International Journal of Research in Medical Sciences
Parasher A et al. Int J Res Med Sci. 2020 Jun;8(6):2365-2370
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20202296

Review Article

Steroid induced psychiatric adverse effects: an overview of risk factors, clinical features and management

Anant Parasher[1]*, Jeplin Bez[2]

[1]Department of Medicine, UCMS and GTB Hospital, New Delhi, India
[2]Department of Psychiatry, Assam Medical College and Hospital, Assam, India

Received: 20 March 2020
Accepted: 22 April 2020

***Correspondence:**
Dr. Anant Parasher,
E-mail: anant02jan@gmail.com

ABSTRACT

Corticosteroids have been in use since the past five decades as anti-inflammatory and immunosuppressive drugs for the treatment of several pathologies such as asthma, allergy, rheumatoid arthritis, and dermatological disorders. Adverse effects include growth retardation in children, immunosuppression, hypertension, hyperglycemia, inhibition of wound repair, osteoporosis, metabolic disturbances, glaucoma, and cataracts. The psychiatric effects of steroids are due to the wide expression of Glucocorticoid Receptors in the brain, and their long-term modulation can lead to functional and anatomical alterations along with hippocampal dysfunction. In most cases, the psychiatric symptoms disappear on cessation of steroid therapy; others may require some form of therapeutic management. A search was conducted for clinically relevant articles from 1971 to 2016 by including the terms corticosteroids, mania, depression, psychosis and cognitive defects. About one-fifth of patients receiving high doses of corticosteroids develop psychiatric symptoms. These symptoms are observed to be dose-dependent and generally occur during the first few weeks of therapy. Lithium has a preventive as well as therapeutic role, while antipsychotics are reserved for high risk cases with predominant psychotic symptoms. Psychiatric effects of long term steroid therapy have become increasingly common nowadays due to long duration of treatment of many chronic respiratory and orthopedic illnesses. Reduction in the dose or complete discontinuation of steroid therapy has been proven beneficial in many patients. Among the therapeutic options, lithium has a definitive role, both in the prevention as well as treatment of psychiatric symptoms. Better co-ordination between the physician and psychiatrist can go a long way to improve the quality of life in these patients.

Keywords: Cognitive deficits, Corticosteroids, Depression, Mania, Psychosis

INTRODUCTION

Over the years, Corticosteroids have thoroughly cemented their place for various clinical indications. They have been in use since the past five decades as anti-inflammatory and immunosuppressive drugs for the treatment of several pathologies such as asthma, allergy, rheumatoid arthritis, and dermatological disorders.[1] Steroids exert their effects through pleiotropic effects of the glucocorticoid receptors on multiple signaling pathways. However, they do have serious adverse effects such as growth retardation in children, immunosuppression, hypertension, hyperglycemia, inhibition of wound repair, osteoporosis, metabolic disturbances, glaucoma, and cataracts.[1] Although there is limited knowledge about the side effects of steroids on central nervous system, the use of corticosteroids is strongly associated with the development of psychiatric/neurological side effects such as agitation, insomnia, catatonia or even psychosis. These effects are due to the wide expression and long term modulation of Glucocorticoid Receptors in the brain, which lead to

increased levels of endogenous corticosteroids. This can lead to functional and anatomical alterations in the hippocampus, which is majorly responsible for the observed side-effects.[1]

REVIEW OF LITERATURE

Incidence

About one-fifth of patients receiving high doses of corticosteroids develop psychiatric symptoms requiring pharmacological treatment, while majority of patients report symptoms reversible upon discontinuation of therapy.[2,3] Symptoms such as insomnia, mood swings, personality changes, severe depression and psychosis have been estimated to develop in 5% to 18% of patients treated with corticosteroids.[4,5] The primary risk factor for the development of corticosteroid-induced symptoms is a high dose of corticosteroids, with risk increasing among patients taking 40 mg or more of prednisone or its equivalent daily.[2,4-7] Some studies have shown that majority of the paediatric population under 10 years of age receiving steroid therapy develops irritability, insomnia as well as deficits of attention and memory.[1,8] Females are seen to be slightly more prone to these effects.[1]

