



Commentary

Corticosteroid-induced psychiatric disturbances: It is time for pharmacists to take notice

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Summary

Corticosteroids are widely used to relieve signs and symptoms arising from many diseases, including common inflammatory and autoimmune disorders affecting a number of organ systems. However, corticosteroids also induce significant adverse effects; in particular, a range of severe psychiatric adverse effects may occur including delirium, depression, mania, psychosis and cognitive/memory impairment. These adverse effects occur in up to 60% of patients taking corticosteroids and recent studies show an increased rate of psychopathologies in this population. Long-term adverse effects on mood and behavior are severely debilitating, thereby influencing the quality of life, employment and health status of individuals taking corticosteroids. Strategies used to manage corticosteroid-induced psychiatric disturbances through psychotropic drugs vary significantly. This commentary summarizes existing literature on mechanisms underlying corticosteroid-induced psychiatric adverse effects and evidence associated with using psychotropic drugs to manage these effects. Despite its importance, there is an absolute dearth in the literature examining pharmacists' understanding and perceptions of psychiatric adverse effects of corticosteroids. Educational programs need to be implemented so that pharmacists can counsel patients about how to recognize corticosteroid-induced psychiatric disturbances. Physicians do not consistently alert patients to watch for behavioral changes, and patients may feel that mood changes they experience fall within the category of 'normal behavior,' and thus are less likely to report them. Given that patients taking corticosteroids usually have complex medical histories, discussions of adverse effects with pharmacists are vital to improve health outcomes in this population.

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Introduction

Corticosteroids such as budesonide, dexamethasone and prednisolone are medications widely used to relieve signs and symptoms arising from many diseases. These diseases include inflammatory and autoimmune disorders, such as asthma, chronic obstructive pulmonary disease, renal diseases, rheumatoid arthritis, inflammatory bowel disease, cancer and autoimmune neurological conditions including multiple sclerosis and chronic neuropathies and myopathies.^{1–5} For example, in cancer, corticosteroids are prescribed to alleviate pain associated with inflammation as well as cancer-related complications such as brain metastasis and spinal cord compression.³ In asthma, corticosteroids are used to control inflammation by inhibiting synthesis and release of inflammatory mediators, and in this population corticosteroids have been shown to lower hospital admission rates, reduce risk of relapse as well as decrease mortality.^{1,6}

Corticosteroids use the intracellular receptor mechanism to suppress inflammation and thus offer symptomatic relief and halt progression of inflammatory response. However, the mechanism of action of corticosteroids is far more complex in terms of their broad spectrum of cognitive and psychiatric symptoms. Corticosteroids can induce a range of psychiatric adverse effects including delirium, depression, mania, psychosis as well as cognitive and memory impairment.^{7–11} The relationship between corticosteroids and psychiatric adverse effects has been known for several decades^{10,12,13}; yet, the exact mechanism of corticosteroid-induced psychiatric disturbances and their clinical management have been poorly characterized. Pharmacists play an important role in patients' education about corticosteroids; however, pharmacists' specialized knowledge regarding corticosteroid-induced psychiatric disturbances may be limited. More focused attention is needed by pharmacists in educating patients and family caregivers to enhance their understanding of this weighty public health issue. Since physicians do not consistently alert patients about these potentially severe psychiatric adverse effects, the role of pharmacists becomes even more significant.

Corticosteroid actions in the brain and the role of the brain serotonin system

Corticosteroid actions in the brain are mediated by two intracellular receptor subtypes, the

glucocorticoid receptor and mineralocorticoid receptor. Both receptors are widely distributed in the brain, with highest levels found in the hypothalamus, pituitary gland and the hippocampus.¹⁴ The receptor-mediated steroid responses are influenced by many factors including various neurotransmitters. One key neurotransmitter system is the serotonergic system: serotonin is affected by corticosteroids^{15–17} and strongly implicated in mood, cognition and behavior.^{17,18}

The central serotonergic system originates predominantly from the brainstem raphe nuclei, the dorsal raphe nucleus (DRN) and median raphe nucleus (MRN).¹⁹ These raphe nuclei differentially innervate various brain regions. For example, in terms of the hippocampus, the DRN neurons provide the majority of the serotonergic innervation in the ventral hippocampus, while MRN neurons project to the dorsal hippocampus.^{19,20} Corticosteroids tightly regulate the activity of the raphe-hippocampal serotonergic system in a number of ways^{14–16} and therefore, it is not surprising that disturbances of cognition, behavior and mood are possible even with the short-term corticosteroid treatment. Additionally, administration of dexamethasone and prednisolone in animals causes neuronal death and alters gene expression in the hippocampus.^{21,22} This neurotoxic effect of corticosteroids could be responsible for the psychiatric adverse effects observed. Thus, the mechanisms involved in psychiatric adverse effects are extremely complex, unpredictable and often severe. By having a sound knowledge of the corticosteroid action in the brain, pharmacists can provide better education to patients and family caregivers on how to readily identify when psychiatric disturbances are possibly occurring so that they can alert the doctor. Identification of corticosteroid-related signs and symptoms in the early stages will help in preventing occurrence of more severe psychiatric adverse effects and psychopathology.

Psychiatric adverse effects associated with corticosteroid use

Psychiatric adverse effects have been reported in up to 60% of patients taking corticosteroids as one of their regular medications,^{10,12} and recent studies have shown an increased rate of psychopathologies in this population.^{10,23} Limited understanding of psychiatric adverse effects in corticosteroid-treated patients is due to a lack of randomized controlled trials, varying definitions

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