotoxicity, gastrointestinal symptoms and hemolytic anemia. Psychiatric symptoms are less frequently reported but do occur. Cases of acute psychosis have been noted, especially among patients taking dapsone for leprosy. Upon discontinuation of the drug, psychotic symptoms generally resolve. Other psychiatric symptoms attributed to dapsone include nervousness and insomnia. [42]

Methotrexate

Methotrexate (MTX) is a synthetic chemical analogue of folic acid that can be administered orally, intravenously, intramuscularly, or subcutaneously. [43] MTX is applied in the treatment of various forms of moderate-to-severe psoriasis, rheumatoid arthritis and other autoimmune diseases. Methotrexate inhibits the action of the enzyme dihydrofolate reductase, which reduces dihydrofolate to tetrahydrofolate (THF). Insufficient THF levels result in intracellular folate deficiencies, subsequently leading to a reduction in the synthesis of purines and pyrimidines—essential components for DNA and RNA strand synthesis. In the treatment of psoriasis, this described mechanism translates into the apoptosis of activated T cells, thereby restricting epithelial hyperplasia, a characteristic feature of the disease. [44] [45]

The psychiatric side effects of methotrexate treatment are rare. In the literature, cases of psychosis and exacerbations of bipolar disorder have been described. A case report documented a patient with bipolar disorder and psoriasis who experienced manic episodes twice after taking methotrexate. Upon discontinuation of the medication and initiation of psychiatric treatment, the symptoms resolved. The authors of the case report identified the use of methotrexate as the most likely cause of the exacerbation of bipolar disorder. [45]

Psoriasis is a condition that can significantly impair the quality of life, leading to anxiety, depression and lower self-esteem. A study involving 60 patients with psoriasis, treated either with methotrexate or biologic therapy, utilized the Beck Anxiety Inventory, Beck Depression Inventory and Dermatology Life Quality Index to assess their psychological well-being. Both groups showed a reduction in the symptoms of depression and anxiety. [46]

CONCLUSIONS:

Due to the high prevalence of dermatological diseases, treating these conditions poses a challenge that an increasing number of clinicians encounter in their clinical practice. Pharmacological treatment of dermatoses is highly diverse, often administered topically but also orally and occasionally parenterally. Accurate diagnosis and appropriate treatment provide patients with the opportunity for a normal life despite their condition. However, the use of any medication carries the risk of adverse effects. Psychiatric side effects of drugs used in dermatology are not frequently listed among the adverse effects. However, given the rising incidence of mental health disorders worldwide, it is important to be aware of them and, if necessary, warn patients.

The most frequently observed psychiatric side effects include depression and anxiety, which are potential adverse outcomes for the majority of the drugs mentioned in the article. Literature also reports episodes of psychosis in patients treated with the mentioned drugs. It

should be noted, however, that psychiatric manifestations mostly subsided upon discontinuation of the causative medication.

Particular attention is warranted for drugs from the group of retinoids, specifically isotretinoin, which is often associated with inducing depression, anxiety and suicidal tendencies in patients. In the case of this medication, the ongoing discussion revolves around whether the adverse impact on mental health is primarily linked to the frequently low self-esteem and pre-existing psychiatric conditions in individuals with acne vulgaris, or if it is a consequence of isotretinoin therapy. Therefore, evaluating the impact of the medication alone on the patient's mental state is challenging.

Effective treatment of dermatological diseases, which are linked to diminished self-worth and a decrease in patients' quality of life, can have a long-lasting positive impact on their mental health. However, this does not exempt physicians from knowing and informing patients about the potential psychiatric side effects of these drugs, even if they are rare.

Disclosures

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