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Oral corticosteroid dosage and clinical presentation of psychiatric conditions after steroid use: A consultation-liaison psychiatry service's experience

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Abstract

Aim: Psychiatric disturbances are the major adverse effects of corticosteroids. There are no consistent conclusions regarding changes in steroid dosage and the incidence of psychiatric conditions, due in part to the lack of consistent evaluation criteria. The purpose of this research was to determine the incidence and dose-dependency of psychiatric conditions as assessed by trained psychiatrists.

Methods: A retrospective chart review was conducted at a university hospital in Japan. We identified inpatients receiving oral prednisolone treatment, who were referred to the consultation-liaison psychiatry team from April 2015 to March 2018. Patients were divided into high-dose (≥0.5 mg/kg/day) and low-dose (<0.5 mg/kg/day) groups. We investigated the associations between steroid dosage and incidence of psychiatric conditions.

Results: A total of 93 patients (35 in the high-dose group, 58 in the low-dose group) were included. Various psychiatric conditions, such as insomnia, delirium, depression, and psychosis, occurred during steroid therapy. The most common condition was insomnia (72%). We observed no significant differences in the patient background characteristics and the incidence of most psychiatric conditions between the high-dose and low-dose groups. However, there were more patients with delirium in the low-dose group than in the high-dose group.

Conclusions: Based on the accurate assessment of psychiatric conditions by psychiatrists, our analysis suggests that, among inpatients referred to a consultation-liaison psychiatry team, the incidence of psychiatric conditions, with the exception of delirium, is independent of the dose of oral prednisolone.

KEYWORDS

consultation-liaison psychiatry, corticosteroid, delirium, steroid psychosis, steroid-induced psychiatric disorder

1 | INTRODUCTION

Corticosteroids are one among the most widely used medications in the world. However, they are known to have multiple adverse effects.[1] Of these, neuropsychiatric adverse effects are clinically important, and include insomnia,[2] emotional lability, mania, depression, psychosis, delirium, confusion, and cognitive impairments.[3-5] The cooccurrence of psychiatric conditions might interfere with the patient's treatment plans. The management of the psychiatric conditions includes withdrawal or tapering of dose of corticosteroids.[6] In cases where the corticosteroid dose cannot be reduced or the therapy cannot be discontinued, the administration of psychiatric medications should be considered.[7] In addition to difficulties in medical management, stigmas toward psychiatric conditions often prevent patients from obtaining access to proper treatment.[8]

The incidence of psychiatric conditions after steroid use is reported to range from 2% to 60%.[9] The relationship between corticosteroid therapy and psychiatric conditions has been assessed in patients with specific diseases, such as systemic lupus erythematosus and multiple sclerosis,[10,11] and the incidence of psychiatric conditions have mostly been reported from the secondary analyses of clinical trials. In a study of patients with lupus nephritis, 32% of the prednisolone-treated group developed severe psychosis, whereas only 3.8% of the patients who did not receive prednisolone developed severe psychosis.[12]

Evidence regarding the association between corticosteroid dosage and the type of psychiatric condition is also inconsistent. Some studies do not show a clear relationship.[6,13] However, a study by the Boston Collaborative Drug Surveillance Program reported an 18.4% incidence of acute psychosis in the group of participants under prednisolone treatment at a dose of more than 80 mg/day, while an incidence of 1.3% was seen in the group taking less than 40 mg/day, suggesting that there is an association between the daily dose and onset of psychosis.[14] Moreover, Newcomer et al demonstrated that a high dose of corticosteroid therapy leads to impairment in declarative memory.[15]

Such inconsistencies in the incidence and dose-dependent effects on psychiatric conditions might reflect the various clinical presentations of the conditions. In addition, various psychiatric conditions have been lumped together under the term *steroid psychosis* whether or not a patient has psychosis.[16] Therefore, studies based on the assessments by trained psychiatrists are necessary to accurately describe the characteristics of steroid-associated psychiatric conditions.

General hospital consultation-liaison psychiatry (CLP) services have grown rapidly in recent years. Thus, psychiatric conditions during and after corticosteroid therapy can be precisely evaluated by psychiatrists or clinical psychologists.[17] However, there are few clinical studies on the psychiatric conditions after steroid use based on neuropsychiatric evaluations conducted by experts.[18]

The aim of this study was to identify the clinical characteristics of patients on corticosteroids who present with psychiatric conditions. We used the CLP team database and patient charts to collect information about the patients, including their mental status as assessed by psychiatrists.

