Don’t Suffer the Coughequences: Dextromethorphan for Methotrexate Induced Neurotoxicity

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Disclosures

- I do not have any actual or potential conflicts of interest to disclose

Objectives

- Describe the proposed mechanisms behind methotrexate induced neurotoxicity and the therapeutic use of dextromethorphan
- Discuss the dosing of dextromethorphan and review relevant literature for the use of dextromethorphan for MTX-induced Neurotoxicity

Background

- Methotrexate-induced neurotoxicity is a frequent complication of both intravenous and intrathecal methotrexate (MTX) therapy
- MTX-induced neurotoxicity has been described in a variety of clinical manifestations ranging from acute to chronic
- The mechanism behind MTX-induced neurotoxicity is poorly understood and likely multifactorial
- There are no currently approved treatment for MTX-induced neurotoxicity and therapy is mostly supportive care

Epidemiology

- ~7% of patients enrolled in Berlin-Frankfurt-Munster (BFM) or Children's Oncology Group (COG) Acute Lymphoblastic Leukemia (ALL) protocols experience MTX-induced neurotoxicity

- MTX-Induced Neurotoxicity occurs most frequently after IT MTX

- Cumulative methotrexate dosing, elevated methotrexate levels, and leukemic involvement of the CNS do not have a direct correlation to the incidence of neurotoxicity

Potential Risk Factors

Age ≥ 10 years

Elevated LFTs

Hispanic

Co-administration of IT MTX in cytarabine or cyclophosphamide regimens

Mateos M et al.Methotrexate-related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. Haematologica. 2022

Clinical Presentation

	Acute	Sub-Acute	Chronic
Onset:	Within **hours** of MTX administration	Within **days to weeks** of MTX therapy	**Months to years** after MTX therapy
Presentation:	• Signs of chemical meningitis • Somnolence • Confusion • Headache • Nausea/Vomiting • Dizziness	• Seizures • Stroke-like symptoms (SLS) • Hemiparesis • Sensory deficits • Aphasia/dysphagia	• Cognitive dysfunction • Behavioral abnormalities • Spasticity

Bhojwani et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014

Methotrexate-SLS Definition

Neurotoxicity occurring within 21 days of intravenous or intrathecal methotrexate with the **following 3 characteristics:**

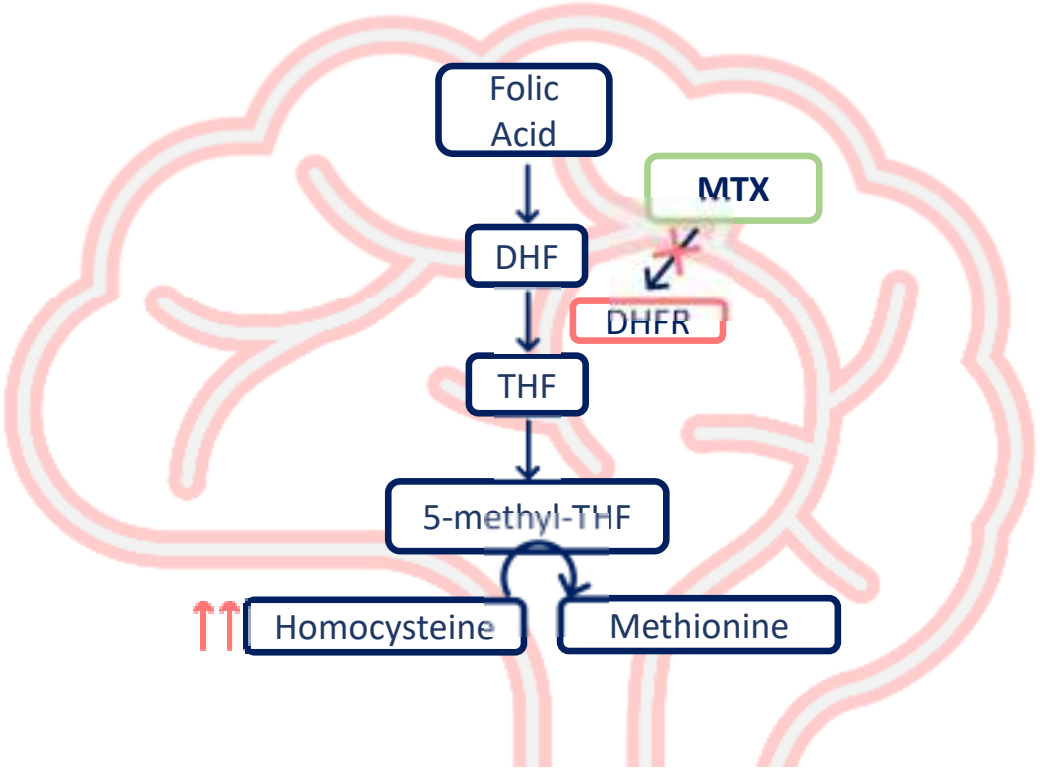
1. New onset of one or more of the following: paresis or paralysis, movement disorder or bilateral weakness, aphasia or dysarthria, altered mental status including consciousness

