
IN THE NAME OF GOD

Psychotoxicity of Immunomodulators In The Renal Patient

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Introduction

- Immunomodulating agents are commonly used in nephrology, both for **inflammatory renal disease** and **post-renal transplant** to suppress graft rejection.

- The **psychiatric side effects** of these agents are among the **most problematic side effects observed.**

- Accurate ascertainment of cases and precise psychiatric diagnosis are necessary for appropriate management.

Corticosteroids

- **Potent anti-inflammatory** drugs that are often a key element of treatment in a variety of renal pathologies, including nephritis associated with SLE, systemic vasculitis, and other forms of glomerulonephritis.

- Unfortunately, **psychiatric complications** related to corticosteroid use **are common and often overlooked**.

- Prevalence of **clinically significant psychiatric symptoms** is typically reported to be between **5 and 10% of patients** using corticosteroids.

Psychiatry Clin Neurosci. 2011;65(6):549–60.

Corticosteroids…

- **Possible side effects:** anxiety, delirium,insomnia, cognitive impairment, depressive & psychotic disorders.

- **Factors likely influence the nature and severity of a psychiatric reaction:**

  - Corticosteroid dosage
  - Chronicity of corticosteroid use
  - Nature of chronic inflammatory illness
  - Comorbid psychiatric illnesses
  - Psychosocial/environmental factors

Psychiatry Clin Neurosci. 2011;65(6):549–60
Psychonephrology 2022

Corticosteroids…

- **A three-tier grading system to characterize the severity of the most common reactions:**

***Grade* 1** : Represents a subclinical **mild euphoria**.

***Grade* 2** : A reversible acute or subacute **mania and/or depression**.

***Grade* 3**: Representing an unmasking of a bona fide **bipolar disorder with relapses** possible even without corticosteroid induction.

Psychiatry Clin Neurosci. 2011;65(6):549–60.

Clinical Pearl

- **Sychiatric side effects** of corticosteroids are **most often depression and/or mania.**
- **Less common** side effects include **delirium and psychosis**.

Int J Res Med Sci. 2020;8(6):2365
Psychonephrology 2022

Timing of Symptom Onset

- **Adverse psychiatric events generally have a rapid onset.**
- The majority of **psychiatric side effects** become evident within **the first 2 weeks of treatment**.
- Symptom onset **has been reported** as early as **day 1 of treatment, though it can occur as late as 2 months.**
- In cases of treatment with **corticosteroids with long half-lives** (e.g., dexamethasone, betamethasone), **psychiatric symptom onset** has been reported **even after discontinuation of the drug.**
- Studies suggest that corticosteroid-induced **mania and psychosis** have onset ***early*** in the course of treatment, whereas the risk of developing **depression** is associated with **more *prolonged or chronic exposure***.

Dose Dependence

- While psychiatric symptoms may develop at **any dose of corticosteroid**, a commonly cited **dose threshold is 40 mg per 24 hours of prednisone**, **above** which **psychiatric symptoms become far more likely** .

- Based on the **Boston Collaborative Drug Surveillance Project**, the incidence of psychiatric events is **1.3% at doses under 40 mg /24 hours**, **4.6% between 41 and 80 mg /24 hours**, and **18.4% for doses of 80 mg /24 hours and above.**

Int J Res Med Sci. 2020;8(6):2365.

Clinical Pearl

- **Clinical tools** are available for estimating probability of adverse drug reactions, including the **Naranjo Adverse Drug Reaction Probability Scale.**

- **Naranjo scores** of **9 or 10** indicate that an event was "**definitely**" an ADR; scores of **5-8** rate the likelihood as "**probable**"; scores of **1-4** are "**possible**"; and scores of **less than 1** are "**doubtful**."

Recommendation

- The risk of psychiatric reactions associated with corticosteroids is dose dependent.
- To minimize this risk, the corticosteroid dose should be kept below the prednisone equivalent of 40 mg per 24 hours.

ClinPharmacol Ther. 1981;30(2):239–45.

