

**SELF-REPORTED DEPRESSIVE SYMPTOMS
FOLLOWING TREATMENT WITH
CORTICOSTEROIDS AND SEDATIVE-HYPNOTICS***

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ABSTRACT

Objective: To evaluate associations between exposure to corticosteroids or sedative-hypnotic medications and incident self-reported depressive symptoms in medical inpatients. *Method:* The study utilized a prospective cohort design, focusing on acute depressive symptoms developing soon after medication exposure. The incidence of self-reported depressive symptoms was evaluated using a modified version of the Center for Epidemiological Studies Depression Rating Scale (CES-D). The incidence of depressive symptoms in subjects newly exposed to corticosteroids and sedative-hypnotics was compared to that of a nonexposed comparison cohort. *Results:* The incidence of self-reported depressive symptoms was elevated in subjects newly exposed to corticosteroids (Risk Ratio = 3.10), although the association did not attain statistical significance ($p = .07$). The risk ratio for sedative-hypnotic exposure was 4.18, a statistically significant finding ($p = .02$). As expected, incident self-reported depressive symptoms were also associated with several psychosocial variables. However, the data did not suggest that the observed associations between drug exposures and depressive symptoms were due to confounding by psychosocial or illness-related variables.

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Conclusions: Depressive symptoms among medical inpatients have a biopsychosocial etiology. Corticosteroids and sedative-hypnotics are biological risk factors for depressive symptoms in this population.

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Key Words: depressive symptoms, etiology, chemically induced, benzodiazepines, sedative-hypnotic drugs, corticosteroids

INTRODUCTION

Depressive symptoms commonly afflict patients in medical settings [1, 2]. Medical populations are also characterized by high rates of medication exposure. Corticosteroids and sedative-hypnotics are two (of several) classes of medications implicated in causing depressive symptoms. However, associations between these medications and depressive symptoms have not been adequately confirmed by prospective studies. We have recently conducted a prospective cohort study examining the incidence of self-reported depressive symptoms in medical inpatients following exposure to corticosteroids and sedative-hypnotics.

The study of drug-induced depression is methodologically complex. For example, studies must be capable of evaluating, and controlling for bias introduced by confounding with other biopsychosocial risk factors for depression. Also, studies must address the possibility that the effect of drug exposures may be modified by other variables, for example, past or family history of depression. Furthermore, studies must be capable of confirming that depressive symptoms follow, rather than precede, exposure to the medications.

Depressive episodes apparently induced by exogenous corticosteroids were noted in early reports describing the clinical use of these medications [3], and were classified as a "grade 3" reaction in a classical paper by Rome and Braceland [4]. More recently, depressive episodes associated with corticosteroid exposure have been described in case reports [5] and case series [6, 7]. Depression is regarded as a side effect of corticosteroids by many authors [8, 9]. Apparently, only one controlled study has been conducted. This was a cross-sectional survey that compared depressive symptom scores in a group of steroid-using and nonsteroid-using patients with chronic obstructive pulmonary disease [10]. The two groups had similar illness severity, as measured by other clinical variables. A significantly higher mean Beck Depression Inventory score was found in the steroid-using group. Unfortunately, since the study used a cross-sectional design, it could not confirm that the two groups were comparable prior to corticosteroid exposure.

It is a common clinical belief that sedative-hypnotics can cause depressive symptoms [11, 12]. However, side effect data from clinical studies of alprazolam and diazepam have not shown an increased risk of depression in relation to

placebo [13]. One post-marketing surveillance study of alprazolam, however, found that depression was the most commonly reported adverse event [14]. Lydiard et al. reported the emergence of Major Depression in fifteen of forty-six patients treated with alprazolam for panic disorder [15]. However, mood disorders frequently coexist with anxiety disorders, hence alprazolam may not have caused the reported depressive episodes.

The clinical belief that sedative-hypnotics are capable of causing depression may be based on early clinical case reports [16, 17]. Subsequently, depression came to be known as one of several "paradoxical reactions" to benzodiazepines [18]. Associations between depression and other (nonbenzodiazepine) sedative-hypnotics have also been reported [19].