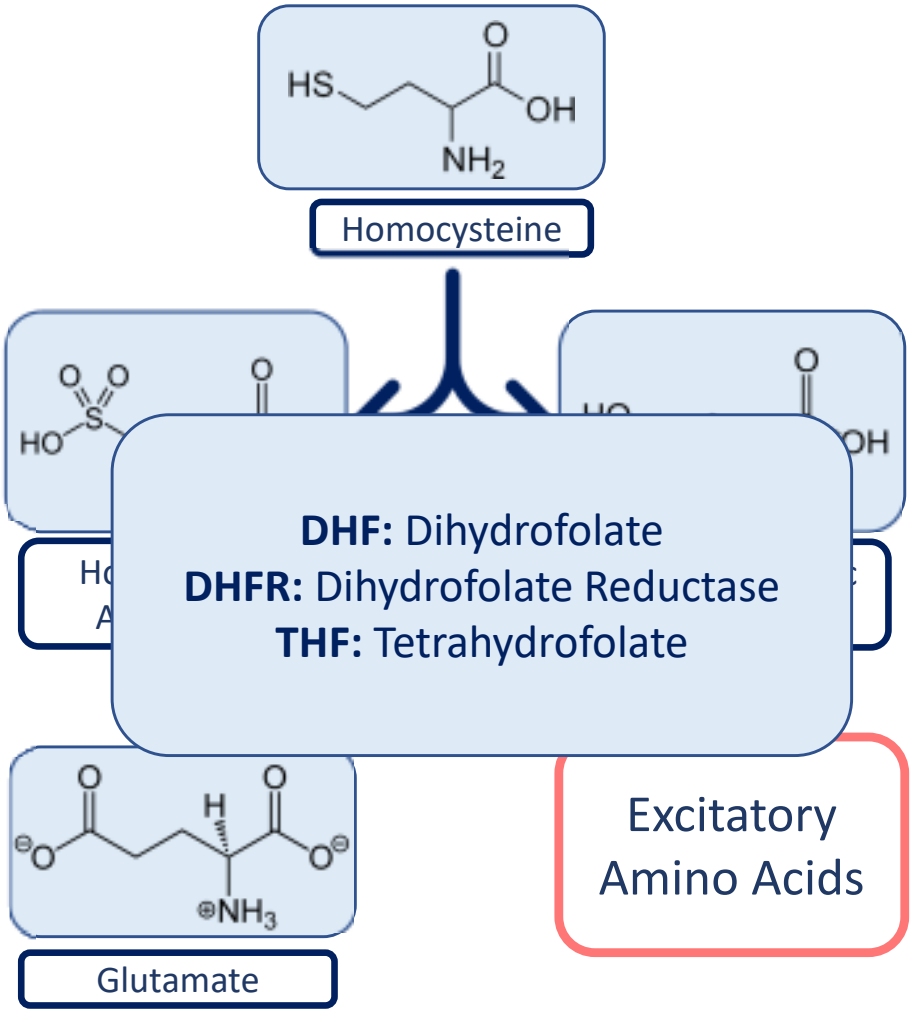
2. White matter changes indicating leukoencephalopathy on MRI or a characteristic clinical course with waxing and waning symptoms usually leading to complete or partial resolution within a week

3. No other identifiable causes

Deepa Bhojwani, Ravi Bansal, Alan S. Wayne; Managing therapy-associated neurotoxicity in children with ALL. Hematology Am Soc Hematol Educ Program 2021

Proposed Mechanism





Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity [published correction appears in Pediatr Neurol. 2014

