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Preliminary communication

An open-label trial of olanzapine for corticosteroid-induced mood symptoms

E. Sherwood Brown[a,*], Wendy Chamberlain[a], Nafisa Dhanani[a], Pooja Paranjpe[a], Thomas J. Carmody[a], Michael Sargeant[a,b]

[a]*Department of Psychiatry, Southwestern (STARS) Program at the University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8849, United States*

[b]*Science Teachers Access to Resources at Southwestern (STARS) Program at the University of Texas Southwestern Medical Center, Dallas, TX 75390-8849, United States*

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Abstract

Background: Prescription corticosteroids are given for a variety of common medical conditions. Psychiatric symptoms including depression, psychosis, and especially mania are common side effects of corticosteroid therapy. However, minimal data are available on the treatment of corticosteroid-induced psychiatric symptoms.

Method: In this study, 12 outpatients with manic or mixed symptoms secondary to corticosteroids were enrolled in a 5-week prospective, open-label trial of olanzapine. Psychiatric symptom measures included the Hamilton Rating Scale for Depression (HRSD), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS). Side effects were monitored with the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Scale (BAS). Weight and blood glucose were obtained at baseline and exit. Olanzapine dosing was flexible beginning at 2.5 mg/day and titrated upward as necessary to a maximum dose of 20 mg/day. Data were analyzed with Wilcoxon signed rank tests using baseline and exit data on all 12 participants.

Results: Participants showed significant reductions in YMRS (primary outcome measure), HRSD, and BPRS scores with no significant change in the SAS, AIMS, BAS, weight, or blood glucose levels. One participant discontinued early due to lack of efficacy.

Conclusion: These data suggest that olanzapine is well tolerated and appears to be useful for mood disturbances associated with corticosteroid therapy. Controlled trials seem warranted to confirm these observations.

Keywords: Olanzapine; Corticosteroid; Prednisone; Mania; Depression

* Corresponding author. Tel.: +1 214 645 8133; fax: +1 214 645 8138.
E-mail address: Sherwood.Brown@UTSouthwestern.edu (E. S. Brown).

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1. Introduction

Since their introduction in the 1950s, corticosteroids have been widely prescribed for a variety of medical conditions such as asthma, rheumatic illnesses, transplant rejection, and dermatological disorders. Case reports of psychiatric side effects including mania, depression, mood lability, or even psychosis during corticosteroid therapy are numerous (Brown and Suppes, 1998; Brown et al., 1999a; Kaufmann, 1982; Wada et al., 2000; Wada et al., 2001a). The psychiatric effects of long-term corticosteroid therapy are not well investigated; however, short-term therapy appears to be primarily associated with manic or hypomanic, rather than depressive, symptoms or psychosis (Brown et al., 2002).

From the time of these first case reports, various classes of psychotropic medications have been used in an effort to prevent or treat corticosteroid-induced psychiatric syndromes. Only one controlled clinical trial has been conducted in patients with psychiatric symptoms secondary to corticosteroids. In this study, Falk et al. (1979) reported that lithium pretreatment might prevent corticosteroid-induced mood symptoms. While 14% of patients receiving corticotropin therapy suffered from mood symptoms, none of the patients receiving corticotropin following lithium pretreatment had a mood disturbance. Case reports suggest that lithium and other mood stabilizers including lamotrigine, carbamazepine, gabapentin, and valproic acid may effectively treat or prevent corticosteroid-induced mood symptoms after their development (Brown, 2003; Brown et al., 2003; Ginsberg and Sussman, 2001; Kahn et al., 1988; Preda et al., 1999; Wada et al., 2001b). Another class of medications that may effectively treat psychiatric symptoms associated with corticosteroids is antipsychotics, including both traditional neuroleptics (Ahmad and Rasul, 1999) and the newer atypical agents (Brown et al., 1999b; Desilva et al., 2002; Goldman and Goveas, 2002; Kramer and Cottingham, 1999). Our group reported a case wherein a patient with depressed mood, insomnia, and suicidal ideation—all attributed to chronic corticosteroid therapy—responded with almost complete amelioration of these symptoms following the initiation of olanzapine therapy at 2.5 mg/day (Brown et al., 1999b). Recently, Goldman and Goveas (2002) reported a case series of five patients with a variety of symptoms including psychosis, anxiety, and mood disturbance, who responded at 2.5–15 mg/day. As symptoms associated with corticosteroids frequently include manic/hypomanic or mixed symptoms and because olanzapine is Food and Drug Administration (FDA)-approved for mania, we wanted to explore the efficacy of olanzapine in a larger sample of patients with prednisone-induced manic symptoms. In the study reported here, we provide data from an open-label trial of olanzapine in 12 patients with corticosteroid-induced manic or mixed symptoms.

