Observational Study

Neuropsychiatric Side Effects After Lumbosacral Epidural Steroid Injections: A Prospective Cohort Study

Suzanna Shermon, DO[1], John Maclean, BS[2], Richard Shim, BS[2], and Chong H. Kim, MD[1]

From: [1]Case Western Reserve University/MetroHealth Medical Center, Cleveland, OH; [2]Case Western Reserve University School of Medicine Cleveland, OH

Address Correspondence: Suzanna Shermon, DO Physical Medicine and Rehabilitation, PGY-4 Case Western/MetroHealth 4229 Pearl Rd Cleveland, OH, 44109 E-mail: sshermon@metrohealth.org

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-19-2023
Revised manuscript received: 11-18-2023
Accepted for publication: 11-28-2023

Free full manuscript: www.painphysicianjournal.com

Background: The central nervous system contains steroid receptors, particularly in the hypothalamic and limbic systems. These systems are responsible for driving certain emotions in humans, especially stress, anxiety, motivation, energy levels, and mood. Thus, corticosteroids may precipitate patients to experience these emotions. Most existing studies report neuropsychiatric side effects after oral or intravenous corticosteroids rather than epidural.

Objectives: This study examines the neuropsychiatric side effects after epidural steroid injections (ESIs), with a focus on whether certain factors in patients' histories further exacerbate symptomatology.

Study Design: Prospective observational cohort study.

Setting: Fluoroscopy suite at an urban academic teaching hospital.

Methods: Patients were called 24 hours and one week after their ESIs and asked if they experienced certain neuropsychiatric symptoms more than usual compared to baseline.

Patients: Seventy-four patients undergoing a lumbosacral ESI (interlaminar (ILESI), caudal or transforaminal (TFESI)) were invited to take part in the study the day of his or her procedure.

Intervention/Measurement: Assessed whether psychiatric history, gender, race, type of ESI, or the number of levels injected affected frequency and duration of neuropsychiatric symptoms at one day and one week after an ESI.

Results: Significantly ($P < 0.05$) more patients with a psychiatric history experienced restlessness and irritability at day one than those without a psychiatric history. At week one, male gender (IRR 2.29, 95% CI 1.37, 3.83, $P = 0.002$), ILESI (IRR 7.75, 95% CI 1.03, 58.6, $P = 0.047$), and 2-level injections (IRR 2.14, 95% CI 1.13, 4.06, $P = 0.019$) were significantly associated to more total symptoms.

Limitations: Single center study, reliance on subjective responses from patients, lack of follow-up after one week post-ESI.

Conclusion(s): This study demonstrates that neuropsychiatric symptoms are rare overall after an ESI, though certain factors may influence patients experiencing these symptoms. Restlessness and irritability were more likely to occur one day after an ESI in those with a psychiatric history. Those who had a 2-level injection were more likely to keep experiencing most symptoms by week one, suggesting a possible correlation between corticosteroid dose and neuropsychiatric symptoms.

Key words: Epidural steroid injections, transforaminal epidural steroid injections, interlaminar epidural steroid injections, caudal epidural steroid injections, neuropsychiatric symptoms, restlessness, irritability, psychiatric history, anxiety, depression, dexamethasone, men, women, race, one-level epidural steroid injection, 2-level epidural steroid injection

Pain Physician 2024: 27:149-159

The primary role of lumbar epidural steroid injection (ESI) is to treat lumbosacral radicular pain and avoid operative intervention (1). Radicular pain often results from mechanical nerve root compression that leads to the production of inflammatory molecules such as phospholipase A2, substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide. These mediators sensitize the dorsal root ganglion, nerve root, and free nerve endings, thus precipitating neuropathic pain. This inflammatory cascade is hypothesized to interrupt the delivery of corticosteroids to the site of inflammation (1-5).

The central nervous system contains steroid receptors for estrogen, progesterone, androgen, glucocorticoid, and mineralocorticoid steroids, particularly in the hypothalamic and limbic systems (6-9). The hypothalamic and limbic systems are responsible for driving certain emotions in humans, especially stress, anxiety, motivation, energy levels, and mood (10-12). Thus, corticosteroids may precipitate patients to experience these emotions.

Several neuropsychiatric symptoms have been reported in the literature after exogenous use of oral and epidural corticosteroids, as well as with endogenous overproduction of steroids, including depression, anxiety, panic attacks, irritability, insomnia, emotional lability, and mania (13-22). Approximately 20-60% of patients who receive corticosteroids experience these symptoms, which may occur anytime from several hours to several weeks after receiving steroids. It may take several days to weeks for symptoms to completely resolve (23-24).

The neuropsychiatric manifestations of corticosteroids have been reported less in the literature than somatic effects, possibly because their complexity and unpredictability make them difficult to study (23). Most of the studies and case reports that are published focus on neuropsychiatric side effects after oral or IV corticosteroids rather than epidural (23). This study examines the neuropsychiatric side effects after epidural steroid injections (ESIs), with a focus on whether certain factors in patients' histories further exacerbate symptomatology.

Methods

This is a prospective observational cohort study analyzing patients who underwent an epidural steroid injection at an urban academic teaching hospital from August 2022 to February 2023. Institutional review board approval was obtained (#STUDY00000063).

Any patient undergoing a lumbosacral ESI (interlaminar (ILESI), caudal, or transforaminal (TFESI)) was invited to take part in the study on the day of his or her procedure. Exclusion criteria included anyone who did not speak English or was under the age of 18. Patients were called at 24 hours and one week after their ESIs. They were asked if they experienced the following symptoms more than usual compared with their baseline mood after their procedures: sad mood, increased energy, restlessness, irritability, decreased concentration, anxiety, aggressive behavior/anger, and poor sleep. Yes/no responses were recorded for each symptom at day one and week one.