Sedative-hypnotics are most often prescribed for anxiety and insomnia, both symptoms that are commonly associated with depression. Therefore, epidemiological confirmation that sedative-hypnotics can cause depression requires the application of prospective study designs capable of confirming that the sedative-hypnotic exposures preceded the onset of depressive symptoms.

METHOD

Potential subjects were identified from a series of new admissions to five acute medical units at the Bow Valley Centre of the Calgary General Hospital. For ethical reasons, the consent form was distributed (on a voluntary basis) by clinical staff on the units. Because of this requirement, the sample was not a consecutive series of admissions, but it resembled a consecutive series in the sense that no eligibility requirements were specified prior to obtaining consent. Consent forms were handed out whenever it was possible to do so. When signed, the consent forms were returned to study personnel. Hospital charts of consenting subjects were reviewed, and the subjects were interviewed to apply eligibility criteria. Drug exposures up to the time of hospital admission were also recorded. Subjects were excluded if they were 1) less than eighteen years old, 2) had a diagnosis of a nonorganic depressive mental disorder, or 3) had a diagnosis of delirium or dementia. Non-excluded subjects were further interviewed to confirm, where possible, the accuracy of the charted drug exposure history. Subsequently, each subject was given a modified (rating symptoms over 4 days, rather than 7 days) version of the Center for Epidemiological Studies Depression Rating Scale (CES-D) [20]. The four-day modification of the scale allowed more frequent ratings of the subjects during the follow-up period (see below). The modified CES-D scale provided a short-term assessment of depressive symptoms at the time of admission to the hospital. Subjects obtaining a score of sixteen or greater (the traditional cut-off for the CES-D scale, which was considered applicable to the modified scale) were regarded as having prevalent depressive symptoms. These subjects were excluded from the study to ensure that all of the subjects who became depressed had incident, rather than prevalent, depressive symptoms.

All subjects were given a demographic questionnaire, measuring age, gender, marital status, income, family size, and educational attainment. The Social Readjustment Rating Scale was used to measure the severity of psychosocial stressors in the previous six months [21, 22]. In addition, each subject was interviewed to determine whether they had a past or family history of depression. To be regarded as indicative of a past or family history, an episode of depression had to be too severe or persistent to be accounted for by psychosocial precipitants, and had to cause significant dysfunction or distress. A global rating of the perceived severity of physical health problems was made using the "Physical Health Spectrum" scale [23]. Certain physical illnesses may cause depressive symptoms. The following physical illnesses were regarded as possible risk factors for depression in this study: adrenal insufficiency, Cushing's syndrome, hyperparathyroidism (or other, e.g., paraneoplastic causes of hypercalcemia), hypothyroidism, hyperthyroidism, Huntington's chorea, multiple sclerosis, pancreatic carcinoma, Parkinson's disease, Sjogren's syndrome, stroke, systemic lupus erythematosus, temporal arteritis, complex partial seizures, and vitamin B-12 or folate deficiency. These conditions were recorded during the chart review, since they could potentially confound observed drug-depressive symptom associations.

The charts of eligible subjects were reviewed daily for as long as they were in the hospital. The chart review determined whether the subject had been started on corticosteroids or sedative-hypnotics, or one of several other drugs that may cause depression (angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers, levodopa, and histamine-2-receptor blockers). Zopiclone was included in the sedative-hypnotic group. A set of ingestion criteria was applied to confirm that the subjects were exposed to at least a minimal usual clinical dose of the medication over a four-day period. For example, subjects exposed to single doses of benzodiazepines prior to endoscopy would not be counted as exposed. Subjects with pre-hospital exposure to corticosteroids and sedative hypnotics were not considered eligible for the corticosteroid or sedative-hypnotic cohorts. This step was taken to ensure that all members of these cohorts were newly exposed to the drugs.