The Naranjo adverse drug reaction probability scale

To assess the adverse drug reaction,
please answer the following questionnaire and give the pertinent score

Questions	Yes	No	Do not know	Score
1. Are there previous *conclusive* reports on this reaction?	1	0	0	
2. Did the adverse event occur after the suspected drug was administered?	2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	2	-1	0	
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	2	0	
6. Did the reaction reappear when a placebo was given?	-1	1	0	
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	1	0	0	
10. Was the adverse event confirmed by any objective evidence?	1	0	0	

Risk Factors

- Paradoxically, current evidence suggests that a **history of previous psychiatric disorders does not appear to increase the risk of an adverse psychiatric event from corticosteroids**.

- Previous psychiatric history **is not an absolute contraindication** to corticosteroid therapy.

- Patients who have had a **previous adverse psychiatric reaction to corticosteroids do not appear to be at an increased risk for a second such reaction.**

Am J Psychiatry. 2014;171(10):1045–51
Psychonephrology 2022

Risk Factors…

- **Age** is another risk factor that has been reported.
- **Older adults** taking corticosteroids are at an **increased risk** of developing **delirium**.
- With the current evidence, there **does not appear to be a clear association** between **age** and the risk of developing **depressive, manic, or psychotic symptoms**.
- There is limited evidence suggesting that **females** are at a **slightly greater risk** of developing a **corticosteroid-induced psychosis** though this has not been consistently demonstrated.

Am J Psychiatry. 2014;171(10):1045–51
Psychonephrology 2022

Treatment of Corticosteroid-Induced Psychiatric Reactions

- **The preferred treatment is tapering and/or discontinuation of the offending corticosteroid.**

- Discontinuation of steroid therapy can be an effective strategy in treating an **acute adverse psychiatric reaction**; however, **full resolution** of symptoms **often takes several weeks.**

- In the case of corticosteroid-induced **psychosis**, about **50%** of cases resolve **within 4 days of corticosteroid discontinuation**, with **the most persistent cases resolving by 14 days.**

Treatment of Corticosteroid-Induced Psychiatric Reactions…

- Corticosteroid-induced **mania** is reported to persist for **up to 3 weeks**, whereas **depressive symptoms** are thought to resolve by **4 weeks** in the absence of psychopharmacological interventions.

- Resolution of corticosteroid-associated **delirium** typically occurs within **days of withdrawal of corticosteroids**.

Table 14.1 Pharmacological treatment of persistent corticosteroid-induced psychiatric symptoms [1, 2]

Symptoms	Primary strategy	Secondary strategy (persistent symptoms, taper not feasible)
Depression	Taper or discontinue corticosteroid	SSRI or mood stabilizer
Mania/ hypomania	Taper or discontinue corticosteroid	Mood stabilizer and/or second- or third-generation antipsychotic
Psychosis	Taper or discontinue corticosteroid	Second- or third-generation antipsychotic

Note: *SSRI* selective serotonin reuptake inhibitor

Cont…

Treatment

Lithium has received attention in the literature for use in the **prevention and treatment of psychiatric adverse events related to corticosteroids;** however, evidence for this is limited, and treatment with **lithium should be avoided in patients with renal disease.**

Mycophenolate

- **Mycophenolate** is used as a steroid-sparing agent to avoid the adverse effects of steroids, including the psychiatric side effects.
- **Mycophenolate** can cross the **blood-brain barrier** and **may** conferred **neuropsychiatric** complications.
- **Depressive and anxiety** symptoms are listed as **possible side effects**, though it seems to be an **uncommon** phenomenon(**less than 10% occurrence**).

Myfortic. Dorval (QC). [Updated 2016 Oct 06; Cited 2021 Feb 7]

Mycophenolate…

- **In one case report**, a 64-year-old woman was treated for **myasthenia gravis** with mycophenolate and developed **severe depression** 4 days after initiating the drug.

- **The severity of her symptoms led to a psychiatric inpatient admission**.

- **Her symptoms resolved within 2 days of discontinuation of mycophenolate but recurred within 2 days of a rechallenge**.


Depressive Disorder Associated with Mycophenolate Mofetil

February 2008 · Pharmacotherapy 28(1):136-9

DOI: 10.1592/phco.28.1.136

Source · PubMed

Heather Draper

Pharmacotherapy.2008;28(1):136–9

Mycophenolate…

Two case reports :

- **In the first:** An adolescent male reported severe anxiety, panic attacks, and inconsolable crying **upon** initiation of mycophenolate **500 mg twice daily**, which resolved upon days of discontinuation.