The following information was obtained from the patients' charts: age, gender, race, body mass index (BMI), whether they had a psychiatric history (yes/no), and if they did, what conditions they were diagnosed with. Patients with a psychiatric history were grouped into 'anxiety disorder,' 'depressive disorder,' 'both,' or 'other.' The following conditions fell under anxiety disorder: anxiety, generalized anxiety disorder, and adjustment disorder with anxiety. The following conditions were considered for depressive disorder: depression, major depressive disorder, mood disorder with depressive features, recurrent depressive disorder, and adjustment disorder with depressive mood. The following conditions were under the category 'other': obsessive-compulsive disorder and post-traumatic stress disorder.

The type of ESI (TFESI, ILESI, or caudal epidural) and number of levels injected were also recorded for data collection. Patients who underwent an ILESI all had one-level procedures. Patients who underwent a TFESI had either a one-level or 2-level procedure. A procedure was considered to be 2-level if 2 spinal levels were injected unilaterally (i.e., L4 and L5 TFESI on the left) or bilaterally (i.e., L4 TFESI bilaterally). Dexamethasone was the steroid of choice for all ESIs. For a TFESI, 0.5 mL of 10 mg/mL of dexamethasone, 0.5 mL of preservative-free 1% lidocaine, and 3 mL of preservative-free normal saline were injected at each level. For an ILESI, 0.5 mL of 10 mg/mL dexamethasone, 0.5 mL of preservative-free 1% lidocaine, and 5 mL of preservative-free normal saline was injected. For a caudal epidural, 0.5 mL of 10 mg/mL dexamethasone, 3 mL of preservative-free 1% lidocaine, and 6.5 mL of preservative-free normal saline was injected.

For statistical analysis, a Fisher's exact test, Pearson's Chi-squared test, and Wilcoxon rank sum test were used to assess for significance (*P* value) in Table 1.

A 2-sample test for equality of proportions and Welch 2-sample t test or paired t test were used for 95% confidence intervals (95% CI) and *P* values in Tables 2-6. The incidence rate ratio was applied in Table 7. Significance was considered for $P < 0.05$.

Results

Seventy-four patients were consented. Four patients were not reached at day one or week one, 2 patients were reached at day one but not week one, and one subject was reached at week one but not day one. The remaining 67 patients were reached at both time points.

As shown in Table 8, 38 (51%) of the patients were female and 36 (49%) were male. The median age was 60 (49,66) years old. Race breakdown is as follows: 53 (76%) White, 13 (19%) African American, 3 (4.3%) Hispanic, one (1.4%) Asian, and 4 unknown (race not provided in their charts). The median BMI was 33 (30,39), with 4 patients' BMI not provided in their charts. Four (5.4%) underwent a caudal ESI, 15 (20%) underwent an ILESI, and 55 (74%) underwent a TFESI. 45 (61%) of patients had a one-level injection, and 29 (39%) had a 2-level injection. 34 (46%) of patients had a psychiatric history: 18 (53%) had an anxiety disorder, 25 (74%) had a depressive disorder, 11 (32%) had both, and 2 (5.9%) had a different type of psychiatric condition.

Our results showed that majority of the patients (> 98%) did not experience any side effects. However, in those patients who did, they generally experienced more symptoms at day one as compared to week one (Table 1). Patients with a psychiatric history experienced symptoms at a higher frequency at day one and week one than patients without a psychiatric history (Table 2). Men, those of Hispanic origin, ILESI, and more levels injected were associated with increased symptoms (Table 7). Women experienced more symptoms at day one, with a decrease in total symptoms by week one. Men experienced more symptoms at week one, with an increase in total symptoms from day one to week one (Table 3). Those who underwent ILESI experienced more symptoms than those who had a TFESI at day one and week one (Tables 4 and 5). Those with a 2-level injection experienced more symptoms by week one than those with a one-level injection (Table 6).

When comparing overall symptoms, regardless of psychiatric history, there was a significant decrease in the number of patients experiencing restlessness from day one (n = 27, 39%) to week one (n = 16, 24%) after an ESI ($P < 0.05$) (Table 1). No other significant changes were noted in the other symptoms between the 2 time points. Table 2 compares the number of patients with and without a psychiatric history who experienced symptoms at one day and one week after their ESIs. There were significantly ($P < 0.05$) more patients with a psychiatric history who experienced restlessness and irritability at day one than those without a psychiatric history. Seventeen (55%) patients with a psychiatric history and 10 (26%) patients without a psychiatric history experienced restlessness at day one (95% CI -54%, -3.2%, $P = 0.03$). Nine (29%) patients with a psychiatric history and 3 (7.9%) patients without a psychiatric history experienced irritability at day one (95% CI -42%, -0.08%, $P = 0.047$). By week one, there was no significant difference between patients with or without a psychiatric history in experiencing restlessness or irritability. The number of patients experiencing restlessness (n = 10, 33%) and irritability (n = 6, 20%) with a psychiatric history decreased

Table 1. *Number of total patients experiencing neuropsychiatric symptoms at day one and week one, regardless of psychiatric history.*

