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

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Abstract

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 behaviour 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 summarises 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 behavioural changes, and patients may feel that mood changes they experience fall within the category of 'normal behaviour', 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.

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' specialised 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 corticosteroids¹⁵⁻¹⁷ and strongly implicated in mood, cognition and behaviour.^{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 ways¹⁴⁻¹⁶ and therefore, it is not surprising that disturbances of cognition, behaviour 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 of steroid-induced behavioural changes and its management, and no clear strategies for identifying patients in need of prophylaxis.¹⁰ Depression tends to occur with long-term corticosteroid use, whereas mania can occur much earlier in the course of treatment and is associated with high-dose preparations. Psychiatric adverse effects are twice as likely to occur during the first five days of corticosteroid treatment; however, their onset is also dependent on the dose prescribed.^{12, 24, 25} Evidence has shown that 26% of patients developed mania and 10% developed depression during therapy with 80 mg/day of prednisolone for five days.²⁵ Psychiatric adverse effects can also occur in patients receiving lower doses of corticosteroids for variable duration (40 mg/day or less of prednisolone and 10 mg/day or less of dexamethasone).^{26, 27} Cognitive impairment and psychosis, presenting with confusion, hallucinations and delusions, have also been reported.^{28, 29} For example, patients with asthma and rheumatologic conditions taking prednisolone exhibited cognitive impairment on neuropsychological tests²⁹ but the dose of prednisolone causing cognitive deficits was not reported. Corticosteroid-induced psychosis was also observed in a paediatric population at doses less than 40 mg/day of prednisolone and less than 10 mg/day of dexamethasone.^{26, 30} Most of the evidence from past research comes from case reports, case series and small trials. Additionally, little research has been conducted globally to

identify the incidence, nature and management of corticosteroid-induced psychiatric adverse effects as well as the pharmacists' understanding of this important social and public health issue. Psychotropic drugs, such as risperidone, aripiprazole and lamotrigine are emerging as the most effective pharmacological agents in reversing corticosteroid-related psychiatric adverse effects.³⁰⁻³⁵ Despite lack of clear guidelines to inform prescribers when to use a specific psychotropic medication and despite lack of unified management strategy there is enough evidence to suggest that antipsychotics and mood stabilisers are the mainstay pharmacological therapy for corticosteroid-induced psychiatric disturbances.

Pharmacological management of psychiatric adverse effects

Literature has shown that management strategies and use of psychotropic drugs for corticosteroid-induced psychiatric disturbances vary significantly. Earlier studies reported that mania arising from corticosteroid use was effectively treated with typical antipsychotic, chlorpromazine³⁶ while a selective serotonin reuptake inhibitor, sertraline, was effective in treating depressive as well as psychotic symptoms associated with corticosteroid use.³⁷ Use of sertraline in managing psychiatric adverse effects in corticosteroid-treated patients supports our notion that the brain serotonin system is altered in some way by corticosteroids. Furthermore, case reports and case series documented use of haloperidol, olanzapine, sodium valproate and lithium for treatment of psychiatric adverse effects. Haloperidol (typical antipsychotic) was effective in managing most psychotic reactions with good therapeutic response³⁸ whereas olanzapine (atypical antipsychotic) was employed for the treatment of subacute mood changes.³⁹ A case study by Abbas and Styra reported an effectiveness of sodium valproate in managing affective symptoms associated with corticosteroid use⁴⁰ whereas administration of lithium during

corticosteroid therapy prevented development of psychotic symptoms.¹⁰ Sodium valproate and lithium are mood stabilising agents that target multiple receptor and neurotransmitter systems including noradrenaline and GABA, thus further confirming complexity of corticosteroid-induced psychiatric disturbances. More recent case studies reported use of risperidone, aripiprazole and lamotrigine in managing corticosteroid-induced psychiatric disturbances. Atypical antipsychotic, risperidone, is one of the most effective short-term pharmacological agents in controlling steroid-related psychiatric adverse effects in a paediatric population.^{30, 35} Furthermore, another atypical antipsychotic, aripiprazole, was identified as one of the most effective psychotropic medications in managing steroid-induced mania without causing excessive sedation.^{32, 34} Moreover, lamotrigine, an anticonvulsant and mood-stabilising medication, was shown to improve declarative memory³¹ and prevent mania³³; in patients taking corticosteroids.

From a review of the literature, it can be observed that diverse classes of medications have been used to manage a range of psychiatric disturbances that develop in patients taking corticosteroids across the lifespan. It appears that prescription of specific pharmacological agents is based predominantly on medical practitioners' choice as there are no clear guidelines or randomized controlled trials to drive prescription process as to what pharmacological agent to use when. Pharmacists should take a stand and work closely with doctors on identifying the best pharmacological agents in managing psychiatric disturbances as many of psychotropic medications currently prescribed have their own debilitating adverse effects.

