

Cyproheptadine: a psychopharmacological treasure trove?

Bassem Badr¹ and Ahmed Naguy^{2*} 

¹Dubai Police Medical Center and Mediclinic Hospital, Dubai, United Arab Emirates, and ²Al-Manara CAP Centre, Kuwait Centre for Mental Health (KCMH), Shuwaikh, State of Kuwait

Editorial

Cite this article: Badr B, and Naguy A (2021). Cyproheptadine: a psychopharmacological treasure trove?. *CNS Spectrums*
<https://doi.org/10.1017/S1092852921000250>

Received: 13 February 2021
 Accepted: 16 February 2021

Key words:

Cyproheptadine; psychiatric uses; psychopharmacology

Author for correspondence:

*Ahmed Naguy
 Email: ahmednagy@hotmail.co.uk

Abstract

Cyproheptadine has a unique pharmacologic portfolio that speaks to the idea of a pluripotent molecule beyond an antiallergic agent which can expand its therapeutic potential to address a multitude of psychiatric indications. Here, authors touch on the topic with focused literature review of extant evidence.

Cyproheptadine, or glutodine, is a first-generation anti-histaminic, that has been on market since the 1960s. It has a unique pharmacologic portfolio that speaks to the idea of a pluripotent molecule beyond an anti-allergic agent which can expand its therapeutic potential to address a multitude of psychiatric indications (Table 1). That said, it should be borne in mind that the level of evidence supporting the use of cyproheptadine in these off-label indications is highly variable, and, hence, sound clinical judgement is necessary for its proper use and placement in real-life psychiatric practice and psychopharmacotherapy algorithms. Here, we briefly touch on some of these indications with helpful some clinical tips and caveats.

Cyproheptadine is H1 histaminergic, M1 muscarinic, 5HT2A serotonergic, and reportedly calcium channel blocker. No significant kinetic interactions are expected. Dosing depends on indication for appetite stimulation: 2 mg × 4 increased to a target of 8 mg × 4 over 3 weeks; serotonin syndrome: 12 mg × 1, then 2 mg q 2 hours till response with a max. 32 mg/day; nightmares: 4 mg qhs but can go up to 24 mg qhs; female anorgasmia: 4–12 mg PRN 1–2 hours before coitus.

Appetite Stimulant

Due to H1 blockade, cyproheptadine can increase the appetite, hence the alternate name *glutodine*. Anticholinergic actions might be contributory too. Cyproheptadine has been used to address stimulant-related appetite suppression in children with attention-deficit/hyperactivity disorder (ADHD),¹ although anticholinergic actions sound counterintuitive as it might negatively impact cognition. Paradoxical aggression has been reported in a 5-year-old boy treated with cyproheptadine given the causal link between serotonin and aggression (serotonin inhibits aggression).² Due to anti-serotonergic properties, cyproheptadine was also reported to induce obsessive-compulsive symptoms of religious and sexual themes (with a fundamental 5HT dysregulation) in a preschool girl.³ Moreover, cyproheptadine has been successfully trialled for weight gain in restrictive anorexia nervosa,⁴ although olanzapine has sounder evidence-base. Similarly, cyproheptadine can be a viable option in avoidant/restrictive food intake disorder (ARFID).⁵

Insomnia

Cyproheptadine has been used to tackle stimulant-induced insomnia in ADHD.⁶ Clonidine or melatonin can be used in lieu without impairing cognitive functions. Use of antihistaminics for insomnia is generally discouraged as tachyphylaxis tends to develop soon (as early as day 3).