Characteristic	Day one, n = 69[1]	Week one, n = 68[1]	*P* value[2]	q value[3]
Sad Mood	1 (1.4%)	6 (8.8%)	0.062	0.2
Increased Energy	17 (25%)	10 (15%)	0.14	0.3
Restlessness	27 (39%)	16 (24%)	0.049	0.2
Irritability	12 (17%)	11 (16%)	0.8	> 0.9
Decreased Concentration	6 (8.7%)	5 (7.4%)	0.8	> 0.9
Anxiety	6 (8.7%)	8 (12%)	0.6	0.8
Aggressive behavior/anger	4 (5.8%)	4 (5.9%)	> 0.9	> 0.9
Poor Sleep	27 (39%)	17 (25%)	0.077	0.2
Total symptoms	1.45 (1.69)	1.13 (1.55)	0.2	0.3

[1]n (%); Mean (SD)
[2]Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test
[3]False discovery rate correction for multiple testing

Table 2. *Comparison of neuropsychiatric symptoms between patients with and without a psychiatric history at day one and week one after an ESI.*

	Day1, N = 74						Week1, N = 74					
Characteristic	**No psychiatric history, n =40[1]**	**Psychiatric history, n = 34[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**	**No psychiatric history, n = 40[1]**	**Psychiatric history, n = 34[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**
Sad Mood	0 (0%)	1 (3.2%)	-3.2%	-12%, 5.9%	> 0.9	> 0.9	2 (5.3%)	4 (13%)	-8.1%	-25%, 9.0%	0.5	> 0.9
NA	2	3					2	4				
Increased Energy	13 (34%)	4 (13%)	21%	-0.77%, 43%	0.078	0.2	6 (16%)	4 (13%)	2.5%	-17%, 22%	> 0.9	>0.9
NA	2	3					2	4				
Restlessness	10 (26%)	17 (55%)	-29%	-54%, -3.2%	0.030	0.2	6 (16%)	10 (33%)	-18%	-41%, 5.9%	0.2	> 0.9
NA	2	3					2	4				
Irritability	3 (7.9%)	9 (29%)	-21%	-42%, -0.08%	0.047	0.2	5 (13%)	6 (20%)	-6.8%	-28%, 14%	0.7	> 0.9
NA	2	3					2	4				
Decreased Concentration	3 (7.9%)	3 (9.7%)	-1.8%	-17%, 13%	> 0.9	>0.9	3 (7.9%)	2 (6.7%)	1.2%	-12%, 15%	> 0.9	> 0.9
NA	2	3					2	4				
Anxiety	2 (5.3%)	4 (13%)	-7.6%	-24%, 9.1%	0.5	0.7	3 (7.9%)	5 (17%)	-8.8%	-28%, 10%	0.5	>0.9
NA	2	3					2	4				
Aggressive behavior/anger	2 (5.3%)	2 (6.5%)	-1.2%	-14%, 11%	> 0.9	>0.9	2 (5.3%)	2 (6.7%)	-1.4%	-14%, 11%	>0.9	>0.9
NA	2	3					2	4				
Poor sleep	12 (32%)	15 (48%)	-17%	-43%, 9.1%	0.2	0.4	9 (24%)	8 (27%)	-3.0%	-27%, 21%	> 0.9	> 0.9
NA	2	3					2	4				
Total symptoms	1.13 (1.45)	1.62 (1.89)	-0.49	-1.3, 0.30	0.2	0.4	0.90 (1.53)	1.21 (1.51)	-0.31	-1.0, 0.40	0.4	> 0.9

[1]n (%); Mean (SD)
[2]Two sample test for equality of proportions; Welch Two Sample t-test
[3]CI = Confidence Interval
[4]False discovery rate correction for multiple testing

by week one. Those without a psychiatric history experienced less restlessness (n = 6, 16%) and more irritability (n = 5, 13%) by week one. There was no significant difference in total symptoms between those with and without a psychiatric history at day one or week one. More patients with a psychiatric history experienced each symptom than those without at each time point.

Table 7 shows the factors associated with a higher likelihood for symptoms at day one and week one. At day one, Hispanic race is associated with more symptoms, with an incidence rate ratio (IRR) of 3.47 (95% CI 1.71, 7.04, $P < 0.001$). At week one, male gender (IRR 2.29, 95% CI 1.37, 3.83, $P = 0.002$), Hispanic race (IRR 2.33, 95% CI 1.07, 5.09, $P = 0.034$), ILESI (IRR 7.75, 95% CI 1.03, 58.6, $P = 0.047$), and the number of levels injected (IRR 2.14, 95% CI 1.13, 4.06, $P = 0.019$) were, all together, significantly associated to more total symptoms.

Each significant characteristic in Table 7 was assessed individually. The only characteristic not included is Hispanic race since there were only 3 patients in that category, with one of them likely an outlier who experienced most symptoms, making the results we found likely skewed. Table 3 shows that women experienced a significant decrease ($P = 0.021$) in restlessness from day one (n = 18, 49%) to week one (n = 7, 20%). Women also ex-

Table 3. *Change in number of patients experiencing neuropsychiatric symptoms from day one to week one after ESI in men and women.*