Each subject was interviewed every five days while in the hospital to obtain an additional modified CES-D rating. If the subject had a CES-D score ≥ 16 , indicating significant depressive symptoms, the subject was regarded as an incident case. If subjects remained nondepressed (< 16 score), they were followed with modified CES-D ratings every five days until incident depressive symptoms emerged, or the subject was discharged from the hospital. If a subject was discharged from the hospital within five days of admission, or within five days of a new drug exposure, the subject was phoned at home to complete a modified CES-D rating, and to confirm continued ingestion of the drug.

The analysis consisted of comparisons (using crude and adjusted risk ratios) between the risk of incident depressive symptoms in subjects newly exposed to corticosteroids or sedative-hypnotics and subjects with no new exposures to these

medications. Subjects who were newly exposed to angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers, levodopa, or histamine-2-receptor blockers were excluded from the nonexposed comparison group prior to calculating the risk ratios. This was an a priori decision designed to ensure that the nonexposed cohort consisted of subjects who were not exposed to any of the drugs usually regarded, in the literature, as being capable of causing depression. In addition to univariate, bivariate, and stratified analyses, a series of logistic regression models were generated. Because of sample size limitations, models with simultaneous control of more than two potential confounders could not be fit. The logistic regression analysis did not identify any effects not evident in the stratified analysis, hence, the modeling results are not described in this article.

Statistical analysis was conducted using a shareware program, "Epi-info," sponsored by the United State Centers for Disease Control and the World Health Organization. All statistical tests utilized two-sided Fisher's exact tests.

RESULTS

During the data collection period, 369 consent forms were signed and returned. Eight (2.2%) of these subjects had been included in the study on a previous admission and were, therefore, excluded. Only one seventeen-year-old subject was excluded because of her age. Twenty-one consenting subjects were excluded because of psychiatric diagnosis: 1) five with delirium, 2) three with dementia, 3) one with delirium and dementia, and 4) twelve with nonorganic depressive disorders. Forty-three of the consenting subjects were excluded because of previous drug exposures (in order to ensure that all drug-exposed subjects were newly exposed) and eighteen subjects were excluded because they withdrew consent. Eighty-six subjects were excluded from the prospective cohort study because they scored sixteen or more on the initial modified CES-D. Of the remaining 192 subjects, fourteen (7.3%) were lost to follow-up before a repeat modified CES-D rating could be obtained, complete follow-up was obtained for 178 subjects.

Ninety-six subjects (53.9%) were male, and eighty-two subjects (46.1%) were female. The subjects ranged in age from twenty to eighty-seven. The age distribution was right skewed, with a median age of sixty years. Forty-six (25.8%) subjects reported a family history and fifty-six (31.5%) reported a past history of depression. After adjusting total family income for family size and place of residence, twenty (11.2%) of the subjects were below the poverty line according to Canadian Government (Statistics Canada) Criteria.

When rated with the Physical Health Spectrum, 135 subjects had "serious disabilities," "other disabilities," or "one or more chronic conditions or impairments." According to previous literature [24], these subjects may be at higher risk of depressive symptoms than subjects suffering from less severe physical illness. Twelve subjects (6.7%) had one or more of the physical conditions regarded as capable of causing depression: two had multiple sclerosis, one subject had

Parkinson's disease, another had Sjogren's syndrome, and there was one case each of systemic lupus erythematosus and temporal arteritis. Three subjects had strokes and three subjects had complex partial seizures. Thirty-seven (20.8%) of subjects scored above the cut-off point of 300 "life change units" on the Social Readjustment Rating Scale.

One hundred and thirty-six (76.4%) of the subjects were followed up with a modified CES-D interview while they were still in the hospital, the remaining forty-two (23.6%) were phoned at home to complete the modified CES-D. Thirty-seven subjects were interviewed more than once in follow-up because they were inpatients for longer than ten days. Fifteen of these subjects were interviewed with more than two follow-up interviews because they were in the hospital longer than fifteen days.

