# Does a steroid dementia syndrome really exist? A brief narrative review of what the literature highlights about the relationship between glucocorticoids and cognition

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## Abstract

Glucocorticoids (GCs) may cause cognitive impairment through complex pathways involving specific receptors. In the human brain, hippocampal CA1 neurons exhibit the highest level of of GCs receptors. Even the elderly expressed these receptors.

The purpose of this brief review is to concentrate on the relationship between GCs and cognition in order to discuss the effects of the so-called steroid dementia in routine clinical practice.

## Introduction

Since the 1950s, when synthetic glucocorticoids (GCs) became available in the physician's pharmacological arsenal, it has been reported that GCs may cause cognitive impairment. In particular, several case reports focused on the effects of acute GCs treatment, such as difficulties in concentration, declarative or working memory, abstraction, and analysis. These manifestations quickly improve after GCs discontinuation. Occasionally, severe cognitive disturbances may persist for an extended period afterward.[1-3]

The aim of this brief narrative review is to focus on the relationship between GCs and cognition.

## A trip in three steps

In 1984, Varney *et al.* highlighted the possibility that reversible dementia could occur during treatment with GCs without psychotic manifestations. In particular, among 1500 patients, they found four who suffered from disturbances in verbal and non-verbal memory, mental speed and efficiency, attention and occupational performances resembling early Alzheimer's disease. GCs discontinuation resulted in the disappearance of such manifestations. There were no psychotic features.[4] The study of Varney *et al.* deserves attention because psychotic manifestations are relatively common in patients using GCs: their incidence rate is estimated to be 15.7 per 100 people using GCs/year; on the contrary, the prevalence of the so-called steroid dementia syndrome is around 1%.

In 2004 and 2007, Wolkowitz *et al.* published a case-series of patients who developed significant cognitive impairment during treatment with GCs. In these patients, the cognitive impairment persisted after GCs discontinuation. The authors proposed the term steroid dementia syndrome as the paradigm of non-reversible dementia. The authors hypothesized that the persistence of cognitive manifestations was a consequence of steroid neurotoxicity.[5,6]

More recently, Ikeda *et al*. reported two elderly patients who suffered from dementia following treatment with GCs. Contrary to earlier descriptions present in published literature, a detailed diagnosis of exclusion of primitive dementias was possible. In particular, brain magnetic resonance imaging (b-MRI) and cerebral blood flow single-photon emission computed tomography (SPECT) showed no degenerative site-specific findings. The authors documented partial recovery during a two-year follow-up.[7]

## Glucocorticoids and cognition: the anatomo-physiological bases

In the human brain, hippocampal CA1 neurons have the highest level of expression of GCs receptors.[8,9] These receptors are well-expressed even in the elderly.[10,11] Once activated, these receptors bind to hormone response elements in the DNA and regulate the transcription of target genes. In particular, cortisol exerts its effects on cognition through two types of receptors: type I [Mineralocorticoid Receptors (MRs)] and type II [Glucocorticoid Receptors (GRs)] with the MRs displaying 6 to 10 times higher affinity for GCs than GRs. These receptors are expressed differently throughout the brain. Indeed, the hippocampus, mainly implicated in episodic memory, expresses both MRs and GRs, whilst the prefrontal cortex, primarily responsible for executive functions, only expresses GRs. In the hippocampus, cortisol only activates the receptors with higher affinity, *i.e.*, MRs, leading to memory enhancement effects. When MRs are saturated, GRs are increasingly activated thus, leading to increasingly detrimental effects on the memory.[12-15] Glutamate accumulation in the hippocampus is an important pathway.[16]

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Key words: Steroid dementia syndrome; Cognitive impairment; Dementia; Glucocorticoids; Adverse drug reaction.

Contributions: CM, AC, conceptualization, formal analysis, data curation, original draft preparation; CM, AC, CR, GR, methodology, investigation, review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Ethical approval: Not needed.

Availability of data and materials: Data and materials are available by the authors.

Received for publication: 27 October 2022.
Revision received: 26 December 2022.
Accepted for publication: 3 March 2023.

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*Geriatric Care 2022; 8:10975*
*doi:10.4081/gc.2022.10975*

The effects of cortisol on executive functions are likely more linear. Indeed, since the prefrontal cortex region only expresses GRs, higher levels of cortisol may lead to worsened executive functions. On the other hand, reversible hippocampal atrophy can follow increased cortisol levels. It is worth to point out that the relationship between hippocampal volume and cortisol levels is bidirectional. Indeed, the hippocampus exerts an inhibitory effect on the hypothalamic-pituitary-adrenal (HPA) axis activity. Therefore, hippocampal atrophy might disinhibit the HPA axis leading to increased cortisol (Figure 1).

## From the pathophysiological bases to the clinical practice

From a theoretical viewpoint, steroid-induced dementia syndrome is possible. Given the current usage of GCs in the management of several conditions, there could be a significant number of overlooked diagnoses.[17,18] On the other hand, a rigorous methodological approach should be followed in routine clinical practice. We should always ask ourselves: how was dementia following treatment with GCs evaluated as an adverse drug reaction (ADR)? Is the link between GCs and dementia casual or coincidental? Only clinical judgment was used in all the listed case reports and case-series, without the use of scales or algorithms.[19,20] The ADR Probability Scale developed by Naranjo and colleagues in 1981 is commonly used in clinical practice to standardize causality assessments. This scale assesses the probability that an adverse event is related to drug therapy using a list of 10 weighted questions that examine some variables, such as temporal association with the drug administration and event occurrence; alternative causes, if any; drug levels; previous patient experience with the same drug.[21] Naranjo's scale has repeatedly documented a significant increase in inter- and intra-rater agreement compared with standard clinical examination alone.[19]