	F, n = 76						M, n = 72					
Characteristic	**Day one, n = 38[1]**	**Week one, n = 38[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**	**Day one, n = 36[1]**	**Week one, n = 36[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**
Sad Mood	0 (0%)	2 (5.7%)	-5.7%	-16%, 4.8%	0.4	> 0.9	1 (3.1%)	4 (12%)	-9.0%	-25%, 6.7%	0.4	> 0.9
NA	1	3					4	3				
Increased Energy	7 (19%)	5 (14%)	4.6%	-15%, 25%	0.8	> 0.9	10 (31%)	5 (15%)	16%	-7.2%, 39%	0.2	> 0.9
NA	1	3					4	3				
Restlessness	18 (49%)	7 (20%)	29%	5.0%, 52%	0.021	0.10	9 (28%)	9 (27%)	0.85%	-22%, 23%	> 0.9	> 0.9
NA	1	3					4	3				
Irritability	8 (22%)	5 (14%)	7.3%	-13%, 28%	0.6	> 0.9	4 (12%)	6 (18%)	-5.7%	-26%, 15%	0.8	> 0.9
NA	1	3					4	3				
Decreased Concentration	3 (8.1%)	1 (2.9%)	5.3%	-7.9%, 18%	0.6	> 0.9	3 (9.4%)	4 (12%)	-2.7%	-21%, 15%	>0.9	> 0.9
NA	1	3					4	3				
Anxiety	4 (11%)	2 (5.7%)	5.1%	-10%, 20%	0.7	> 0.9	2 (6.2%)	6 (18%)	-12%	-31%, 6.8%	0.3	> 0.9
NA	1	3					4	3				
Aggressive behavior/anger	1 (2.7%)	1 (2.9%)	-0.15%	-7.9%, 7.6%	>0 .9	> 0.9	3 (9.4%)	3 (9.1%)	0.28%	-14%, 15%	>0.9	> 0.9
NA	1	3					4	3				
Poor Sleep	14 (38%)	6 (17%)	21%	-2.1%, 43%	0.090	0.3	13 (41%)	11 (33%)	7.3%	-19%, 34%	0.7	> 0.9
NA	1	3					4	3				
Total Symptoms	1.45 (1.55)	0.76 (1.08)	0.68	0.18, 1.2	0.010	0.086	1.25 (1.81)	1.33 (1.85)	-0.08	-0.67, 0.50	0.8	> 0.9

[1]n (%); Mean (SD)
[2]Two sample test for equality of proportions; Paired t-test
[3]CI = Confidence Interval
[4]False discovery rate correction for multiple testing

Table 4. *Difference between number of patients experiencing neuropsychiatric symptoms after a TFESI and LESI at day one and week one.*

	Day one, n = 70						Week one, N = 70					
Characteristic	**TFESI, n = 55[1]**	**LESI, n = 15[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**	**TFESI, n = 55[1]**	**LESI, n = 15[1]**	**Difference[5]**	**95% CI[3,5]**	***P* value[5]**	**q value[4]**
Sad Mood	1 (2.0%)	0 (0%)	2.0%	-3.9%, 7.9%	> 0.9	> 0.9	5 (10%)	1 (7.1%)	2.9%	-16%, 22%	> 0.9	> 0.9
NA	5	0					5	1				
Increased Energy	13 (26%)	3 (20%)	6.0%	-22%, 34%	0.9	> 0.9	8 (16%)	2 (14%)	1.7%	-21%, 24%	> 0.9	> 0.9
NA	5	0					5	1				
Restlessness	20 (40%)	6 (40%)	0.00%	-28%, 28%	> 0.9	> 0.9	9 (18%)	7 (50%)	-32%	-65%, 0.84%	0.036	0.3
NA	5	0					5	1				
Irritability	8 (16%)	3 (20%)	-4.0%	-31%, 23%	> 0.9	>0.9	7 (14%)	4 (29%)	-15%	-45%, 16%	0.4	0.8
NA	5	0					5	1				
Decreased Concentration	4 (8.0%)	2 (13%)	-5.3%	-28%, 18%	> 0.9	>0.9	4 (8.0%)	1 (7.1%)	0.86%	-15%, 17%	> 0.9	> 0.9
NA	5	0					5	1				
Anxiety	3 (6.0%)	2 (13%)	-7.3%	-30%, 15%	0.7	>0.9	6 (12%)	1 (7.1%)	4.9%	-16%, 26%	> 0.9	> 0.9
NA	5	0					5	1				
Aggressive behavior/anger	2 (4.0%)	1 (6.7%)	-2.7%	-19%, 14%	> 0.9	>0.9	2 (4.0%)	2 (14%)	-10%	-34%, 13%	0.4	0.8
NA	5	0					5	1				
Poor Sleep	19 (38%)	7 (47%)	-8.7%	-42%, 24%	0.8	>0.9	11 (22%)	6 (43%)	-21%	-54%, 12%	0.2	0.7
NA	5	0					5	1				
Total Symptoms	1.27 (1.62)	1.60 (1.59)	-0.33	-1.3, 0.64	0.5	>0.9	0.95 (1.43)	1.60 (1.88)	-0.65	-1.8, 0.44	0.2	0.7

[1]n (%); Mean (SD)
[2]Two sample test for equality of proportions; 2-sample test for equality of proportions without continuity correction; Welch Two Sample t-test
[3]CI = Confidence Interval
[4]False discovery rate correction for multiple testing
[5]Two sample test for equality of proportions; Welch Two Sample t-test

perienced a significant decrease in total symptoms (*P* = 0.01) from day one (1.45 symptoms on average (SD = 1.55)) to week one (0.76 symptoms on average (SD = 1.08)).

Table 4 compares the number of patients experiencing each symptom after a TFESI and ILESI at day one and week one. At week one, there was a significantly higher (*P* = 0.036) percentage of patients experiencing restlessness after receiving an ILESI (n = 7, 50%) than a TFESI (n = 9, 18%). When comparing the change in number of patients experiencing each symptom at day one and week one (Table 5), a significant decrease (*P* = 0.028) in restlessness was noted in patients who underwent a TFESI from day one (n = 20, 40%) to week one (n = 9, 18%).

Table 6 compares the change in number of patients experiencing neuropsychiatric symptoms at day one and week one after a one-level injection and a 2-level injection. Those with a one-level injection had a significant decrease (*P* = 0.04) in total symptoms from day one (1.36 symptoms on average (SD = 1.57)) to week one (0.87 symptoms on average (SD = 1.39)).