Twenty-two (12.4%) subjects had a score of 16 or greater on the CES-D scale during follow-up. These subjects were classified as incident cases of depression. Of the 178 subjects in the prospective cohort study, ninety-two were not newly exposed to any of the medications that may cause depression. These subjects formed the control cohort, and five of them (5.4%) developed incident depressive symptoms. Six of the thirty-six subjects (16.7%) who were newly exposed to corticosteroids developed incident depressive symptoms during their hospital stay. The crude risk ratio for corticosteroid exposure was therefore 3.10 ($p = .07$), a value associated with a 95 percent confidence interval of 1.00 to 9.42. The confidence interval is indicative of a strong trend toward statistical significance. The most common reasons for prescription of corticosteroids were: rheumatoid arthritis, chronic obstructive pulmonary disease, and acute bronchial asthma.

Risk ratios for each of the variables regarded as potential confounder may be found in Table 1. Several of the potential confounders had risk ratios greater than one: less than grade school education (risk ratio versus grade 12 education or greater: 2.16, $p = .14$), unemployment (risk ratio: 3.14, $p = .01$), poverty (risk ratio: 2.91, $p = .02$), Physical Health Spectrum rating (risk ratio: 3.19, $p = .11$), physical illness that may cause depression (risk ratio: 2.18, $p = .17$). Although not all of these associations are statistically significant, the elevated risk ratios make these variables potential confounders of the drug-depressive symptom association. However, stratification on these variables did not provide evidence that the association between corticosteroid exposure and depressive symptoms was inflated due to confounding by these variables. The stratified analysis is summarized in Table 1. Some of the stratum specific risk ratios assume undefined or zero values due to small numbers within the strata. However, there are no stratifications where the stratum-specific risk ratios approximate null values, as would be expected if the apparent drug-depression association were due to confounding.

The apparent association between corticosteroids and incident depressive symptoms appeared stronger in subjects reporting a past history of depression

Table 1. Crude Risk Ratios for Potential Confounders, and Stratified Risk Ratios for Corticosteroid and Sedative-Hypnotic Exposures, by Potential Confounder

Potential Confounder	Proportion Depressed	Risk Ratio for Potential Confounder	Stratified Risk Ratios (Corticosteroids)	Stratified Risk Ratios (Sedative-Hypnotics)
Age > 44 years	16/133		3.32	2.30
Age 18-44 years	6/45	1.11	2.30	9.88
Males	13/96		3.07	5.41
Females	9/82	.81	2.92	3.07
Married or single	19/131		undefined	undefined
Sep., div., widowed	3/47	.44	2.31	3.07
Grade 12 or higher	11/100		7.65	15.69
Grade 9 to Grade 12	6/57	.96	7.75	3.88
< Grade 9 education	5/21	2.16	0	0
Not unemployed ^a	15/155		.73	5.13
Unemployed	7/23	3.14	6.25	0
Above poverty line	16/155		14.18	20.53
Below poverty line	6/20 ^{d****}	2.91	0	0
Not "high" stress	17/141		2.81	3.42
"High" stress (>300 pts)	5/37	1.12	3.80	6.33
Less severe illness ^{b**}	2/43		0	0
More severe illness ^{**}	20/135	3.19	3.00	4.47
No depressogenic illness	19/166		6.67	9.52
Depressogenic illness ^{***}	3/12	2.18	0	0

^aEmployed, disabled, or retired.

^bSerious disabilities, other disabilities or one or more chronic conditions or impairments on the Physical Health Spectrum Scale.

^cSee Methods section.

^dTotal < 178 due to missing family income data on three subjects.

Note: Undefined and zero values in certain cells are due to zero values in the denominator and numerator of the risk ratio respectively.

(stratum specific risk ratio: 3.88, $p = .12$) or family history of depression (stratum specific risk ratio: 6.90, $p = .07$).