2 | METHODS

This study was conducted at the Department of Neuropsychiatry at the University of Tokyo Hospital in Japan. The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of The University of Tokyo Hospital, Approval No. 3349-13. An opt-out policy was applied for collecting and analyzing data with patients' anonymity preserved.

The information of all patients who are referred to the CLP team, including age, sex, and past medical history, is recorded in our case information database. Using this database, we retrieved the data of inpatients referred to the CLP team from April 2015 to March 2018, during treatment with corticosteroids. Patients who were referred for psychiatric evaluation to determine their eligibility for transplantation were excluded. In this study, we analyzed patients who received oral prednisolone. However, patients receiving other corticosteroids in addition to oral prednisolone, and those who had already finished treatment with oral prednisolone before the consultation were excluded from the analysis.

We retrospectively reviewed the patient charts and collected the following data: demographics, mental status as assessed by psychiatrists, past psychiatric history, and corticosteroid dose at the time of consultation. A single patient might have been diagnosed with multiple conditions at the same time.

2.1 | Statistical analysis

In order to assess the associations between prednisolone dose and psychiatric conditions, we compared the incidence of reported psychiatric conditions and patient backgrounds between high-dose (≥0.5 mg/kg/day) and low-dose (<0.5 mg/kg/day) groups.[19,20]

We used Student's *t* test to compare the averages of continuous variables and chi-squared tests to compare the proportions of categorical variables between the groups. We also performed a sensitivity analysis by excluding the patients with past history of psychiatric disorders. The threshold for significance was $P < .05$.

3 | RESULTS

3.1 | Demographic characteristics of patients

In all, 2175 patients were referred to the CLP team during the study period. Of these, 175 patients were on corticosteroids during their hospitalization by the time of consultation. Twenty-one patients who were referred for transplantation eligibility, 48 patients who did not receive oral prednisolone, 6 patients with combined use of

TABLE 1 Patient background characteristics and conditions by dose of oral prednisolone

	All (N = 93)	High-dose (N = 35)	Low-dose (N = 58)	
	n (%)	n (%)	n (%)	*P*-value
Age (≥65 years)	51 (54.8)	17 (48.6)	34 (58.6)	.345
Females	57 (61.3)	18 (51.4)	39 (67.2)	.129
Psychiatric history	24 (25.8)	9 (25.7)	15 (25.9)	.987
Condition				
Insomnia	67 (72.0)	26 (74.3)	41 (70.7)	.708
Delirium	25 (26.9)	5 (14.3)	20 (34.5)	.033*
Depression	15 (16.1)	7 (20.0)	8 (13.8)	.430
Agitation	14 (15.1)	4 (11.4)	10 (17.2)	.448
Cognitive impairment	9 (9.7)	3 (8.6)	6 (10.3)	.779
Steroid-induced psychosis	4 (4.3)	3 (8.6)	1 (1.7)	.115

*P-value <.05.

oral prednisolone and other corticosteroids, and 7 patients who had already finished treatment with oral prednisolone were excluded. Finally, 93 patients were included for analysis. Of these, 54.8% of the patients were above 65 years of age, 61.3% were women, and 25.8% had a past history of psychiatric disorders. The average age at the time of consultation was 62.5 years (standard deviation, 17.8 years).

3.2 | Associations between mental status and prednisolone exposure

Characteristics of all 93 oral prednisolone recipients and comparisons between the high-dose group (n = 35) and the low-dose group (n = 58) are presented in Table 1. We identified 67 cases of insomnia (high-dose: 26, low-dose: 41, *P* =.708), 25 cases of delirium (high-dose: 5, low-dose: 20, *P* =.033), 15 cases of depression (high-dose: 7, low-dose: 8, *P* =.430), 14 cases of agitation (high-dose: 4, low-dose: 10, *P* =.448), and 9 cases of cognitive impairment (high-dose: 3, low-dose: 6, *P* =.779). Four patients (high-dose: 3, low-dose: 1, *P* =.115) were diagnosed with steroid-induced psychosis, based on the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) criteria of corticosteroid-induced psychotic disorder or bipolar and related disorders.

There was no significant difference in the background characteristics of patients with delirium between the two groups (Table 2). Furthermore, the distribution of each condition was consistent across the 3 years, as shown in Table 3. The results of the sensitivity analysis, excluding the patients with past history of psychiatric disorders, are presented in Table S1. The results remained similar to the main analysis.