- **In the second :**A female patient taking mycophenolate **500 mg twice** daily developed significant irritability and anhedonia **after 8 weeks of mycophenolate initiation**. Her symptoms fully **resolved within 6 weeks of mycophenolate discontinuation**, and there was **no recurrence of symptoms within 4 years of subsequent follow-up**.

Mycophenolate Mofetil and mood changes in children with skin disorders. Pediatr Dermatol. 2016;33(3):e216–7.

Mycophenolate…

- Psychiatric side effects appear to be isolated to symptoms of **depression and anxiety.**

- There is **no readily available literature** describing case reports of **mania or psychosis attributable to therapy with mycophenolate**.

Tacrolimus

In nephrology, a recent randomized controlled trial demonstrated the efficacy of tacrolimus monotherapy as an alternative to corticosteroid therapy in the treatment of minimal change disease.


CJASN ePress. Published on January 17, 2020 as doi: 10.2215/CJN.06180519

Article

Randomized, Controlled Trial of Tacrolimus and Prednisolone Monotherapy for Adults with *De Novo* Minimal Change Disease

A Multicenter, Randomized, Controlled Trial

Clin J Am Soc Nephrol. 2020;15(2):209–18.

Tacrolimus…

- **About 40–60% of patients on tacrolimus** may develop **mild to moderate neurotoxic effects** including **headaches, paresthesias, tremors, and sleep disturbance .**

- More **severe neurotoxic effects** are found in **5–9%** of patients, including **confusion, lethargy, dysarthria, seizures, coma, and posterior reversible encephalopathy syndrome.**

- **Tacrolimus-induced encephalitis** can have a clinically variable presentation.

- **Catatonia and psychosis** have been described as **rare sequelae** of **tacrolimus therapy**, **even when blood levels are apparently therapeutic**.

- **Delirium risk, with older adults** being particularly **vulnerable.**

Gen Hosp Psychiatry. 2012;34(2):209–e209

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Tacrolimus-induced encephalopathy

- Tacrolimus-induced encephalopathy and peripheral neuropathy presenting with confusion and bilateral foot drop is **rare in patients who underwent renal transplantation**.

- The diagnosis of tacrolimus neurotoxicity should exclude other neuropathies caused by vascular, infectious, inflammatory or metabolic reasons.

Korean J Pediatr. 2011 Jan; 54(1): 40–44. PMCID: PMC3040365
Published online 2011 Jan 31. doi: 10.3345/kjp.2011.54.1.40 PMID: 21359060

A case of tacrolimus-induced encephalopathy after kidney transplantation

Myoung Uk Kim, M.D.,[1] Sae Yoon Kim, M.D.,[1] Su Min Son, M.D.,[2] and Yong Hoon Park, M.D.[1]

An 11-year-old girl presented with sudden onset of neurologic symptoms, hypertension, and psychiatric symptoms, with normal kidney function, after kidney transplantation.

- **First:** encephalopathy occurred after administration of tacrolimus and improved after discontinuation of the drug.

- **Second:** the development of right-side hemiplegia could not be explained by conventional MRI; but through diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) of white matter tract, visualization was possible.

Tacrolimus-Induced Catatonia

Catatonia, as defined by DSM-5, is characterized by three or more of the following symptoms:

- ❑ Catalepsy
- ❑ Waxy flexibility
- ❑ Stupor
- ❑ Agitation
- ❑ Mutism
- ❑ Negativism
- ❑ Posturing
- ❑ Mannerism
- ❑ Stereotypies
- ❑ Grimacing
- ❑ Echolalia
- ❑ Echopraxia

Tacrolimus-Induced Catatonia…

- **Long-standing use of tacrolimus** without catatonic symptoms **does *not* preclude** the possibility of developing **new onset neuropsychiatric side effects**.