Discussion

The purpose of this study was to assess the frequency of neuropsychi-

atric symptoms at one day and one week after an ESI and factors that increase the likelihood of neuropsychiatric symptomatology. The breakdown of the factors examined is shown in Table 8.

Restlessness and irritability are some of the most common systemic side effects experienced after an ESI (25). Other systemic symptoms commonly experienced after an ESI include euphoria, mania, depression, and insomnia (25). While there is minimal literature on neuropsychiatric symptoms after an ESI, some reports have been published on these symptoms after oral corticosteroids. One study defined 4 categories of psychiatric symptoms after an ESI in those with a psychiatric history. Sixty percent of their patients fell into grades 1 and 2, experiencing increased energy, restlessness, insomnia, and flight of ideas; 30% of their patients fell into grade 3, experiencing mood swings, lethargy, hopelessness, and restlessness. The remaining 10% in grade 4 experienced extreme fluctuations in mood, delusions, and hallucinations (26). Another study found that the most common steroid-induced psychiatric disorders included depression (35%), mania (31%), psychosis (14%), delirium (13%), and mixed states (6%) (27). To our knowledge, no studies

Table 5. *Comparing change in number of patients experiencing neuropsychiatric symptoms from day one to week one in those after a TFESI and LESI.*

	TFESI, n = 110						LESI, n = 30					
Characteristic	**Day one, n = 55[1]**	**Week one, n = 55[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**	**Day one, n = 15[1]**	**Week one, n = 15[1]**	**Difference[5]**	**95% CI[3,5]**	***P* value[5]**	**q value[4]**
Sad Mood	1 (2.0%)	5 (10%)	-8.0%	-19%, 3.2%	0.2	0.5	0 (0%)	1 (7.1%)	-7.1%	-28%, 13%	> 0.9	> 0.9
NA	5	5					0	1				
Increased Energy	13 (26%)	8 (16%)	10%	-7.8%, 28%	0.3	0.6	3 (20%)	2 (14%)	5.7%	-27%, 39%	> 0.9	> 0.9
NA	5	5					0	1				
Restlessness	20 (40%)	9 (18%)	22%	2.7%, 41%	0.028	0.2	6 (40%)	7 (50%)	-10%	-53%, 33%	0.9	> 0.9
NA	5	5					0	1				
Irritability	8 (16%)	7 (14%)	2.0%	-14%, 18%	> 0.9	> 0.9	3 (20%)	4 (29%)	-8.6%	-47%, 29%	> 0.9	> 0.9
NA	5	5					0	1				
Decreased Concentration	4 (8.0%)	4 (8.0%)	0.00%	-11%, 11%	> 0.9	> 0.9	2 (13%)	1 (7.1%)	6.2%	-22%, 34%	> 0.9	> 0.9
NA	5	5					0	1				
Anxiety	3 (6.0%)	6 (12%)	-6.0%	-19%, 7.2%	0.5	0.7	2 (13%)	1 (7.1%)	6.2%	-22%, 34%	> 0.9	> 0.9
NA	5	5					0	1				
Aggressive behavior/anger	2 (4.0%)	2 (4.0%)	0.00%	-7.7%, 7.7%	> 0.9	> 0.9	1 (6.7%)	2 (14%)	-7.6%	-37%, 22%	> 0.9	> 0.9
NA	5	5					0	1				
Poor Sleep	19 (38%)	11 (22%)	16%	-3.7%, 36%	0.13	0.4	7 (47%)	6 (43%)	3.8%	-36%, 44%	> 0.9	> 0.9
NA	5	5					0	1				
Total Symptoms	1.27 (1.62)	0.95 (1.43)	0.33	-0.10, 0.75	0.13	0.4	1.60 (1.59)	1.60 (1.88)	0.00	-1.0, 1.0	> 0.9	> 0.9

[1]n (%); Mean (SD)
[2]Two sample test for equality of proportions; 2-sample test for equality of proportions without continuity correction; Paired t-test
[3]CI = Confidence Interval
[4]False discovery rate correction for multiple testing
[5]Two sample test for equality of proportions; Paired t-test

Table 6. *Comparing change in number of patients experiencing neuropsychiatric symptoms at day one and week one after a one-level injection and a two-level injection.*

	1, n = 90						2, n = 58					
Characteristic	**Day one, n = 45[1]**	**Week one, n = 45[1]**	**Difference[2]**	**95% CI[2,3]**	***P* value[2]**	**q value[4]**	**Day one, n = 29[1]**	**Week one, n = 29[1]**	**Difference[5]**	**95% CI[3,5]**	***P* value[5]**	**q value[4]**
Sad Mood	0 (0%)	1 (2.4%)	-2.4%	-9.6%, 4.7%	> 0.9	> 0.9	1 (3.6%)	5 (19%)	-15%	-35%, 4.9%	0.2	> 0.9
NA	4	4					1	2				
Increased Energy	11 (27%)	6 (15%)	12%	-7.6%, 32%	0.3	0.6	6 (21%)	4 (15%)	6.6%	-17%, 31%	0.8	> 0.9
NA	4	4					1	2				
Restlessness	17 (41%)	9 (22%)	20%	-2.6%, 42%	0.10	0.4	10 (36%)	7 (26%)	9.8%	-18%, 38%	0.6	> 0.9
NA	4	4					1	2				
Irritability	7 (17%)	6 (15%)	2.4%	-16%, 21%	> 0.9	> 0.9	5 (18%)	5 (19%)	-0.66%	-22%, 20%	>0.9	> 0.9
NA	4	4					1	2				
Decreased Concentration	4 (9.8%)	1 (2.4%)	7.3%	-5.4%, 20%	0.4	0.6	2 (7.1%)	4 (15%)	-7.7%	-28%, 12%	0.6	> 0.9
NA	4	4					1	2				
Anxiety	3 (7.3%)	4 (9.8%)	-2.4%	-17%, 12%	> 0.9	> 0.9	3 (11%)	4 (15%)	-4.1%	-25%, 17%	>0.9	> 0.9
NA	4	4					1	2				
Aggressive Behavior/Anger	3 (7.3%)	3 (7.3%)	0.00%	-11%, 11%	> 0.9	> 0.9	1 (3.6%)	1 (3.7%)	-0.13%	-10%, 9.9%	>0.9	> 0.9
NA	4	4					1	2				
Poor Sleep	16 (39%)	9 (22%)	17%	-4.9%, 39%	0.2	0.5	11 (39%)	8 (30%)	9.7%	-19%, 38%	0.6	> 0.9
NA	4	4					1	2				
Total Symptoms	1.36 (1.57)	0.87 (1.39)	0.49	0.02, 1.0	0.040	0.4	1.34 (1.86)	1.31 (1.69)	0.03	-0.67, 0.74	> 0.9	> 0.9