Autism Spectrum Disorder (ASD)

Hyperserotonemia has been reported in 40% of ASD population.⁷ A positive 8-week randomized controlled trial (RCT) has attested to the superiority of combined anti-serotonergic cyproheptadine with haloperidol over haloperidol alone for behavioral dyscontrol in ASD with no difference in extrapyramidal syndromes (EPS) or side effects.⁸

Nightmares in PTSD

Cyproheptadine can improve sleep architecture and REM (rapid eye movement) sleep pattern. It has been used to address distressing nightmares in patients with posttraumatic stress disorder

Table 1. Cyproheptadine Uses

Off-Label Uses of Cyproheptadine in Psychiatry
Appetite stimulant—ADHD, anorexia nervosa, ARFID
Insomnia—ADHD
Schizophrenia—negative symptom domain
ASD—behavioral facets
Toxic serotonin syndrome
Selective Serotonin Reuptake Inhibitor (SSRIs)-induced sexual dysfunction
SSRIs-induced sweating
Nightmares in PTSD
Antipsychotic-induced akathisia and tardive dyskinesia
Functional dyspepsia
Neuropsychiatric sequelae of antiretroviral treatment in HIV
Migraine

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ARFID, avoidant/restrictive food intake disorder; ASD, autism spectrum disorder; PTSD, posttraumatic stress disorder.

(PTSD) in a dose range of 4 to 24 mg/day.⁹ Prazosin and possibly gabapentin remain better alternatives.

SSRIs-Related Sexual Dysfunction

Given 5HT_{2A} antagonistic actions, cyproheptadine has been used as an antidote to the commonly encountered SSRIs-induced sexual dysfunction including female anorgasmia.¹⁰ Add-on bupropion, mirtazapine, ginkgo biloba, or phosphodiesterase PD-5 inhibitors (eg, sildenafil) are better options. It behooves clinicians to be vigilant and mindful to the fact that cyproheptadine, by virtue of anti-serotonergic actions, can nullify antidepressant actions with a resultant dynamic failure and treatment “pseudo-resistance.”

SSRIs-Related Sweating

Diaphoresis (hyperhidrosis), which can be socially embarrassing, has been reported to affect 1 in 5 persons on antidepressants. Via central antiserotonergic actions, cyproheptadine has been reported to help with diaphoresis.¹¹ Other options include benzotropine, mirtazapine or aripiprazole.

Akathisia

Neurobiological underpinnings of akathisia include D₂ blockade, 5HT_{2A} overstimulation, GABA deficiency, M₁ Cholinergic overactivity, and, noradrenergic overactivity.¹² Cyproheptadine, by blocking 5HT_{2A} and M₁ receptors can be an attractive option for antipsychotic-induced akathisia.¹³ Antidepressants, mirtazapine and mianserin, have been used similarly. β blockers and benzodiazepines remain first-line options, though. Of related interest, cyproheptadine was reported as a treatment option for tardive dyskinesia.¹⁴

Serotonin Syndrome

Cyproheptadine has been deployed as antidote in toxic serotonin syndrome. Case reports abound in literature.¹⁵ Medetomidine,

benzodiazepines, or chlorpromazine are alternative symptomatic options besides stopping the offending agent. Similarly, cyproheptadine has been successfully used in serotonin-producing carcinoid tumor.

Schizophrenia

Add-on cyproheptadine to haloperidol has been demonstrated in one RCT to outperform haloperidol with placebo in treatment of negative symptom domain.¹⁶ Alleviation of EPS could be contributory as shown in another 6-week RCT.¹⁷ A case report of a 66-year-old female patient, who developed clozapine-induced agranulocytosis after 10 weeks of clozapine treatment was subsequently successfully treated with a combination of loxapine and cyproheptadine. This combination is thought to mimic the pharmacological profile of clozapine, rendering it as a possible alternative to traditional clozapine treatment.¹⁸

Abdominal Migraine and Cyclic Vomiting in Children

As serotonin is highly expressed in gut, cyproheptadine has been successfully reported to mitigate functional dyspepsia and irritable bowel syndrome. Use of cyproheptadine in migraine¹⁹ is akin to the use of pizotifen, another antihistaminic commonly prescribed for migraine prophylaxis (and appetite stimulation as well).

Neuropsychiatric Sequelae of Efavirenz in Patients with AIDS

A positive RCT has attested to efficacy of cyproheptadine to mitigate neuropsychiatric sequelae of the antiretroviral agent, efavirenz in HIV-positive patients, which is pretty common in 50% of cases.²⁰ Use of cyproheptadine can be advantageous here to help with cachexia as well.