The incidence rate of psychiatric symptoms is directly correlated to the dose and duration of glucocorticoid exposure.[9] These adverse events are dose and time dependent, and remission often results from the suspension of the treatment or decreasing the dose of steroids.[2] The overall incidence of neuropsychiatric effects due to corticosteroids ranges from 2 to 60%; the wide range reflecting variability of dose, duration of administration, and the genetic predisposition based on polymorphisms of the Glucocorticoid Receptors.[10]

Risk factors

Although high corticosteroid dosage is the primary risk factor for psychiatric adverse effects, it does not predict the type of effect, its severity or the duration of symptoms.[2,11] Female patients are at a higher risk of corticosteroid-induced psychosis, even after considering the higher incidence of chronic illnesses in women that require long term steroid therapy, such as Rheumatoid arthritis and SLE. Factors such as age, previous history of psychiatric illnesses or steroid induces psychiatric symptoms are not associated with increased incidence of corticosteroid-induced psychosis.[11] No significant difference has been observed in the incidence or frequency of psychiatric side effects following the different routes of administration of steroids i.e. intra-articular injections, topical or systemic route.[1]

Mechanism of psychiatric effects by steroids

Glucocorticoids possess several endocrinological properties, and have known effects on glucose, lipid and protein metabolism, muscular function, electrolyte balance, cardiovascular system, hematopoietic system, gastric and reproductive functioning.[12] Another important role of endogenous glucocorticoids is the control over feeling of hunger, sleep-wake cycle and the processes of learning and memory. These actions are effected through interaction with specific receptors located in the pre-frontal cortex, hippocampus, and baso-lateral amygdala.[13] Steroid receptors are expressed in different areas of the brain and act through the regulation of various neurotransmitters, including serotonin and dopamine.[14] In the CNS, glucocorticoid effects are exerted at the hippocampal level, a structure intimately involved in the limbic system, which is responsible for the processing of emotional information and memory.[15] Overproduction of cortisol through the activation of the hypothalamic-pituitary-adrenal axis via negative feedback results in its high endogenous levels, which ultimately lead to hippocampal atrophy causing dementia and cognitive dysfunction.[16,17]

A brief overview of the pathophysiology has been given in Figure 1.

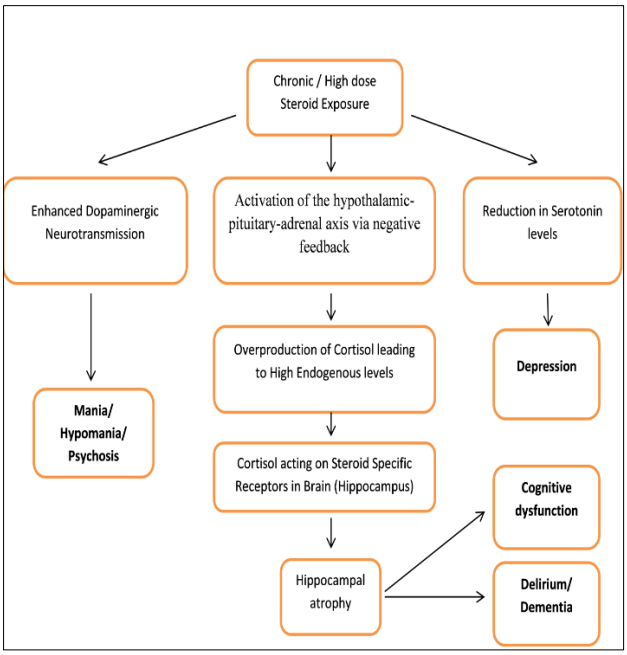

Figure 1: Mechanisms of steroid induced psychiatric adverse effects.

DISCUSSION

Clinical features

Steroid induced psychological changes range from mild symptoms such as anxiety, insomnia and irritability, to severe symptoms such as mania, psychosis, delirium and depression.[12,18] Mania and hypomania are more commonly and more frequently reported in patients, as compared to depressive symptoms and psychosis.[11] Although cognitive deficits have also been reported, they

generally subside with withdrawal or dose reduction of the steroid.[19,20] A three tier grading system is used to gauge the severity of symptoms; treatment being required in grade 2/ grade 3 symptoms (Table 1).[19]

Table 1: Grading scale for corticosteroid induced psychiatric symptoms.[19]

Grade	Symptoms
1	Mild euphoria
2	Acute or sub-acute mania and/or depression
3	Bipolar symptoms with relapses