[1]n (%); Mean (SD)
[2]Two sample test for equality of proportions; 2-sample test for equality of proportions without continuity correction; Paired t-test
[3]CI = Confidence Interval
[4]False discovery rate correction for multiple testing
[5]Two sample test for equality of proportions; Paired t-test

exist in the literature that assess these symptoms after an ESI based on psychiatric history.

Similar to these prior studies, restlessness and poor sleep were the most common symptoms at day one (39% each) and week one (24% and 25%, respectively) in this study (Table 1). A significant decrease is noted in restlessness from day one to week one. These results suggest that restlessness is common but also likely to be temporary. Increased energy and irritability were also commonly experienced by patients at day one (25% and 17% , respectively) and week one (15% and 16%, respectively), which is consistent with reported symptoms after ESIs and oral corticosteroids (Table 1) (18-27). More patients with a psychiatric history may experience restlessness and irritability on the first day after an ESI than those without (Table 2). Additionally, more patients with a psychiatric history continue to experience restlessness (33%) and irritability (20%) at week one than those without a psychiatric history (16% and 13%, respectively). These results potentially indicate that those with a psychiatric history may experience restlessness and irritability immediately after an ESI more often than those without a psychiatric history.

No other significant changes were noted in to-

Table 7. *Incidence rate ratios and confidence intervals evaluating likelihood of experiencing neuropsychiatric symptoms based on gender, age, BMI, race, psychiatric history, procedure type, and number of levels injected at day one and week one after an ESI.*

Characteristic at day one	IRR[1]	95% CI[1]	*P* value
Gender			
F	—	—	
M	1.09	0.70, 1.70	0.7
Age	0.99	0.97, 1.01	0.3
BMI	1.00	0.97, 1.02	0.8
Race			
White	—	—	
African American	1.37	0.79, 2.37	0.3
Hispanic	3.47	1.71, 7.04	< 0.001
Asian	0.00	0.00, Inf	> 0.9
Psychiatric History	1.09	0.69, 1.73	0.7
Procedure			
Caudal	—	—	
LESI	0.82	0.32, 2.11	0.7
TFESI	0.82	0.33, 2.02	0.7
Number of Levels	1.05	0.63, 1.75	0.8

[1] IRR = Incidence Rate Ratio, CI = Confidence Interval

Characteristic at week one	IRR[1]	95% CI[1]	*P* value
Gender			
F	—	—	
M	2.29	1.37, 3.83	0.002
Age	1.00	0.98, 1.02	0.9
BMI	1.01	0.98, 1.04	0.4
Race			
White	—	—	
African American	1.46	0.79, 2.71	0.2
Hispanic	2.33	1.07, 5.09	0.034
Asian	0.00	0.00, Inf	> 0.9
Psychiatric history	1.40	0.84, 2.33	0.2
Procedure			
Caudal	—	—	
LESI	7.75	1.03, 58.6	0.047
TFESI	2.74	0.35, 21.4	0.3
Number of levels	2.14	1.13, 4.06	0.019

[1] IRR = Incidence Rate Ratio, CI = Confidence Interval

tal or individual symptoms between the 2 time points, regardless of psychiatric history. Some papers suggest that it may take several days for neuropsychiatric symptoms to develop and several weeks for them to dissipate after corticosteroids (18-27). Our results corroborate this since patients continue to experience most symptoms, regardless of psychiatric history, by week one. Both groups experienced a decrease in total average symptoms by week one. Those with a psychiatric history had more total symptoms at day one and week one (Table 2).

Table 8. *Patient demographics, including gender, age, race, BMI, psychiatric history, and procedure information.*

Characteristic	n = 74[1]
Gender	
F	38 (51%)
M	36 (49%)
Age	60 (49, 66)
Race	
White	53 (76%)
African American	13 (19%)
Hispanic	3 (4.3%)
Asian	1 (1.4%)
Unknown	4
BMI	33 (30, 39)
Unknown	4
Psychiatric History	34 (46%)
Procedure Type	
Caudal	4 (5.4%)
LESI	15 (20%)
TFESI	55 (74%)
Number of levels injected	
1	45 (61%)
2	29 (39%)
Psychiatric History	n = 34[1]
Anxiety Disorder	18 (53%)
Depressive Disorder	25 (74%)
Both	11 (32%)
Other	2 (5.9%)

[1]n (%)

Certain factors may influence patients experiencing neuropsychiatric symptoms at day one and week one after an ESI (Table 7). Hispanic race may be a factor in experiencing more symptoms at day one. Meanwhile, a combination of Hispanic race, male gender, ILESI performed, and more levels injected increased the likelihood of experiencing more symptoms. We assessed each of these individually to examine if any alone affectedaffected symptomatology. Results for race were not included as part of the results due to the data likely being skewed from one outlier, as mentioned earlier.