Five of the twenty-two subjects (22.7%) who were newly exposed to sedative-hypnotics were subsequently classified as having exceeded the threshold for incident depressive symptoms. As described previously, five of the ninety-two nonexposed subjects (5.4%) were classified as depressed. The resulting crude risk ratio for sedative-hypnotic exposure was 4.18, with a 95 percent confidence interval of 1.33 to 13.19. A two-sided Fisher's exact test was statistically significant, $p = .02$. Stratification on the potential confounders did not suggest that the observed association was due to confounding by these variables (see Table 1). There was no evidence of stronger associations in strata defined by a past or family history of depression. The reasons for prescription of sedative-hypnotics were often not clear from the records. Presumably, most of the sedative-hypnotic treated patients were receiving symptomatic treatment for anxiety or insomnia.

DISCUSSION

These data suggest that corticosteroids and sedative-hypnotics may produce depressive symptoms as a side effect. This finding provides some support for long-held clinical suspicions about these drugs.

An association between corticosteroid exposure and depression seems biologically plausible given the overlapping clinical symptomatology of Cushing's syndrome and Major Depressive Episode [25]. In fact, increased endogenous production of steroids may be one mechanism by which stressful life events precipitate episodes of depression [26].

Since this study was conducted using volunteer medical inpatients (rather than a random sample), the results may not be generalizable to other medical inpatient populations. However, the prospective design should offer protection against selection bias. Subjects were selected into the cohorts based on their drug exposures. Selection bias could occur if the selection process also depended in some way on whether the potential subjects were depressed. However, this is unlikely since no eligible subjects were depressed at the time of selection.

The use of symptom rating scales in physically ill subjects has been criticized on the premise that some symptoms of physical illness may cause elevations in depressive symptom ratings. In turn, this could lead to false positive outcomes on the scales. However, since this effect should apply equally to each of the comparison groups, measurement bias should not have inflated the risk ratios. In fact, if the CES-D had a tendency to produce false positives in each of the comparison groups, the expected result would be non-differential misclassification bias. This form of bias always produces a tendency to underestimate the strength of association.

Since subjects treated with corticosteroids tend to be very ill, it is unlikely that depressive symptoms can be prevented by reducing exposure rates to

corticosteroid medications. Nevertheless, increased clinical awareness of the problem may be beneficial. For example, health care providers with an awareness that corticosteroids can cause depression, may be more able to provide extra support or reassurance to their patients. The implications for sedative-hypnotic use may be more immediate. In medical populations, these medications tend to be prescribed for the treatment of insomnia or anxiety in an effort to improve patients' mental state or comfort level. However, since they may cause depressive symptoms in some patients, there should be a critical evaluation of whether their global effect is positive or negative.

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND SEVERE PSYCHIATRIC SIDE EFFECTS

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ABSTRACT

Objective: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively in the treatment of pain. This study explored the possibility that psychiatric side effects may be both more frequent and more severe than thought previously. *Method:* Four psychiatric outpatients, three with affective disorders and one with schizophrenia, were treated with NSAIDs for a complaint of pain. The NSAIDs were withdrawn, then restarted for three patients, and then withdrawn again one or more times. The patients were evaluated while on and off NSAIDs. *Results:* All four patients developed moderate to severe depression and one became severely paranoid while on NSAIDs initially. When the NSAID was withdrawn there was remission of the depressive symptoms and in one case the accompanying paranoia. The depressive symptoms were reproduced when the NSAID was restarted in five instances (involving only 3 of the patients) and remitted when the NSAID was discontinued. One of these three patients also became paranoid in two instances. The paranoia remitted when the NSAID was discontinued. *Conclusions:* These findings suggest that NSAIDs can induce or exacerbate reproducible symptoms (depression, paranoia) in patients with either affective disorder or schizophrenia. These adverse effects may be more severe and frequent than thought previously. NSAID-treated patients should be studied for NSAID-induced psychiatric side effects.

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Key Words: nonsteroidal anti-inflammatory drug, NSAID, side effects, depression, bipolar affective disorder, schizophrenia, psychosis, delirium