TABLE 2 Background characteristics of patients with delirium by dose of prednisolone

	High-dose (N = 5)		Low-dose (N = 22)		*P*-value
Age in years	69.4	(20.4)	73.3	(15.3)	.636
Weight in kg	55.6	(8.3)	50.5	(12.8)	.404
Females	1	(20.0)	11	(50.0)	.223
Psychiatric history	0		0		

Note: Data are shown as mean (standard deviation: age and weight) or n (%: females).

4 | DISCUSSION

This study investigated the incidence of psychiatric conditions in patients receiving oral corticosteroid therapy at different doses. In this study, we identified 93 patients treated with steroids who developed various psychiatric conditions such as insomnia, delirium, depression, and psychosis. The most common condition was insomnia. There were no significant differences in the patient background characteristics (age, sex, past medical history of psychiatric conditions) between the high-dose and low-dose groups. Additionally, the incidences of psychiatric conditions in both groups were mostly similar. However, there were more patients with delirium in the low-dose group than in the high-dose group.

The psychiatric conditions shown in this study may be influenced by underlying diseases, such as neurological diseases or preexisting psychiatric conditions. Patients with physical diseases that may present psychiatric symptoms are likely to have a prior psychiatric consultation. Therefore, we performed a sensitivity analysis by excluding the patients with a history of psychiatric consultation. Nevertheless, we found that the findings did not change significantly.

Previous studies have shown mixed results on psychiatric conditions after steroid use, due in part to the difficulty in the assessment of the complicated mental status. In the present study, using the assessments and diagnoses made by psychiatrists in the CLP team, we reviewed all patients, who presented with psychiatric conditions during treatment with oral prednisolone. We found that patients on a low oral dose of prednisolone had a higher incidence

TABLE 3 Patient psychiatric conditions by year

	2015		2016		2017	
	High-dose	Low-dose	High-dose	Low-dose	High-dose	Low-dose
	(N = 14)	(N = 19)	(N = 12)	(N = 19)	(N = 9)	(N = 20)
	n	n	n	n	n	n
Condition						
Insomnia	12	14	9	14	5	13
Delirium	3	6	0	4	2	10
Depression	2	4	3	1	2	3
Agitation	2	3	2	3	0	4
Cognitive impairment	1	3	2	1	0	2
Steroid-induced Psychosis	0	0	2	1	1	0

of delirium than did patients on a high oral dose. This suggests that the CLP team should consider even low-dose steroid users to be at risk for delirium. This result differs from previous studies suggesting that there is no difference in conditions based on the dose.[6] The difference in results might be explained by several reasons. First, some of the patient background characteristics might not have been considered in previous studies. In the present study, we confirmed no difference in the age, sex, and weight between the two groups; however, other physical characteristics of the patients, such as immobility, reduced oral intake, and cognitive status, might have influenced the susceptibility to delirium.[21] Second, the doctors and nurses might have been more inclined to request a consultation by the CLP team for patients who were on a higher dose of prednisolone than for patients on a lower dose. In patients on a higher dose of prednisolone, the inpatient ward staffs were more likely to refer the patient to the CLP team upon observing even a slight change in mental status. Third, since steroid use is a recognized risk factor for delirium, the physicians might have avoided using high doses of prednisolone in the patients having high risk for delirium.

There are several limitations in this study. First, patients in this study were limited to those who were referred to the consultation-liaison team of the psychiatry department. The threshold of referral to the CLP team might depend on the department mainly in charge of the patient. Second, this study was performed at a university hospital, and the patients may have had a complicated physical status. Third, as an observational study, this study cannot identify the causality between corticosteroid treatment and the onset of psychiatric conditions. The psychiatric disturbances of the patients cannot be clearly and solely attributed to corticosteroid use. Fourth, we could not accurately evaluate the duration of steroid therapy or cumulative steroid amount. These might have affected the psychiatric conditions. Finally, diagnoses in our study were made by the attending psychiatrists based on their clinical assessments. Further prospective studies based on prespecified scales or checklists would be imperative to confirm our findings.

5 | CONCLUSIONS

In summary, we performed a retrospective observational study of patients with psychiatric conditions after oral prednisolone treatment for physical diseases. There were no significant differences in the background characteristics or psychiatric conditions of patients receiving high-dose or low-dose oral prednisolone, with the exception of delirium: delirium was more common in the low-dose group than in the high-dose group.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

Conception and design of the study: YY, YT, YO, HY, YK, KI, KK, SK Acquisition and analysis of data: YY, YT, YO, HY Drafting of the manuscript or figures: YY, YT

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of The University of Tokyo Hospital, Approval No. 3349-13.