Conclusion

Psychiatric adverse effects including delirium, depression, mania, psychosis and cognitive/memory impairment occur in a large proportion of patients taking corticosteroids as their regular medications. These are very serious adverse effects which can be severely debilitating for the patient. Currently, there are no clinical guidelines on the most appropriate treatment of psychiatric adverse effects, and a choice of pharmacological agent is based predominantly on medical practitioners' preference. Additionally, physicians do not consistently alert patients taking corticosteroids to watch for behavioural changes, and therefore pharmacists' role in patient education becomes even more significant. A more proactive approach should be taken whereby unique educational programs are implemented in pharmacy practice to specifically focus on counselling patients and family caregivers in relation to corticosteroid use. Counselling should focus on identification of corticosteroid-related signs and symptoms, which patients and caregivers could alert the doctor about, which in turn can lead to better tracking of psychiatric adverse effects before they become psychopathological in nature. An extensive utilisation of pharmacists' expertise via their regular contacts with patients and caregivers could lower the rates of relapse and hospital admissions, and improve patients' quality of life thus significantly reducing emotional and economic burden in society.

References

1. Fiel SB, Vincken W. Systemic corticosteroid therapy for acute asthma exacerbations. *J Asthma* 2006;43: 321-331.
2. Goodin DS. Glucocorticoid treatment of multiple sclerosis. *Handb Clin Neurol* 2014;122: 455-464.
3. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst Rev* 2015;4: CD010756.
4. Kuenzig ME, Rezaie A, Seow CH, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014;8: CD002913.
5. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;9: CD001288.
6. Self TH, Chrisman CR, Jacobs AR, Vo NH, Winton JC. Preventing emergency department visits and hospitalizations for asthma by use of oral corticosteroids at home: are we adhering to national guidelines? *J Asthma* 2010;47: 1123-1127.
7. Bhangle SD, Kramer N, Rosenstein ED. Corticosteroid-induced neuropsychiatric disorders: review and contrast with neuropsychiatric lupus. *Rheumatol Int* 2013;33: 1923-1932.
8. Brown ES, Khan DA, Nejtek VA. The psychiatric side effects of corticosteroids. *Ann Allergy Asthma Immunol* 1999;83: 495-504.
9. Brown ES, Suppes T. Mood symptoms during corticosteroid therapy: a review. *Harv Rev Psychiatry* 1998;5: 239-246.
10. West S, Kenedi C. Strategies to prevent the neuropsychiatric side-effects of corticosteroids: a case report and review of the literature. *Curr Opin Organ Transplant* 2014;19: 201-208.
11. Young KD, Preskorn SH. Neuroscientific basis of corticosteroid-induced changes in human cognitive and emotional processing: implications for affective illness. *J Psychiatr Pract* 2013;19: 309-315.
12. Bolanos SH, Khan DA, Hanczyc M, Bauer MS, Dhanani N, Brown ES. Assessment of mood states in patients receiving long-term corticosteroid therapy and in controls with patient-rated and clinician-rated scales. *Ann Allergy Asthma Immunol* 2004;92: 500-505.
13. Clark LD, Bauer W, Cobb S. Preliminary observations on mental disturbances occurring in patients under therapy with cortisone and ACTH. *N Engl J Med* 1952;246: 205-216.
14. de Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. *Endocr Rev* 1998;19: 269-301.
15. Joels M, Van Riel E. Mineralocorticoid and glucocorticoid receptor-mediated effects on serotonergic transmission in health and disease. *Ann N Y Acad Sci* 2004;1032: 301-303.
16. Meijer OC, de Kloet ER. Corticosterone and serotonergic neurotransmission in the hippocampus: functional implications of central corticosteroid receptor diversity. *Crit Rev Neurobiol* 1998;12: 1-20.
17. Vazquez DM, Neal CR, Jr., Patel PD, Kaciroti N, Lopez JF. Regulation of corticoid and serotonin receptor brain system following early life exposure of glucocorticoids: long term implications for the neurobiology of mood. *Psychoneuroendocrinology* 2012;37: 421-437.
18. Fink G, Sumner BE, McQueen JK, Wilson H, Rosie R. Sex steroid control of mood, mental state and memory. *Clin Exp Pharmacol Physiol* 1998;25: 764-775.
19. Hornung JP. The human raphe nuclei and the serotonergic system. *J Chem Neuroanat* 2003;26: 331-343.