The hypomanic effects of bolus steroid therapy have also been seen in the form of "steroid euphoria" in which the patients with chronic obstructive pulmonary disease treated with oral prednisolone developed a sense of well-being with reduced anxiety and depression when compared with patients receiving placebo, even in the absence of improvement in lung function.[21] Cognitive effects of corticosteroids appear to occasionally include severe disturbances consistent with dementia or delirium[22,23], but milder and specific reversible and dose-dependent deficits in verbal or declarative memory are seen in otherwise healthy individuals, even during several days of corticosteroid administration.[20,24,25] As the hippocampal area of the brain contains the highest density of Glucocorticoid receptors, most of the cognitive abnormalities are consistent with dysfunction of the hippocampus.[26,27]

Psychiatric symptoms can develop early or late during the course of steroid therapy, and even in some cases after the completion of treatment; the risks of side effects increasing at higher dosages.[2,28-30] In the majority of cases, the symptoms present within the first five days of treatment[31] as has been shown in several studies which concluded an average of roughly eleven days after the beginning of steroid treatment to the onset of psychiatric symptoms.[32] Most of the patients develop symptoms in the first six weeks, and roughly half of them within the first two weeks.[1] The duration and resolution of psychiatric symptoms varies widely among patients, following steroid withdrawal. Delirium often resolves within a few days, psychosis within a week, mania within few weeks, whereas depression can persist for an even longer period.[18] Discontinuation of long-term glucocorticoid therapy is often associated with an increased risk of both depression and delirium, and individuals being treated with long acting glucocorticoids are particularly at risk.[33]

Treatment and prevention of steroid induced psychiatric effects

Patients who are planned for systemic corticosteroid treatment should be advised of potential side effects, including behavioural changes. The patient should be seen in follow-up within a week after initiating therapy and should be asked about mood swings and symptoms of depression, and observed for signs of mania, such as rapid speech and insomnia.[34] It has been suggested in some studies that *lithium therapy* may prevent corticosteroid-induced psychiatric disturbances.[8] Prophylactic therapy with lithium or other agents may be started in patients who are at a high risk of self-harm/suicide if psychotic symptoms develop, or have developed psychiatric symptoms multiple times previously after repeated corticosteroid use.[5]

In most cases, the psychiatric symptoms disappear on cessation of steroid therapy. In other patients, dose reduction or discontinuation of the systemic corticosteroids has been seen to be associated with improvement in psychiatric symptoms.[2,12,35,36] Tapering of the steroid dose to less than 40 mg daily is recommended as a first step to manage corticosteroid-induced psychosis, and may be sufficient to improve psychiatric symptoms without requiring additional medications. Psychopharmacologic treatment is recommended when symptoms are too severe or when tapering of the steroid dose is not feasible.[37]

Lithium has proven effective for treatment of the acute phase of corticosteroid-induced psychiatric symptoms including both mania and depression.[38,39] It should be started at 600 to 900 mg/day and a blood level should be obtained in five days, preferably ten to twelve hours after the last dose.[34] In older adults taking corticosteroids for autoimmune illnesses that affect renal function, lithium may be difficult to use safely.[4] Although mood stabilizers such as lithium appear to be effective, *carbamazepine should probably be avoided* as this medication induces the metabolism of some corticosteroids, potentially lowering plasma steroid levels and increasing symptoms of the underlying disease process.[40,41] Other useful alternatives may be valproic acid, neuroleptics, and atypical antipsychotics.[2,21,28,42-46] Benefits have also been seen with phenytoin, lamotrigine, risperidone, quetiapine, and gabapentin.[47]

Antipsychotics are associated with several adverse effects and should be used only for psychosis, or when non-pharmacologic options have failed and patients become a threat to themselves or others. A low-dose atypical antipsychotic (e.g. olanzapine, risperidone, quetiapine) in conjunction with appropriate monitoring can be useful in alleviating symptoms of steroid-induced psychosis; the lowest effective dose recommended for the shortest effective duration.[37] Newer atypical agents have lower incidences of dystonic reactions and extrapyramidal side effects, making these medications safe and effective for psychiatric symptoms during corticosteroid therapy. Dosage of olanzapine starting at 2.5 mg at night and increasing up to 20 mg/day may be useful.[34]