2. Methods

Twelve outpatients between the ages of 18 and 65 years from University of Texas Southwestern Medical Center-affiliated clinics, or recruited from offsite flyer postings, who were receiving corticosteroids and experiencing clinically significant manic or mixed symptoms (defined as a Young Mania Rating Scale (YMRS) (Young et al., 1978) score≥10) related to corticosteroid use were included. This YMRS cutoff was selected to include people with clinically significant manic or hypomanic symptoms but—given the outpatient design—not limit the sample to only those with severe mania. Patients were excluded if they had received a psychiatric diagnosis of schizophrenia or bipolar disorder (patients with a history of major depressive disorder were included), were primarily non-English-speaking, were pregnant or nursing, had a history of contraindications to olanzapine, had initiated or changed the dose of other psychotropic medication within the past 2 weeks, or had alcohol or drug abuse within the past 3 months. After having completed an IRB-approved informed consent process, demographic information including past corticosteroid use, alcohol and drug use, and psychiatric history was obtained using a structured clinical interview (SCID-IV, clinician version) (First et al., 1995). Baseline measures of psychiatric status were obtained using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), YMRS, and Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), and physical side effects were ascertained with the Simpson Angus Extrapyramidal Rating Scale (SAS) (Simpson and Angus, 1970), Abnormal Involuntary

Movement Scale (AIMS) (Guy, 1976), and Barnes Akathisia Scale (BAS) (Barnes, 1989). Routine laboratory analyses including blood glucose levels were obtained at baseline and exit, and vital signs were assessed. Subjects were given 2.5 mg of olanzapine QHS in an open-label fashion, which was increased in 2.5- to 5.0-mg increments (up to 20 mg daily) weekly based on response and side effects. At each of the five weekly follow-up appointments, rating scales for mood and side effects were repeated. Pill counts were conducted at each appointment. Subjects were paid US$50 at week 2 and US$50 upon completion of the study at week 5.

Data were analyzed on a personal computer using SPSS version 11.5 software. All 12 participants were included in the analyses (intent-to-treat sample) using baseline and exit scores, with the last observation carried forward. The Wilcoxon signed rank test was used for the analysis of the outcome measures with α set at 0.05. This nonparametic test was selected due to the relatively small sample size examined.

3. Results

Demographic characteristics of the participants are provided in Table 1. All the patients met diagnostic criteria based on the SCID for a prednisone-induced mood disorder, with five having manic features and seven having mixed features. Eleven of 12 participants completed the study. One participant discontinued from the study on the third visit while receiving olanzapine at 7.5 mg/day due to minimal improvement in irritability and insomnia.

Table 1
Demographic characteristics of subjects (n=12)

Characteristics	Value
Age in years, mean (±S.D.)	44.0 (12.9)
Gender, *n* (%)	
Male	2 (16.7%)
Female	10 (83.3%)
Race, *n* (%)	
Caucasian	9 (75%)
African–American	2 (16.7%)
Hispanic	1 (8.3%)
Psychiatric diagnosis, *n* (%)	
Prednisone-induced mood disorder	
With manic features	5 (41.7%)
With mixed features	7 (58.3%)
Olanzapine dosage (mg/day)	
Mean maximum dosage (±S.D.)	9.2 (5.6)
Mean dose at exit (±S.D.)	8.5 (5.7)
Prednisone dosage (mg/day)	
Mean dose at baseline (±S.D.)	14.4 (8.8)
Mean dose at exit (±S.D.)	14.0 (11.3)
Mean time on prednisone in months (±S.D.)	45.5 (46.1)

Table 2
Outcome measures (±S.D.) from baseline to exit (n=12) during olanzapine therapy

Outcome measure	Baseline	Exit	*p*
HRSD	17.83 (4.82)	9.25 (6.58)	0.005
YMRS	15.25 (3.84)	5.83 (4.69)	0.002
BPRS	34.92 (7.69)	26.08 (5.09)	0.006
Weight[a]	192.09 (47.76)	197.09 (41.36)	0.16
Blood glucose[b]	98.58 (21.38)	117.33 (60.16)	0.39
AIMS	0.58 (0.99)	0.33 (0.65)	0.19
BAS	0.50 (0.79)	0.17 (0.57)	0.10
SAS	1.83 (2.1)	2.25 (2.56)	0.29

HRSD=Hamilton Rating Scale for Depression; YMRS=Young Mania Rating Scale; BPRS=Brief Psychiatric Rating Scale; AIMS=Abnormal Involuntary Movement Scale; BAS=Barnes Akathisia Scale; SAS=Simpson Angus Scale.

[a] Based on n=11.

[b] Based on n=10.