INFORMED CONSENT

Because of the retrospective and noninvasive nature of the study, the need for individual informed consent was waived. Disclosures about the study and opportunities for participants to opt out were made at the hospital.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions. This data has not been approved for public sharing by the Ethics Committee. Based on the request for data sharing by researchers, the data can only be provided after the Ethics Committee's approval and an opt-out procedure.

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REFERENCES

1. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy - a systematic review and meta-analysis. Arch Intern Med. 1999;159:941–55. 10.1001/archinte.159.9.941
2. Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am. 2002;31:15–36. 10.1016/s0889-8529(01)00005-6
3. Brown ES, Chandler PA. Mood and cognitive changes during systemic corticosteroid therapy. Prim Care Companion J Clin Psychiatry. 2001;3:17–21. 10.4088/pcc.v03n0104
4. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. Am J Psychiatry. 2012;169:491–7. 10.1176/appi.ajp.2011.11071009
5. Bell G. Steroid-induced psychiatric disorders. Nordisk Psykiatrisk Tidsskrift. 1991;45:437–41. 10.3109/08039489109106169
6. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes - a report of 14 cases and a review of the literature. J Affect Disord. 1983;5:319–32. 10.1016/0165-0327(83)90022-8
7. Muzyk AJ, Holt S, Gagliardi JP. Corticosteroid psychosis: stop therapy or add psychotropics? Curr Psychiatr. 2010;9:61–8.
8. Knaak S, Mantler E, Szeto A. Mental illness-related stigma in healthcare: barriers to access and care and evidence-based solutions. Healthc Manage Forum. 2017;30:111–6. 10.1177/0840470416679413
9. 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;19:201–8. 10.1097/MOT.0000000000000065
10. Hodgins GE, Saltz SB, Gibbs EP, Gonzalez R, Regan J, Nemeroff C. Steroid-induced psychosis in the pediatric population: a new case and review of the literature. J Child Adolesc Psychopharmacol. 2018;28:354–9. 10.1089/cap.2018.0017
11. Camara-Lemarroy CR, Ibarra-Yruegas BE, Rodriguez-Gutierrez R, Berrios-Morales I, Ionete C, Riskind P. The varieties of psychosis in multiple sclerosis: a systematic review of cases. Mult Scler Relat Disord. 2017;12:9–14. 10.1016/j.msard.2016.12.012
12. Cade R, Spooner G, Schlein E, Pickering M, de Quesada A, Holcomb A, et al. Comparison of azathioprine, prednisone, and heparin alone or combined in treating lupus-nephritis. Nephron. 1973;10:37–56. 10.1159/000180176
13. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology. 1996;21:25–31. 10.1016/0306-4530(95)00031-3
14. Boston Collaborative Drug Surveillance P. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther. 1972;13:694–8. 10.1002/cpt1972135part1694
15. 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 Psychiatry. 1999;56:527–33. 10.1001/archpsyc.56.6.527
16. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics. 2012;53:103–15. 10.1016/j.psym.2011.12.007
17. Grassi L, Mitchell AJ, Otani M, Caruso R, Nanni MG, Hachizuka M, et al. Consultation-liaison psychiatry in the general hospital: the experience of UK, Italy, and Japan. Curr Psychiatry Rep. 2015;17:44. 10.1007/s11920-015-0581-1
18. Nishimura K, Omori M, Sato E, Katsumata Y, Gono T, Kawaguchi Y, et al. New-onset psychiatric disorders after corticosteroid therapy in systemic lupus erythematosus: an observational case-series study. J Neurol. 2014;261:2150–8. 10.1007/s00415-014-7472-y
19. Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet. 2019;10188:2344–58. 10.1016/S0140-6736(19)30546-X
20. Tagawa A, Watanuki Y, Hayashi M, Shinohara T, Kobayashi S, Kenmotsu H, et al. Familial occurrence of bronchiolitis obliterans associated with pulmonary aspergillosis. Kansenshogaku Zasshi. 2007;3:291–6. 10.11150/kansenshogakuzasshi1970.81.291. (in Japanese)
21. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354:1157–65. 10.1056/NEJMra052321

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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