It should be noted that all antipsychotics can prolong the QTc interval, and that the 'typical' antipsychotics increase the risk of stroke in patients with dementia.[37, 48-50]

A simple management algorithm has been described below (Figure 2).[37]

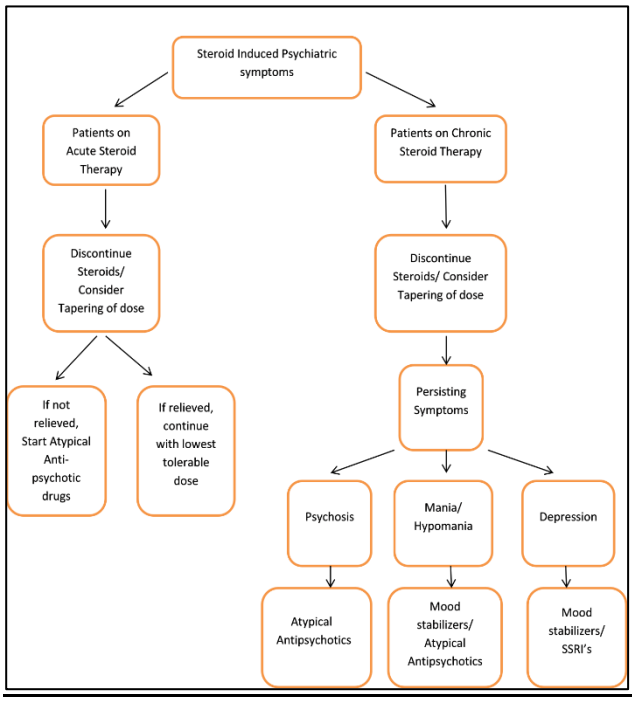

Figure 2: Management of steroid induced psychiatric symptoms.

On the other hand, *tricyclic antidepressants* can lead to a significant worsening of symptoms as suggested by Hall et al, and Blazer et al.[17,28,43] They found that tricyclic antidepressants were associated with either increased agitation and psychosis in patients on steroids, or a poor response to tricyclic antidepressants in patients with depression during corticosteroid therapy. However, the use of fluoxetine, a newer Selective Serotonin Reuptake Inhibitor (SSRI), showed improvement in symptoms of depression during corticosteroid therapy in one patient.[47] Thus, SSRI's may offer a much more superior option as compared to the TCA's among anti-depressants.

At present, there are no specific pharmacotherapies for cognitive impairment in humans. Some experimental studies in animals have shown the effectiveness of agents that enhance the reuptake of serotonin and inhibit glutamate release (e.g., phenytoin), in preventing and even reversing the hippocampal damage associated with corticosteroids.[34,51,52] As these were only experimental animal studies, more research is needed to develop newer and effective therapies for cognitive dysfunction in humans.

CONCLUSION

Steroids have become an absolute necessity in the present clinical scenario. As their use for emergency indications as well as chronic ailments cannot be halted, the clinician has to make sure that they are administered in justified doses and for an appropriate duration. Psychiatric effects of long term steroid therapy have become increasingly common nowadays due to long duration of treatment of many chronic respiratory and orthopedic illnesses. Reduction in the dose or complete discontinuation of steroid therapy although not feasible in all patients, has often been proven beneficial in many studies. Among the therapeutic options, lithium has a definitive role, both in the prevention as well as treatment of psychiatric symptoms. Antipsychotics may be used only for the frank psychotic symptoms, whereas tricyclic anti-depressants are not advised due to worsening of the clinical profile. The patients need to be thoroughly counselled regarding their symptoms, and support groups may offer a healthy cushion to cope with the distress caused due to these ill effects. Better co-ordination with a psychiatrist and a more pro-active role on the part of the primary care physician, both can go a long way to improve the quality of life in these patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ciriaco M, Ventrice P, Russo G, Scicchitano M, Mazzitello G, Scicchitano F, et al. Corticosteroid-related central nervous system side effects. J Pharmacol Pharmacotherapeut. 2013 Dec;4(Suppl1):S94-8.
2. Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clini Pharmacol Therap. 1972 Sep;13(5part1):694-8.
3. Wolkowitz OM. Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. Psychoneuroendocrinol. 1994 Jan 1;19(3):233-55.
4. Zagaria MA. Systemic Corticosteroid–Associated Psychiatric Adverse Effects. US Pharm. 2016;41(7):16-18.
5. Cerullo MA. Corticosteroid-induced mania: Prepare for the unpredictable. Curr Psychiatry. June 2006. Available at: www.currentpsychiatry.com/index.php?id=22661&tx_ttnews[tt_news]=171412. Accessed 22 June 2016.
6. Brown ES, Suppes T, Khan DA, Carmody III TJ. Mood changes during prednisone bursts in outpatients with asthma. J Clini Psychopharmacol. 2002 Feb 1;22(1):55-61.
7. Goldstein ET, Preskorn SH. Mania triggered by a steroid nasal spray in a patient with stable bipolar disorder. Am J Psychiatr. 1989;146:1076-7.
8. George ME, Sharma V, Jacobson J, Simon S, Nopper AJ. Adverse effects of systemic glucocorticosteroid therapy in infants with hemangiomas. Arch Dermatol. 2004 Aug 1;140(8):963-9.