Patients were receiving corticosteroids for the following medical illnesses: rheumatoid arthritis (n=3), systemic lupus erythematosis (n=3), asthma (n=1), vasculitis (n=1), hypopituitarism secondary to a closed-head injury (n=1), Crohn's disease (n=1), prevention of renal transplant rejection (n=1), and Behcet's disease (n=1). Additional medical conditions for which they were receiving treatment included: osteoporosis (n=2), hyperlipidemia (n=2), hypertension (n=2), glaucoma (n=2), type 2 diabetes (n=2), scoliosis (n=1), past breast cancer (n=1), asthma (n=1), chronic obstructive pulmonary disease (n=1), Bell's palsy (n=1), non-alcoholic steatohepatitis (n=1), hypothyroidism (n=2), migraine headaches (n=1), and Ménière disease (n=1). Several patients had corticosteroid dose changes during the study. However, the mean dose did not change significantly (p=0.7) from baseline to exit (Table 2). Ten participants were taking prednisone while one received prednisolone and one hydrocortisone. Dosages used for calculating the means were prednisone equivalents (Stiefel et al., 1989) for the patients taking corticosteroids other than prednisone.

Psychiatric medications taken by the participants at study entry include 20 mg/day citalopram (*n*=1), 30 mg/day citalopram (*n*=1), 10 mg of doxepin QHS PRN sleep (*n*=1), 10 mg/day fluoxetine (*n*=1), 75 mg/day venlafaxine (*n*=1), 1 mg/day lorazepam (*n*=1), and 50 mg of trazodone QHS. As per protocol, no changes in these medications occurred within 2 weeks prior to study entry. One psychiatric medication change occurred during the trial. A patient asked for and was given permission to discontinue doxepin for sleep at week 2 of the trial as she felt that her sleep had improved with olanzapine therapy to the point that doxepin was no longer needed. She remained off doxepin for the remainder of the study. Other medications included vitamin or mineral supplements (*n*=9), estrogen supplements (*n*=7), narcotic analgesics (*n*=6), antineoplastic/immunosuppressant agents (*n*=6), antihypertensives (*n*=5), diuretics (*n*=5), H_2 antagonists (*n*=4), nonsteroidal antiinflammatory drugs (*n*=4), antihistamines (*n*=4), other analgesics (*n*=3), antilipemics (*n*=3), thyroid supplements (*n*=3), proton pump inhibitors (*n*=3), antibiotics (*n*=3), steroid inhalers (*n*=2), â-agonist inhalers (*n*=2), anticonvulsants (*n*=2), oral hypoglycemics (*n*=2), muscle relaxants (*n*=2), antidiuretics (*n*=1), ocular hypotensives (*n*=1), antidiarrheals (*n*=1), and anorexogenic agents (*n*=1).

As can be seen in Table 2, participants showed significant improvement in YMRS (primary outcome measure), HRSD, and BPRS scores during the study. Scores on the SAS, AIMS, and BAS, as well as weight and blood glucose levels, did not change significantly from baseline to exit (Table 2).

As olanzapine is an FDA-approved and widely available medication, one option offered to participants who completed the study and showed a favorable response was to continue olanzapine therapy with their physician's approval. A total of nine participants elected this option, with the three exceptions being the patient who withdrew early, a patient who could not afford the copay required by her insurance company, and a patient who was troubled by morning sedation after initiating olanzapine even though this side effect had resolved by the time of study completion. As long-term follow-up was not part of the study design, additional efficacy and tolerability data after study completion are not available on these patients.

4. Discussion

These findings demonstrate significant decreases in YMRS, HRSD, and BPRS scores during olanzapine treatment in patients with corticosteroid-induced manic or mixed symptoms. The results are consistent with anecdotal reports on the efficacy of olanzapine for mood symptoms with corticosteroids (Brown et al., 1999b; Goldman and Goveas, 2002).

Olanzapine was also well tolerated in this sample. As expected, measures of extrapyramidal symptom severity did not significantly change (Leucht et al., 1999). The finding of a nonsignificant change in weight or blood glucose is more interesting. Corticosteroids are associated with a number of systemic side effects including obesity, diabetes, osteoporosis, and peptic ulcers (Schäcke et al., 2002). Significant weight gain and insulin resistance have been reported in some patients with schizophrenia given atypical antipsychotics (Ananth et al., 2003; Newcomer et al., 2002). Thus, patients taking corticosteroids could be vulnerable to weight gain and insulin resistance during olanzapine therapy. Our findings do not seem to support this assumption. However, it is important to note that our study has a small sample size and, thus, may not have sufficient power to detect meaningful changes in these side effects. Additionally, blood glucose levels and weight were obtained at clinic appointments; thus, variation in the time of the last meal could affect both measures. As an overall numerical increase in weight and blood glucose levels was observed, these findings could have reached statistical significance if a larger sample of patients had been studied.

This investigation has several limitations, including an open-label design and a small sample size. Although the sample size is small, this is the second largest trial reported on a medication for corticosteroid-induced psychiatric symptoms. Another limitation is the multiple medical diagnoses and other medications received by the patients, which complicate our ability to assess olanzapine effects. However, this limitation is inherent in working with corticosteroid-treated patients.

In summary, a group of patients with corticosteroid-induced manic or mixed symptoms showed symptomatic improvement with olanzapine therapy at relatively low dosages. Side effects were infrequent

and relatively mild. Larger controlled trials of olanzapine in this population seem warranted.

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