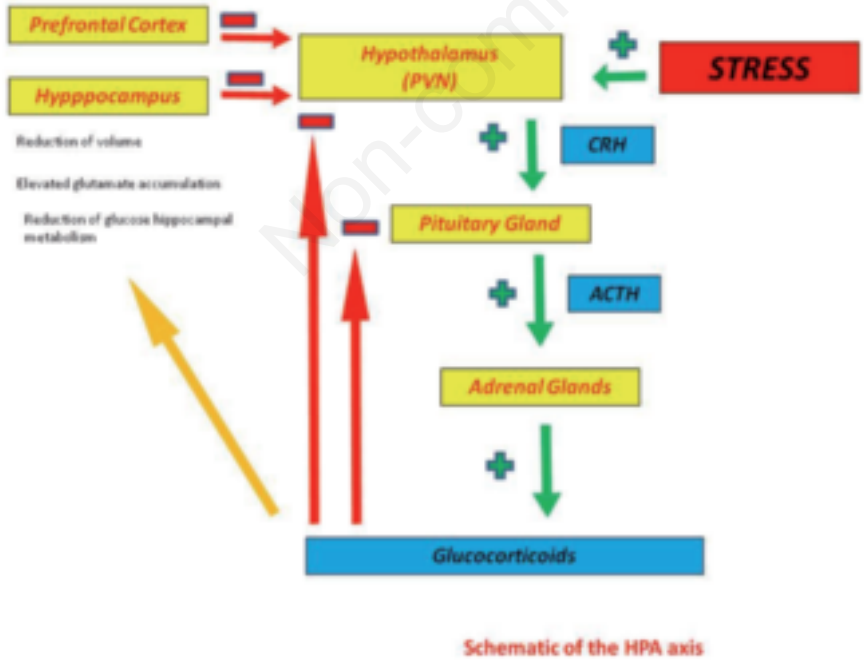
According to a correct causality assessment of the ADRs, alternative causes should always be excluded. For instance, some systemic diseases requiring treatment with GCs may cause cognitive impairment themselves. Primary Sjogren's syndrome (pSS) is a systemic autoimmune inflammatory disease not seldom diagnosed in elderly people;[22] pSS may cause cognitive impairment (from the so-called Sjögren's Syndrome fog to a frank dementia).[23] In some pSS patients, treatment with GCs is mandatory.[24]

Some drugs may cause or exacerbate cognitive impairment (Table 1). Long-acting benzodiazepines and anti-cholinergic drugs are the most common ones. Drugs may impair cognition indirectly via metabolic effects, such as hypoglycaemia, by alterations of immunological factors within the central nervous system, by actions that interfere with synaptic transmission, or by direct neurotoxicity (modified tau protein phosphorylation has been proposed as a factor capable of modifying the neuronal cytoskeleton).[25-28]

The lack of a validated scale or algorithm is a relevant methodological limit in approaching the relationship between GCs and dementia. Nonetheless, this relationship is not linear because a close temporal association is not always present and a reversible dementia is not the rule, contrary to psychiatric adverse events.

Steroid-induced psychosis is considered a type of substance-induced psychotic disorder. According to the Diagnostic and statistical manual of mental disorders, hallucinations and delusions shortly following a course of steroids are the main manifestations. Mania, depressive symptoms and anxiety can be present in some patients. In the most severe cases, patients may experience suicidal ideation or become aggressive and violent. These manifestations cannot be better explained by another condition or substance; they significantly interfere with the patient's ability to function, and cannot occur exclusively during the course of a delirium.[29] A differential diagnosis between drug-induced and primary psychoses should be assessed in all older patients with polypharmacy.[30,31]

The mean time of symptom onset is approximately 11.5 days. However, psychiatric manifestations may appear just 3-4 days after treatment initiation.[32-34] Dosage is




PVN, paraventricular nucleus; CRH, Corticotropin-releasing hormone; ACTH, Adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal.

**Figure 1. Schematic of the hypothalamic-pituitary-adrenal axis.**

**Table 1. Drugs that may cause or exacerbate cognitive impairment.**

| Drugs with effect also on cognitive functions |
|---|
| Alpha 1 blockers |
| Antihypertensives |
| Antiarrhythmic |
| Antibiotics |
| Anticonvulsants |
| Antihistamines |
| Antispasmodic |
| Antidepressants |
| Benzodiazepines |
| Bronchodilator |
| Opioids |
| Others |

the most relevant risk factor. For instance, according to the results of the Boston Collaborative Drug Surveillance Program (that evaluated 718 hospitalized patients on prednisone treatment) 4.6% of patients receiving doses >40 mg/day had psychiatric manifestations, and the incidence rose to 18.4% for patients receiving >80 mg/day.[35] On the other hand, the doses of GCs are unlikely to be related to the severity or duration of psychiatric manifestations.

## A final perspective

Our brief narrative review confirms that a steroid dementia syndrome exists. According to several experts' opinion, steroid dementia syndrome is an overlooked diagnosis. Therefore, the possibility that older patients may suffer from this condition should not be excluded *a priori* in our clinical practice.

However, its identification presents some difficulties. All the other conditions being able to favour cognitive impairment are to be identified and carefully assessed; b-MRI and SPECT may help.

Discontinuation of GCs should be favoured (when and if possible) in doubtful cases, at least as an *ex adiuvantibus* criterion. Patients should be followed over time, because steroid dementia syndrome is not always reversible.

Finally, psychiatric features following treatment with GCs could conceal a cognitive impairment. Therefore, a cognitive assessment is mandatory, once the psychiatric manifestations have disappeared or significantly improved.

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