9. 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 Aller, Asthma Immunol. 2004 May 1;92(5):500-5.
10. Lewis GP, Jusko WJ, Burke CW, Graves L. The Boston Collaborative Drug Surveillance Program: prednisolone side effects and serum protein levels. Lancet. 1971;2:779-81.
11. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clini Proceed. 2006 Oct 1;81(10):1361-1367.
12. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes: a report of 14 cases and a review of the literature. J Affective Disord. 1983 Nov 1;5(4):319-32.
13. Fietta P, Fietta P, Delsante G. Central nervous system effects of natural and synthetic glucocorticoids. Psychiatr Clini Neurosci. 2009 Oct;63(5):613-22.
14. Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Therap. 2002 Oct 1;96(1):23-43.
15. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. Am J Psych. 2012 May;169(5):491-7.
16. Falk WE, Mahnke MW, Poskanzer DC. Lithium Prophylaxis of Corticotropin-lnduced Psychosis. JAMA. 1979 Mar 9;241(10):1011-2.
17. Hall RC, Popkin MK, Kirkpatrick B. Brief communication: Tricyclic Exacerbation Of Steroid Psychosis. J Nervous Mental Dis. 1978 Oct 1;166(10):738-42.
18. Gagliardi JP. Corticosteroid psychosis: Stop therapy or add psychotropics?. Curr Psychi. 2010 Jan;9:61-9.
19. Sirois F. Steroid psychosis: a review. Gen Hosp Psych. 2003 Jan 1;25(1):27-33.
20. Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. Glucocorticoid-induced impairment in declarative memory performance in adult humans. J Neurosci. 1994 Apr 1;14(4):2047-53.
21. Swinburn CR, Wakefield JM, Newman SP, Jones PW. Evidence of prednisolone induced mood change ('steroid euphoria') in patients with chronic obstructive airways disease. Br J Clini Pharmacol. 1988 Dec;26(6):709-13.
22. Varney NR, Alexander B, MacIndoe JH. Reversible steroid dementia in patients without steroid psychosis. Am J Psych. 1984 Mar;141:369–372.
23. Stoudemire A, Anfinson T, Edwards J. Corticosteroid-induced delirium and dependency. Gen Hosp Psych. 1996 May 1;18(3):196-202.
24. Wolkowitz OM, Rubinow D, Doran AR, Breier A, Berrettini WH, Kling MA, et al. Prednisone effects on neurochemistry and behavior: preliminary findings. Arch Gen Psych. 1990 Oct 1;47(10):963-8.
25. Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, et al. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Arch Gen Psych. 1999 Jun 1;56(6):527-33.
26. Brown ES, Rush AJ, McEwen BS. Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. Neuropsychopharmacol. 1999 Oct;21(4):474-84.
27. De Kloet ER, Vreugdenhil E, Oitzl MS, Joëls M. Brain corticosteroid receptor balance in health and disease. Endocr Rev. 1998 Jun 1;19(3):269-301.
28. Hall RC, Popkin MK, Stickney SK, Gardner ER. Presentation of the steroid psychoses. J Nerv Mental Dis. 1979 Apr;167:229-236.
29. Khan DA, Brown ES, Suppes P, Carmody TJ. Mood changes during prednisone bursts for asthma. Am J Respir Crit Care Med. 1999;159(3):A919.
30. Wada K, Yamada N, Suzuki H, Lee Y, Kuroda S. Recurrent cases of corticosteroid-induced mood disorder: clinical characteristics and treatment. J Clini Psychiatry. 2000 Apr;61(4):261-7.
31. McEwen BS. Allostasis, allostatic load, and the aging nervous system: role of excitatory amino acids and excitotoxicity. Neurochem res. 2000 Oct 1;25(9-10):1219-31.
32. Ling MH, Perry PJ, Tsuang MT. Side effects of corticosteroid therapy: psychiatric aspects. Archi Gen Psych. 1981 Apr 1;38(4):471-7.
33. Fardet L, Nazareth I, Whitaker HJ, Petersen I. Severe neuropsychiatric outcomes following discontinuation of long-term glucocorticoid therapy: a cohort study. J Clin Psychiatry. 2013;74(4):e281-6.
34. Brown ES, Chandler PA. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. Prim Care Compan J Clin Psych. 2001;3(1):17-21.
35. Wada K, Yamada N, Sato T, Suzuki H, Miki M, Lee Y, et al. Corticosteroid-induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. Psychosom. 2001 Nov 1;42(6):461-6.
36. Bender BG, Lerner JA, Kollasch E. Mood and memory changes in asthmatic children receiving corticosteroids. J Am Acad Child Adolesc Psych. 1988 Nov 1;27(6):720-5.
37. Gagliardi JP, Muzyk AJ, Holt S. When steroids cause psychosis. Available at: www.the-rheumatologist.org/article/when-steroids-cause-psychosis. Accessed 9 June 2016.
38. Kemp K, Lion JR, Magram G. Lithium in the treatment of a manic patient with multiple sclerosis: a case report. Dis Nerv Syst. 1977 Mar;38:210-11.
39. Terao T, Yoshimura R, Shiratuchi T, Abe K. Effects of lithium on steroid-induced depression. Biolog Psych. 1997;41(12):1225-6.
40. Putignano P, Kaltsas GA, Satta MA, Grossman AB. The effects of anti-convulsant drugs on adrenal function. Horm Metab Res. 1998;30(06/07):389-97.