This list is by no means all-inclusive. As data accrues, therapeutic potential of cyproheptadine expands. Definitely, large, well-conducted trials are sorely needed to define the real place of cyproheptadine in psychiatric pharmacopeia.

Disclosures. The authors have no competing interests or financial affiliations.

References

- Naguy A. Stimulants use in attention-deficit/hyperactivity disorder kids—triumph or tribulation? *J Can Acad Child Adolesc Psychiatry*. 2016;25(3):136–137.
- Strayhorn JM. Case study: cyproheptadine and aggression in five-year-old boy. *J Am Acad Child Adolesc Psychiatry*. 1998;37(6):668–670.
- Kaya I, Suleyman F, Coskun M. Cyproheptadine-induced obsessive-compulsive symptoms in a preschool child. *Klinik Psikofarmakoloji Bulteni*. 2016;26(1):72–74.
- Miniati M, Mauri M, Ciberti A, *et al*. Psychopharmacological options for adult patients with anorexia nervosa. *CNS Spectr*. 2016;21(2):134–142.
- Naguy A, Roshdy R, Al-Mutairi A, *et al*. Mirtazapine improved eating patterns in avoidant/restrictive food intake disorder. *Am J Ther*. 2021. doi: 10.1097/MJT.0000000000001338.
- Naguy A. Clonidine use in psychiatry: panacea or panache? *Pharmacology*. 2016;98(1–2):87–92.
- Naguy A, Ali M, Elsoni D, *et al*. A case of prepubertal low-functioning autism with behavioral decompensation favourably responding to tianeptine. *J Clin Psychopharmacol*. 2019;39(5):524–525.
- Akhondzadeh S, Erfani S, Mohammadi MR, *et al*. Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial. *J Clin Pharm Ther*. 2004;29(2):145–150.

9. Hammer MB, Robert S, Frueh BC. Treatment-resistant posttraumatic stress disorder: strategies for intervention. *CNS Spectr*. 2004;**9**(10):740–752.
10. Stimmel GL, Gutierrez MA. Sexual dysfunction and psychotropic medications. *CNS Spectr*. 2006;**11**(8 Suppl 9):24–30.
11. Marcy TR, Britton ML. Antidepressant-induced sweating. *Ann Pharmacother*. 2005;**39**(4):748–752.
12. Naguy A. Akathisia—a psychopharmacologic treatment ‘menu’. *Asia Pac psychiatry*. 2017;**9**(4):12290. doi: [10.1111/appy.12290](https://doi.org/10.1111/appy.12290).
13. Lohr JB, Eidt CA, Alfaraj AA, et al. The clinical challenges of Akathisia. *CNS Spectr*. 2015;**20**(S1):1–16.
14. Kurata K, Hosokawa K, Koshino Y. Treatment of neuroleptic induced tardive dyskinesia with cyproheptadine. *J Neurol*. 1977;**215**(4):295–298.
15. Huska MT, Catalano G, Catalano MC. Serotonin syndrome associated with the use of escitalopram. *CNS Spectr*. 2007;**12**(4):270–274.
16. Akhondzadeh S, Mohammadi MR, Amini-Nooshabadi H, et al. Cyproheptadine in treatment of chronic schizophrenia: a double-blind, placebo-controlled study. *J Clin Pharm Ther*. 1999;**24**(1):49–52.
17. Lee HS, Song DH, Kim JH, et al. Cyproheptadine augmentation of haloperidol in chronic schizophrenic patients: a double-blind placebo-controlled study. *Int Clin Psychopharmacol*. 1995;**10**(2):67–72.
18. Aboueid L, McCarthy RH. Loxapine and cyproheptadine combined limit clozapine rebound psychosis and may also predict clozapine response. *Case Rep Psychiatry*. 2016;**2016**:6123913.
19. Silberstein SD. Current management: migraine headache. *CNS Spectr*. 2017;**22**(S1):1–13.
20. Dabaghzadeh F, Ghaeli P, Khalili H, et al. Cyproheptadine for prevention of neuropsychiatric adverse effects of efavirenz: a randomized clinical trial. *AIDS Patient Care STDS*. 2013;**27**(3):146–154.