20. McQuade R, Sharp T. Functional mapping of dorsal and median raphe 5-hydroxytryptamine pathways in forebrain of the rat using microdialysis. *J Neurochem* 1997;69: 791-796.
21. Haynes LE, Griffiths MR, Hyde RE, Barber DJ, Mitchell IJ. Dexamethasone induces limited apoptosis and extensive sublethal damage to specific subregions of the striatum and hippocampus: implications for mood disorders. *Neuroscience* 2001;104: 57-69.
22. Kajiyama Y, Iijima Y, Chiba S, et al. Prednisolone causes anxiety- and depression-like behaviors and altered expression of apoptotic genes in mice hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34: 159-165.
23. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics* 2012;53: 103-115.
24. Brown ES, Suppes T, Khan DA, Carmody TJ, 3rd. Mood changes during prednisone bursts in outpatients with asthma. *J Clin Psychopharmacol* 2002;22: 55-61.
25. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. *Psychoneuroendocrinology* 1996;21: 25-31.
26. Drozdowicz LB, Bostwick JM. Psychiatric adverse effects of pediatric corticosteroid use. *Mayo Clin Proc* 2014;89: 817-834.
27. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006;81: 1361-1367.
28. Appenzeller S, Bertolo MB, Costallat LT. Cognitive impairment in rheumatoid arthritis. *Methods Find Exp Clin Pharmacol* 2004;26: 339-343.
29. Frol AB, Vasquez A, Getahun Y, Pacheco M, Khan DA, Brown ES. A comparison of clinician-rated neuropsychological and self-rated cognitive assessments in patients with asthma and rheumatologic disorders. *Allergy Asthma Proc* 2013;34: 170-175.
30. Bag O, Erdogan I, Onder ZS, Altinoz S, Ozturk A. Steroid-induced psychosis in a child: treatment with risperidone. *Gen Hosp Psychiatry* 2012;34: 103 e105-106.
31. Brown ES, Wolfshohl J, Shad MU, Vazquez M, Osuji IJ. Attenuation of the effects of corticosteroids on declarative memory with lamotrigine. *Neuropsychopharmacology* 2008;33: 2376-2383.
32. Kimmel RJ, Combs H. Steroid-induced mania treated with aripiprazole. *Psychosomatics* 2012;53: 181-183.
33. Preda A, Fazeli A, McKay BG, Bowers MB, Jr., Mazure CM. Lamotrigine as prophylaxis against steroid-induced mania. *J Clin Psychiatry* 1999;60: 708-709.
34. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat Rev Drug Discov* 2004;3: 353-359.
35. Ularntinon S, Tzuang D, Dahl G, Shaw RJ. Concurrent treatment of steroid-related mood and psychotic symptoms with risperidone. *Pediatrics* 2010;125: e1241-1245.
36. Bloch M, Gur E, Shalev A. Chlorpromazine prophylaxis of steroid-induced psychosis. *Gen Hosp Psychiatry* 1994;16: 42-44.
37. Beshay H, Pumariega AJ. Sertraline treatment of mood disorder associated with prednisone: a case report. *J Child Adolesc Psychopharmacol* 1998;8: 187-193.
38. Wada K, Yamada N, Sato T, et al. Corticosteroid-induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. *Psychosomatics* 2001;42: 461-466.
39. Brown ES, Khan DA, Suppes T. Treatment of corticosteroid-induced mood changes with olanzapine. *Am J Psychiatry* 1999;156: 968.
40. Abbas A, Styra R. Valproate prophylaxis against steroid induced psychosis. *Can J Psychiatry* 1994;39: 188-189.

Table 1

Psychotropic drugs used in the management of corticosteroid-induced adverse effects

Drug name/class	Indications for use	Specific information in relation to adverse effects
Aripiprazole (atypical antipsychotic)	Mania	Akathisia, light-headedness, significant drug interactions involving the CYP isoenzymes; careful titration of the dose required
Chlorpromazine (typical antipsychotic)	Mania	Endocrine abnormalities (gynecomastia, amenorrhea, infertility), sedation, anticholinergic effects, orthostatic hypotension; not recommended for older people and people of child-bearing age
Haloperidol (typical antipsychotic)	Psychosis	Extrapyramidal side effects, neuroleptic malignant syndrome, orthostatic hypotension; not recommended for older people
Lamotrigine (mood stabilizer)	Cognitive and/or memory impairment	Diplopia, dizziness, ataxia, severe skin reaction (Stevens-Johnson syndrome); risk enhanced with rapid increase in dose
Lithium (mood stabilizer)	Psychosis	Fatigue, nephrotoxicity, skin reactions (acne, psoriasis), polyuria, vertigo, weight gain

Olanzapine
(atypical antipsychotic)

Mood changes

Metabolic changes (weight gain, hyperglycemia, type-2 diabetes), sedation, increased risk of stroke and mortality in older dementia patients

Risperidone
(atypical antipsychotic)

Psychosis

Akathisia, orthostatic hypotension, hyperprolactinaemia, increased risk of stroke and mortality in older dementia patients

Sertraline
(antidepressant SSRI)

Depression and psychosis

Abnormal platelet aggregation (bruising, gut/vaginal bleeding), dizziness, insomnia, serotonin syndrome (agitation, confusion, hyperthermia, muscle rigidity)

Sodium valproate
(mood stabilizer)

Mood changes

Ataxia, drowsiness, paresthesia, affects blood clotting mechanisms thus increasing bleeding time