41. Patsalos PN, Duncan JS. Antiepileptic drugs. Drug Saf. 1993 Sep 1;9(3):156-84.
42. Himelhoch S, Haller E. Extreme mood lability associated with systemic lupus erythematosus and stroke successfully treated with valproic acid. J Clini Psychopharmacol. 1996 Dec 1;16(6):469-70.
43. Blazer DG, Petrie WM, Wilson WP. Affective psychosis following renal transplant. Dis Nerv Syst. 1976;37:663-7.
44. Silva RG, Tolstunov L. Steroid-induced psychosis: report of case. J Oral Maxillofac Surg. 1995 Feb 1;53(2):183-6.
45. Baloch N. 'Steroid psychosis': a case report. The Br J Psych. 1974 Jun;124(583):545-6.
46. Brown ES, Khan DA, Suppes T. Treatment of corticosteroid-induced mood changes with olanzapine. Am J Psych. 1999 Jun 1;156(6):968.
47. Wyszynski AA, Wyszynski B. Treatment of depression with fluoxetine in corticosteroid-dependent central nervous system's Sjogren's syndrome. Psychosomat. 1993;34:173-7.
48. Antipsychotics. Available at: Merckmanual.com. www.merckmanuals.com/professional/geriatrics/drug-therapy-in-the-elderly/drug-categories-of-concern-in-the-elderly. Accessed 7 June 2016.
49. Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 20th ed. Hudson, OH: Lexicomp; 2015: 942-945.
50. Epocrates Plus Version 15.12.1. Updated May 9. Available at: Epocrates.com. 2016. Accessed 15 June 2016.
51. Magariños AM, McEwen BS, Flügge G, Fuchs E. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. J Neurosci. 1996 May 15;16(10):3534-40.
52. Magariños AM, Deslandes A, McEwen BS. Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. Eur J Pharmacol. 1999 Apr 29;371(2-3):113-22.

Cite this article as: Parasher A, Bez J. Steroid induced psychiatric adverse effects: an overview of risk factors, clinical features and management. Int J Res Med Sci 2020;8:2365-70.