Women were more likely to have a significant decrease in experiencing restlessness and total symptoms than men (Table 3). Women experience a significant decline in restlessness from day one (49%) to week one (20%) (Table 3). In general, there is a decline in the number of women and a slight increase in the number of men experiencing most symptoms from day one to week one. Several studies suggest that women may be more likely to experience neuropsychiatric symptoms than men (13,27,28). These studies focus on oral steroidtherapy rather than ESIs. The results of our study suggest that women are more likely to experience restlessness and total symptoms at day one after an ESI than men—however, the number of men experiencing most symptoms increases by week one, with women recovering quicker. There is evidence for differences in the levels of neuroactive steroids in the nervous system between genders, which has led to gender differences in disease response to numerous neurological conditions (29). These findings may, in part, explain the gender difference in experiencing neuropsychiatric symptoms after steroid use in this study.

There was no significant difference between the number of patients experiencing any individual symptom after an ILESI or TFESI at day one or week (Table 4). Those who underwent an ILESI experienced more symptoms on average than those who had a TFESI at both time points. There was a statistically significant decline in the number of patients experiencing restlessness from day one to week one (Table 5). Total symptoms decreased from day one (1.27) to week one (0.95) after a TFESI but stayed the same after an ILESI between the 2 time points. The reasoning behind this is unclear since equal doses of dexamethasone (5 mg) were used in both procedures. McGrath et al (30) showed similar results to our study: patients who had an ILESI experienced more systemic side effects than those who had a TFESI. Triamcinolone was the steroid of choice, and equal volumes were used in both procedure types. There was no clear explanation for these findings.

There was a significant decrease in total symptoms from day one to week one in those who had a one-level injection (Table 6). However, no major changes were noted in total symptoms for those who had a 2-level injection, suggesting these patients had more difficulty with symptom recovery. These results are likely due to the increased dose of steroid in a 2-level injection. Two-level injections were only done in TFESIs and had twice the dose (10 mg) of dexamethasone than a one-level TFESI (5 mg). Prior studies have shown that corticosteroid neuropsychiatric side effects are thought to be dose-dependent. The Boston Collaborative Drug Surveillance Program showed a positive correlation between psychiatric symptoms and corticosteroid dose: 1.3% symptoms in patients receiving less than 40 mg/day prednisone, 4.6% symptoms in patients receiving 41 mg/day to 80 mg/day, and 18.4% symptoms in patients receiving more than 80 mg/day (31). Other studies demonstrated an increased marginal risk of experiencing psychiatric symptoms with a prednisone dose exceeding 40 mg/day (27, 32). 40 mg of prednisone is equipotent to 6 mg of dexamethasone (33), possibly explaining why those with a 2-level injection experienced more neuropsychiatric symptoms since their dexamethasone dose exceeded 6 mg.

To the best of our knowledge, there are no studies indicating a correlation between dexamethasone and neuropsychiatric symptoms. One case report described neuropsychiatric symptoms in a patient after a TFESI using 10 mg of dexamethasone (34). However, other case reports describe neuropsychiatric symptoms with triamcinolone and methylprednisolone after ESIs and intra-articular steroid injections (35-37). This suggests that neuropsychiatric symptoms are likely not dependent on choice of steroid, but rather on the dose used.

Limitations

Some limitations of our study include it being a single-center study design with a small sample size. Based on the method of patient recruitment, it was difficult to control the number of patients in each category, creating statistical imbalances. The primary endpoints assessed relied on subjective answers from patients regarding neuropsychiatric symptoms experienced. Additionally, our results indicate that many of the patients still experienced symptoms at week one. Since there was no follow-up after week one, it is difficult to know the full duration of symptoms for some of the patients. Lastly, we did not associate these symptoms with pain scores that patients had before and/or after their ESIs.

Conclusion

This study demonstrates that neuropsychiatric symptoms are rare overall after an ESI, though certain factors may influence patients experiencing these symptoms. Restlessness and irritability were more likely to occur one day after an ESI in those with a psychiatric history. Those who had a 2-level injection were more likely to keep experiencing most symptoms by week one, suggesting a possible correlation between corticosteroid dose and neuropsychiatric symptoms.

