MAYO CLINIC

REVIEW

Psychiatric Adverse Effects of Pediatric Corticosteroid Use

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Abstract

Corticosteroids, highly effective drugs for myriad disease states, have considerable neuropsychiatric adverse effects that can manifest in cognitive disorders, behavioral changes, and frank psychiatric disease. Recent reviews have summarized these effects in adults, but a comprehensive review on corticosteroid effects in children has not been published since 2005. Here, we systematically review articles published since then that, we find, naturally divide into 3 main areas: (1) chronic effects of acute prenatal and neonatal exposure associated with prematurity and congenital conditions; (2) immediate behavioral effects of acute exposure via oncological protocols; and (3) acute behavioral effects of sporadic use in children and adolescents with other conditions. PsycInfo, MEDLINE, Embase, and Scopus were queried to identify articles reporting psychiatric adverse effects of corticosteroids in pediatric patients. Search terms included *corticosteroids, adrenal cortex hormones, steroid psychosis, substance-induced psychoses, glucocorticoids, dexamethasone, hydrocortisone, prednisone, adverse effects, mood disorders, mental disorders, psychosis, psychotic, psychoses, side effect, chemically induced, emotions, affective symptoms, toxicity, behavior, behavioral symptoms, infant, child, adolescent, pediatric, paediatric, neonatal, children, teen*, and *teenager*. Following guidelines for systematic reviews from the Potsdam Consultation on Meta-Analysis, we have found it difficult to draw specific conclusions that are more than general impressions owing to the quality of the available studies. We find a mixed picture with neonates exposed to dexamethasone, with some articles reporting eventual deficits in neuropsychiatric functioning and others reporting no effect. In pediatric patients with acute lymphoblastic leukemia, corticosteroid use appears to correlate with negative psychiatric and behavioral effects. In children treated with corticosteroids for noncancer conditions, adverse effects have been observed both during treatment and after cessation, although the data from article to article are not consistent enough to establish dose relationships. By and large, inhaled corticosteroids are considered safe and free of severe neuropsychiatric effects. Although both antipsychotic medications and benzodiazepines have been used to treat corticosteroid-induced mania and psychosis, no unified management strategy has emerged. Large-scale standardized investigations are needed to clarify the psychiatric effect of corticosteroids on children in all these conditions. Meanwhile, there is general agreement that patients as well as caregivers should be warned of the potential for behavioral adverse effects when patients receive these drugs.

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The prescription of corticosteroids is ubiquitous in many disease states, ranging from allergic, renal, and respiratory disorders to inflammatory, malignant, and dermatologic conditions. Like the metaphorical double-edged sword, these drugs offer symptomatic relief and halt disease progress while inducing troublesome adverse effects. Corticosteroids reduce inflammation by entering cells and binding as agonists to cytosolic glucocorticoid receptors. Once bound, these receptors transactivate the β-2 adrenergic receptor gene, the lipocortin-1 gene, the IL-10 gene, and the NF-κB inhibitor gene to produce anti-inflammatory effects.[1] Many other genes are transactivated as well, and these are thought to produce the unwanted adverse effects.

Over the 2-decade span of childhood, corticosteroids are first used neonatally in cases of prematurity, low birth weight, bronchopulmonary dysplasia (BPD), heart defects, and suspected congenital adrenal hyperplasia. Later, indications for systemic corticosteroids include malignant diseases such as acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma (HL); autoimmune conditions such as Crohn disease, multiple sclerosis, and immune thrombocytopenic purpura; and oral surgical procedures (prevention of postoperative edema), Duchenne muscular dystrophy, nephrotic syndrome, and

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ARTICLE HIGHLIGHTS

- Whether neonatal exposure to dexamethasone is associated with chronic adverse psychiatric effects is unclear.
- Corticosteroid use in acute lymphoblastic leukemia correlates with negative psychiatric and behavioral effects.
- Acute corticosteroid exposure may produce adverse psychiatric events at any point during treatment and even after cessation.
- Dose-behavioral dyscontrol relationships cannot be calculated owing to the paucity of large comparable studies.
- Inhaled corticosteroids appear generally safe and free of severe neuropsychiatric adverse effects.
- Management strategies for psychiatric adverse reactions vary, but antipsychotic medications and/or benzodiazepines may be effective.
- Educating patients and parents will improve surveillance and decrease the likelihood of adverse events going unrecognized.

asthma. Among the extensive potential adverse effects of chronic use are osteoporosis, avascular necrosis of bones, Cushingoid body habitus, acne, hypertension, gastritis, amenorrhea, glaucoma, diabetes mellitus, and immunosuppression.[2]

These somatic adverse effects notwithstanding, this article focuses on the neuropsychiatric adverse effects that may accompany corticosteroid use. In the acute setting, these effects may include mood elevation ranging from mild euphoria to full-blown mania, insomnia, depression, and frank psychosis. With regard to psychosis, corticosteroid medications may mimic stress and alter the hypothalamic-pituitary-adrenal axis, producing a state of heightened psychosis risk as described in the stress-vulnerability model of schizophrenia.[3,4]

The neuropsychiatric adverse effect profile of corticosteroids has been relatively well characterized and reviewed in adults, but the pediatric literature is less definitive.[5] In adults, the most common adverse effects of short-term corticosteroid therapy are euphoria and hypomania, and symptoms tend to arise early in the treatment cycle. In contrast, long-term therapy tends to induce depressive symptoms. Dosage correlates with the incidence of adverse effects in adults, but dose is not related to the severity of adverse effects.[5]

As for pediatric data, in a 2005 article, the last to summarize the psychiatric adverse effects of corticosteroid use in children, Stuart et al[6] stated the need for better studies to calculate incidence and prevalence. They suggested that it is difficult to establish a dose-response effect owing to the complex interplay of genetics, individual susceptibility, and environmental stressors.[6] From the available evidence, they were unable to delineate clear risk factors, although some studies suggested that oral dexamethasone (DEX) may cause more adverse effects than do other corticosteroids.[6] Of note, the article by Stuart et al considers cancer-associated corticosteroid use and noncancer applications as one category and it does not discuss neonatal exposure. This article expands the literature by reviewing the pediatric studies published since 2005, by delineating oncological protocols from other corticosteroid regimens, and by including articles covering prenatal and neonatal corticosteroid exposure. We focus on these areas because most of the articles written since 2005 fall into these categories.

METHODS

With the goal of performing a systematic review, an experienced research librarian conducted a literature search in June 2013 using PsycInfo, MEDLINE, Embase, and Scopus to identify English language journal articles reporting psychiatric adverse effects of corticosteroids in pediatric patients aged 0 to 18 years. The search terms *corticosteroids*, *psychiatric effects*, and *pediatric populations* were adjusted to each database to include database-appropriate subject headings, pharmacological actions, or thesaurus terms, and these terms were supplemented with keyword searches. Search terms included *corticosteroids, adrenal cortex hormones, steroid psychosis, substance-induced psychoses, glucocorticoids, dexamethasone, hydrocortisone, prednisone, adverse effects, mood disorders, mental disorders, psychosis, psychotic, psychoses, side effect, chemically induced, emotions, affective symptoms, toxicity, behavior, behavioral symptoms, infant, child, adolescent, pediatric, paediatric, neonatal, children, teen*, and *teenager*. Bibliographies from key articles were also searched, and Scopus was used to identify articles citing key articles.

Owing to the relative scarcity of large-scale standardized studies, all types of research reports with any level of relevant data were

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