- Sikavi et al. describe an acute onset **catatonia after 16 years of exposure to tacrolimus**, which **resolved within 1 week of switching to an alternative immunosuppressant.**

CLINICAL CASE DISCUSSIONS

Catatonia Due to Tacrolimus Toxicity 16 Years After Renal Transplantation: Case Report and Literature Review

SIKAVI, DANIEL; MCMAHON, JENNIFER MD; FROMSON, JOHN A. MD

Author Information

Journal of Psychiatric Practice: November 2019 - Volume 25 - Issue 6 - p 481-484
doi: 10.1097/PRA.0000000000000425

case report and literature review. J Psychiatr Pract. 2019;25(6):481–4.

Treatment of tacrolimus-induced catatonia

- ✓ **Reducing the dose of tacrolimus, or substitution with a different immunosuppressive agent.**

- ✓ **Acute management :regular scheduled doses of benzodiazepines.**

- (**lorazepam** 1 mg IV q6h, titrated to 3–4 mg IV q6h as needed based on the clinical presentation, to an **upper limit of 16–24 mg per 24 hours**). **High doses of benzodiazepines are often required to confer maximum therapeutic benefit.**

- If **symptoms of catatonia are not relieved within 48–72** hours of optimized **medical** management, **ECT** should be considered.

Tacrolimus-Induced Psychosis

- Krishna et al. describes a **43-year-old male** with **no past psychiatric history** who developed **psychosis after starting tacrolimus** .

- Obayi described a **21-year-old female** with **no past psychiatric history** who developed psychosis, which resolved completely after withdrawal of the medication.

- Bersani et al. described mania with **psychotic symptoms** in a 46-year-old male **17 years post-transplant.** In this case, the patient's serum tacrolimus level was supratherapeutic. Symptoms resolved gradually with a reduction of dose.

Gen Hosp Psychiatry. 2013;35(3):327.e5–6.
Int J Sci Rep. 2018;4(7):192.
Case Rep Psychiatry. 2013;2013:926395.

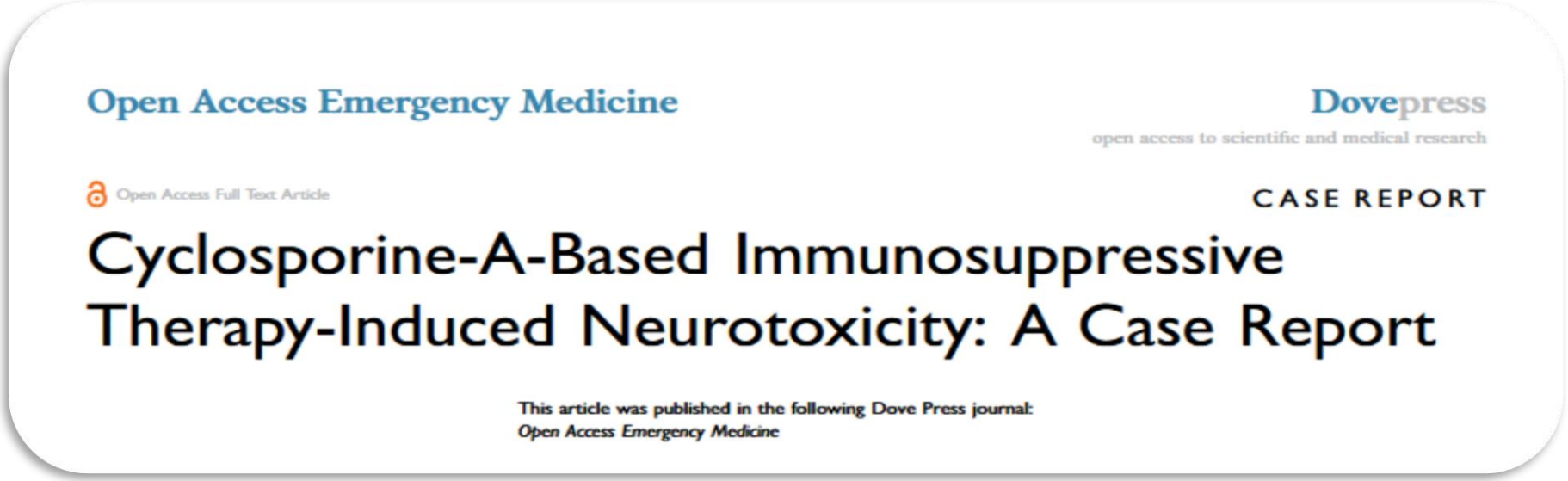
Tacrolimus-Induced Psychosis…

- ✓ Cases reports **underscore** the importance of **routine monitoring** of **mental status during treatment with tacrolimus.**

- ✓ **Psychosis is a rare side effect but one that develops at any time during treatment with tacrolimus, regardless of whether tacrolimus blood levels are therapeutic or toxic.**

- ✓ **Treatment recommendations :**

- Reduction of dose or substitution for an alternative immunosuppressive agent.
- **Second- or third-generation antipsychotics** have also been used successfully.