References

1. Hassan KZ, Sherman Al. Epidural Steroids. (Updated 2023 Jul 17). In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: www.ncbi.nlm.nih.gov/books/NBK537320/
2. Dower A, Davies MA, Ghahreman A. Pathologic basis of lumbar radicular pain. *World Neurosurg* 2019; 128:114-121.
3. Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. *J Bone Joint Surg Am* 2006; 88 Suppl 2:68-71.
4. Xu W, Ding W, Sheng H, Lu D, Xu X, Xu B. Dexamethasone suppresses radicular pain through targeting the L-PGDS/PI3K/Akt pathway in rats with lumbar disc herniation. *Pain Pract* 2021; 21:64-74.
5. Hasvik E, Haugen AJ, Grøvle L. Symptom descriptors and patterns in lumbar radicular pain caused by disc herniation: A 1-year longitudinal cohort study. *BMJ Open* 2022; 12:e065500.
6. Falvo E, Diviccaro S, Melcangi RC, Giatti S. Physiopathological role of neuroactive steroids in the peripheral nervous system. *Int J Mol Sci* 2020; 21:9000.
7. Melcangi RC, Giatti S, Garcia-Segura LM. Levels and actions of neuroactive steroids in the nervous system under physiological and pathological conditions: Sex-specific features. *Neurosci Biobehav Rev* 2016; 67:25-40.
8. Lloyd-Evans E, Waller-Evans H. Biosynthesis and signalling functions of central and peripheral nervous system neurosteroids in health and disease. *Essays Biochem* 2020; 64:591-606.
9. Poisson M, Pertuiset BF, Moguilewsky M, Magdelenat H, Martin PM. Les récepteurs de stéroides du sytème nerveux central. Implications en neurologie (Steroid receptors in the central nervous system. Implications in neurology). *Rev Neurol (Paris)* 1984; 140:233-248.
10. Rajagopalan A, Jinu KV, Sailesh KS, Mishra S, Reddy UK, Mukkadan JK. Understanding the links between vestibular and limbic systems regulating emotions. *J Nat Sci Biol Med* 2017; 8:11-15.
11. Markia B, Kovács ZI, Palkovits M. Projections from the vestibular nuclei to the hypothalamic paraventricular nucleus: morphological evidence for the existence of a vestibular stress pathway in the rat brain. *Brain Struct Funct* 2008; 213:239-245.
12. Doll A, Hölzel BK, Mulej Bratec S, et Al. Mindful attention to breath regulates emotions via increased amygdala-prefrontal cortex connectivity. *Neuroimage* 2016; 134:305-313.
13. Akid I, Nesbit S, Nanavati J, Bienvenu OJ, Smith TJ. Prevention of steroid-induced neuropsychiatric complications with neuroleptic drugs: A review. *Am J Hosp Palliat Care* 2022; 39:472-476.
14. Kazi SE, Hoque S. Acute psychosis following corticosteroid administration. *Cureus* 2021; 13:e18093.
15. Jasani R, Deacon JW, Sertich A. Corticosteroid-induced mania after previous tolerance of higher doses. *Cureus* 2021; 13:e17719.
16. Fischer M, Kim PY. Corticosteroid-induced psychosis after a single transforaminal epidural steroid injection. *WMJ* 2019; 118:91-94.
17. Kim BR, Lee JW, Lee E, Kang Y, Ahn JM, Kang HS. Intra-articular facet joint steroid injection-related adverse events encountered during 11,980 procedures. *Eur Radiol* 2020; 30:1507-1516.
18. Vangeison CT, Roys JP, Catalanotto MN, etc al. Medication-induced mood disorders following epidural steroid injections in patients with pain: A case series. *Clin Case Rep* 2023; 11:e7415.
19. Starkman MN. Neuropsychiatric findings in Cushing syndrome and exogenous glucocorticoid administration. *Endocrinol Metab Clin North Am.* 2013; 42:477-488.
20. Dorn LD, Burgess ES, Dubbert B, et al. Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. *Clin Endocrinol (Oxf)* 1995; 43:433-442.
21. Vangeison C, Roys J, Catalanotto M, et al. Medication-induced mood disorders following epidural steroid injections: A case series. Authorea 2022; 11:e7415.
22. Gable M, Depry D. Sustained corticosteroid- induced mania and psychosis despite cessation: A case study and brief literature review. *Int J Psychiatry Med* 2015; 50:398-404.
23. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics* 2012; 53:103-115.
24. Kusljic S, Manias E, Gogos A. Corticosteroid-induced psychiatric disturbances: It is time for pharmacists to take notice. *Res Social Adm Pharm* 2016; 12:355-360.
25. King W, Miller DC, Smith CC; Spine Intervention Society's Patient Safety Committee. Systemic effects of epidural corticosteroid injection. *Pain Med* 2018; 19:404-405.
26. Rome HP, Braceland FJ. The psychological response to ACTH, cortisone, hydrocortisone, and related steroid substances. *Am J Psychiatry* 1952; 108:641-651.
27. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *J Affect Disord* 1983; 5:319-332.
28. Jensen A, Castro AW, Ferretti MT, Martinkova J, Vasilevskaya A, Santuccione Chadha A, Tartaglia MC. Sex and gender differences in the neurological and neuropsychiatric symptoms of long COVID: A narrative review. *Ital J Gender-Specific Med* 2022; 8:18-28.
29. Giatti S, Diviccaro S, Serafini MM, et al. Sex differences in steroid levels and steroidogenesis in the nervous system: Physiopathological role. *Front Neuroendocrinol* 2020; 56:100804.
30. McGrath JM, Schaefer MP, Malkamaki DM. Incidence and characteristics of complications from epidural steroid injections. *Pain Med* 2011; 12:726-731.
31. Acute adverse reactions to prednisone in relation to dosage. *Clin Pharmacol Ther* 1972; 13:694-698.
32. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *Am J Psychiatry* 2012; 169:491-497.
33. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013; 9:30.
34. Fischer M, Kim PY. Corticosteroid-induced psychosis after a single transforaminal epidural steroid injection. *WMJ* 2019; 118:91-94.
35. Benyamin RM, Vallejo R, Kramer J, Rafeyan R. Corticosteroid induced psychosis in the pain management setting. *Pain Physician* 2008; 11:917-920.
36. Samala RV, Ciocon JO. Steroid-induced hallucination following intra-articular administration: A case report and brief review. *J Am Med Dir Assoc* 2011; 12:609-610.
37. Lally L, McCarthy G, Meehan K. Hyperactive delirium following administration of intra-articular corticosteroid. *BMJ Case Rep* 2017; 2017:bcr2016217483.