Proposed Mechanism

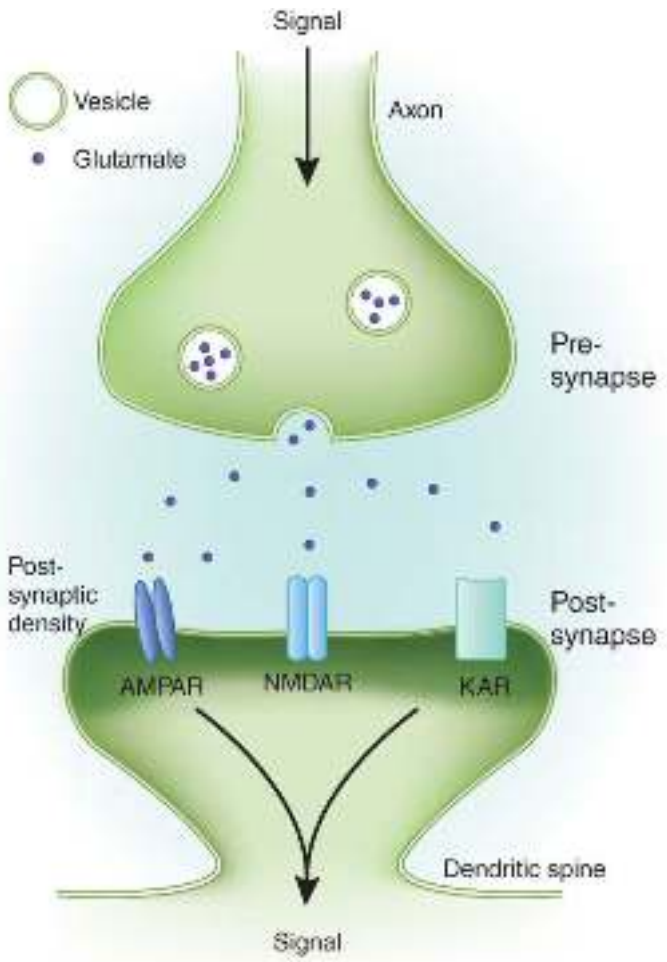
↑ Homocysteine

↓

↑ Glutaminergic Activity

↓

Neuroexcitatory Effects



Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity [published correction appears in Pediatr Neurol. 2014

Alternative Mechanisms

- High levels of homocysteine has been associated with endothelial injury and pre-mature cerebrovascular disease
- Methotrexate has been shown to increase adenosine from fibroblasts and endothelial cells in vivo
- Adenosine dilates cerebral blood vessels and slows neurotransmitter release possibly accounting for MTX-induced neurotoxicity

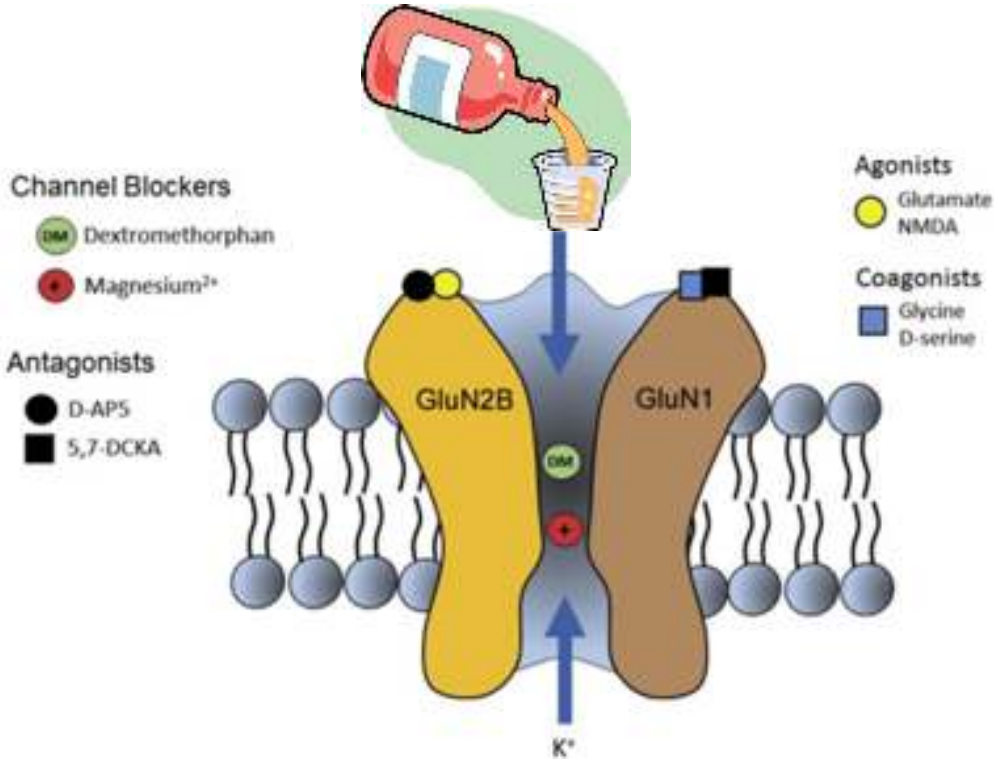
Pushpakumar S, et al. Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. Curr Med Chem. 2014;21(32):3662-72
Bernini et al. Aminophylline for methotrexate induced neurotoxicity. Lancet 1995.