A 31-year-old male with a history of kidney transplantation was treated with CsA and mycophenolate mofetil, for 18 years. He had been referred to the emergency department with complaints of **generalized tonic- clonic seizure** for 1 minute and 15 minutes of the post- ictal phase. Almost all laboratory tests including CSF analysis were within normal limits. **Brain MRI** findings were compatible with CsA-based neurotoxicity.

- **CsA neurotoxicity is more common in intravenous therapy, early days of CsA administration, P450 inhibitors administration, and following liver transplantation.**

CsA Neurotoxicity…

- Different forms of CsA neurotoxicity : **tremor, paresthesia, confusion, ataxia, neuralgia, hemiplegia, occipital seizures, and transient cortical blindness**.

- **MRI findings have almost diagnostic value: signal changes within the cerebral cortex and juxtacortical white matter of the occipital lobes, posterior temporal, parietal, and frontal lobes.**

- **It is necessary to consider the risk of CsA neurotoxicity following kidney transplantation, which needs further investigation into the mechanism of CsA neurotoxicity.**

The NEW ENGLAND JOURNAL of MEDICINE

Cyclosporine Neurotoxicity

June 13, 1991
N Engl J Med 1991; 324:1744-1745
DOI: 10.1056/NEJM199106133242417

- Neurologic complications of cyclosporine therapy are frequent, usually occurring during the **first month** after the beginning of treatment.
- We report the case of a child who underwent liver transplantation and had a seizure late in her course. **The identification of cyclosporine and its metabolites in the CSF suggested a perturbation of the blood–brain barrier.**
- **Neurologic complications** of cyclosporine therapy have been attributed to a number of **concomitant factors** : **hypertension, hypomagnesemia, or hypocholesterolemia.**

Cyclophosphamide

- Cyclophosphamide has some significant systemic side effects, but **no significant psychiatric side effects** are cited in the literature and product monographs .

- **No case studies** have been published that describe **psychiatric reactions** directly attributable to treatment with cyclophosphamide.

Procytox, Mississauga (ON) [Updated 2012 Sept 7; cited 2021 Feb 07].

Hydroxychloroquine

- The **most common** psychiatric side effects are **affective lability** (reported in 1–10%) and **rare reports of nightmares, suicidal behavior, depression and psychosis.**

- With the limited case reports available and with heterogeneous presentations, it is difficult to define specific risk factors for the development of psychiatric side effects.

- **Numerous case reports describe new onset psychiatric symptoms in individuals with no past psychiatric history.**

Inflammopharmacology. 2018;26(5):1141–9.

Treatment

Withdrawal of hydroxychloroquine and/or treatment with a symptom-appropriate psychopharmacological agent.

Key Takeaways

- The most common psychiatric side effects related to **corticosteroid** treatment **are depression and mania**, **followed by mixed mood disorders, psychosis, and delirium.**

- Psychiatric adverse drug events with **mycophenolate** are **rare**; however, case reports of **depressive symptoms and anxiety symptoms** have been documented.

- **No common or serious psychiatric adverse reactions** are associated with **cyclophosphamide**.

Key Takeaways…

- About **40–60%** of patients on tacrolimus may develop **mild to moderate neurotoxic** effects including **headaches, paresthesias, tremors, and sleep disturbance.**

- **It is necessary to consider the risk of CsA neurotoxicity following kidney transplantation.**

- **The only** relatively **common** psychiatric side effect of **hydroxychloroquine** is **emotional lability**.

- **Further investigation should be directed towards the psychopharmacology and pathology of immunosuppressive agents and their role in psychiatric disorder.**


Have
a nice
day :)