Management of MTX-Induced Neurotoxicity

- Consider differential diagnosis (hemorrhage, infection, CNS relapse, etc.)
- Obtain appropriate imaging (MRI/CT)
- Supportive care management
  - Seizure management
  - Swallow evaluation
  - Intubation if required

Bhojwani et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014

So Why Cough Syrup?



Dextromethorphan

- A widely used antitussive
- Low-affinity, non-competitive NMDA receptor antagonist
- Favorable safety profile

Dextromethorphan Dosing

Cough Suppressant Dosing:

Adult: 20 mg every 4 hours

Children: (6-12 years): 10 mg every 4 hours

MTX-Induced Neurotoxicity Dosing:

Adult/Children: 1-3 mg/kg once-twice daily

Pushpakumar S, et al. Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. Curr Med Chem. 2014;21(32):3662-72
Bernini et al. Aminophylline for methotrexate induced neurotoxicity. Lancet 1995.

Retrospective Review

Study	Population	n (#)	Dextromethorphan Dosing
Drachtman et al. 2002	Ages 13-32 with severe subacute MTX-Neurotoxicity	5	1-2 mg/kg/dose (x1 or TID)

Drachtman RA, Cole PD, Golden CB, et al. Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. Pediatr Hematol Oncol. 2002;19(5):319-327. doi:10.1080/08880010290057336.

Retrospective Review

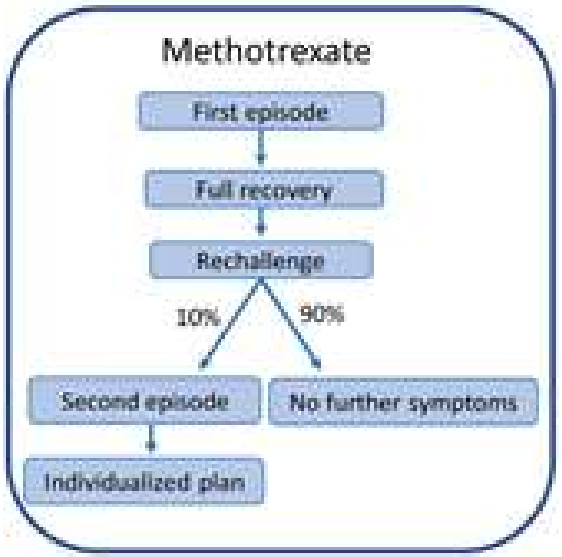
Study	Population	n (#)	Dextromethorphan Dosing
Afshar et al. 2014	Ages 2-18 with subacute MTX-neurotoxicity	18 16 received IT MTX and 2 received IV	1-3 mg/kg/day
Results			

Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity [published correction appears in Pediatr Neurol. 2014

Methotrexate Re-challenge

Should methotrexate be re-challenged in someone who has previously developed MTX-induced neurotoxicity?

- There is no clear data to suggest that prior toxicity will put patients at higher risk for developing neurotoxicity
- ~90% of patients do not develop recurrent symptoms
- Consider implementing leucovorin rescue 24 and 36 hours after subsequent IT MTX doses
- Consider aminophylline or dextromethorphan prophylaxis for subsequent doses



Bhojwani, et al. Managing therapy-associated neurotoxicity in children with ALL. Hematology Am Soc Hematol Educ Program 2021

Bhojwani et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014

Summary

- MTX-induced neurotoxicity has been seen in children and adults receiving both IV and IT MTX therapy
- There are various proposed mechanism to explain MTX-induced neurotoxicity
- Dextromethorphan may be used in combination with supportive care strategies to treat neurotoxicity
- Early dextromethorphan administration may be beneficial in providing a quicker treatment response
- MTX re-challenge is appropriate after prior MTX-induced neurotoxicity

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