

Role of Cyproheptadine in Various Psychiatric Conditions

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ABSTRACT

Though cyproheptadine is commonly used for treatment of different allergic conditions, the molecule is effective in different psychiatric conditions mainly due to antiserotonin property. Cyproheptadine can be used in different psychiatric conditions like functional gastrointestinal disorders, serotonin syndrome, akathisia, tardive dyskinesia, anorexia nervosa, stimulant-induced weight loss, antidepressant induced sexual dysfunction, neuropsychiatric adverse effects associated with efavirenz therapy in HIV positive patients, migraine type headache, augmentation agent in schizophrenia. As the molecule is not very costly, its use can help in improving psychiatric practice in developing nations.

Keywords: Antidepressants, Improving psychiatric practice, Schizophrenia.

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INTRODUCTION

Cyproheptadine belongs to the first generation piperidine—a subgroup of the first generation antihistamine. Cyproheptadine is commonly used for the treatment of different allergic conditions. However, it was found to be effective in the treatment of some psychiatric conditions also.^{1,2}

Along with the antihistamine property cyproheptadine has antiserotonin property by antagonizing action on 5-HT₂ receptor. It also has anticholinergic, antidopaminergic, and antiandrogenic property.³

CYPROHEPTADINE IN CHILDHOOD FUNCTIONAL GASTROINTESTINAL DISORDERS

Functional dyspepsia is characterized by increased gastric sensitivity to distension. Gastric (mainly fundic area) contraction and relaxation are regulated by 5-HT₂ receptors. So, cyproheptadine with its 5-HT_{2A} antagonistic property is effective in these cases.⁴

Nociceptive stimulation of 5-HT_{1B}, 5-HT_{2A}, and 5-HT₆ receptors in excessive manner is implicated in functional abdominal pain. 5-HT_{2A} antagonism and calcium channel blocking property in intestinal muscles are implicated in the use of cyproheptadine in functional abdominal pain.⁵

5HT level is found to be increased in diarrhea predominant irritable bowel syndrome. Therefore, cyproheptadine with its antiserotonin property is useful in the treatment of irritable bowel syndrome.^{5,6}

Cyproheptadine is effective in the treatment of abdominal migraine, cyclical vomiting of children also.^{7,8}

CYPROHEPTADINE IN SEROTONIN SYNDROME

Serotonin syndrome is a life threatening condition due to increased serotonergic activity in the central nervous system (CNS) and characterized by altered mental status, autonomic dysfunction, and abnormalities of neuromuscular function. Serotonergic drugs like selective serotonin reuptake inhibitors (SSRIs) when used in combination, in high doses or in sensitive individuals can cause serotonin syndrome by increased neurotransmission in CNS by stimulation of the postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors.³

Cyproheptadine can be used as an antidote for serotonin syndrome because of the antagonistic action on 5-HT_{2A} receptor.

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An initial dose of 12 mg of cyproheptadine is recommended, followed by 2 mg every 2 hours until clinical response is seen. Maintenance dose of 8 mg of cyproheptadine six hourly is recommended.^{9–11} Several case reports have shown that cyproheptadine is effective in mild to moderate cases of serotonin syndrome, but its efficacy in severe cases has not been studied properly.

CYPROHEPTADINE IN ANOREXIA NERVOSA

Cyproheptadine has H₁ antihistaminic action and it also promotes growth hormone secretion. Due to these actions, it is used to increase appetite and help in gaining weight. Cyproheptadine is effective in treating anorexia nervosa. Probably nonbulimic type of anorexia nervosa patients responds better to cyproheptadine.^{12,13}

CYPROHEPTADINE IN STIMULANT-INDUCED WEIGHT LOSS, ANOREXIA AND INSOMNIA

Children and adolescents with attention deficit hyperactivity disorder often develop the problem of anorexia, weight loss, and insomnia on using the stimulants, which may lead to poor compliance to the treatment. Cyproheptadine has been shown to promote weight gain and it also improves sleep quality. Commonly night time dose of 4–8 mg of cyproheptadine is used.¹⁴

CYPROHEPTADINE IN ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

Sexual dysfunction is a known side effect of antidepressants. Nowadays, sexual dysfunctions are often reported by the patients

taking antidepressants probably because of the expanded indications for antidepressants, increase in the number of antidepressant prescription, greater emphasis on the biological model of depression, increased willingness to discuss sexual problems, increased awareness of the adverse effects of drugs, etc.

Selective SSRIs are commonly used antidepressants nowadays. Though they are excellent antidepressants, they too have some important adverse effects like sexual dysfunction which can lead to compliance problems.

Probably the serotonergic property, effect on α_1 adrenergic receptor, indirect inhibitory effect on dopamine are the causes responsible for sexual dysfunction like anorgasmia, delayed ejaculation, decreased libido, and erectile dysfunction.¹⁵ Serotonin inhibits nitric oxide synthase (an enzyme involved in the pathway to achieve penile erection/lubrication) and this action is probably mediated by 5-HT₂ receptors.

Cyproheptadine has 5-HT₂ antagonist actions and so it improves sexual function. Cyproheptadine (4–12 mg/day) can be used 1–2 hours before the sexual activity or daily basis.¹⁶

CYPROHEPTADINE IN THE TREATMENT OF AKATHISIA

According to DSM-IV-TR, akathisia is characterized by a subjective feeling of restlessness and by objectively observed typical movements such as shuffling of the legs, pacing, rocking from foot to foot, or the inability to sit down or stand still (American Psychiatry Association, 2000). Akathisia can be of different types depending on the time of onset—acute, chronic or tardive akathisia.

Not only the first generation but also atypical antipsychotics can cause akathisia. The prevalence of akathisia in patients with schizophrenia varies and is in-between 5% and 37%. Other psychotropic medications like SSRI, monoamine oxidase inhibitor, and tricyclic antidepressants have been found to be associated with akathisia. Not only in patients with schizophrenia or mood disorders, but akathisia may also be seen in a wide range of other conditions like Parkinsonian syndromes and traumatic brain injury patients.

The exact pathophysiology underlying akathisia is not known properly. It is thought that basal ganglia and striatal circuitry dysfunction are probably responsible for developing akathisia and the key neurotransmitters are gamma-aminobutyric acid (GABA), serotonin and dopamine. Dopaminergic motor function in nigro-striatal pathway is modulated by GABA and serotonin. An imbalance between dopaminergic and serotonergic neurotransmitter system is implicated in the development of akathisia.

Drugs with 5-HT_{2A} antagonistic property can be helpful in the treatment of akathisia. Cyproheptadine (8–16 mg/day) can be used to treat antipsychotic induced akathisia due to its 5-HT_{2A} antagonistic property. This mechanism is probably by counteracting antipsychotic induced dopamine D₂ receptor blockade resulting in enhanced dopamine neurotransmission. In one study, cyproheptadine was found to be equally effective compared with propranolol in the treatment of akathisia.¹⁷

CYPROHEPTADINE IN TARDIVE DYSKINESIA

Tardive dyskinesia is a type of abnormal, involuntary movement disorder usually involving face and sometimes limbs, which emerges as one of the adverse effects of antipsychotic drugs,

especially the typical ones. The risk of tardive dyskinesia increases with higher doses and longer durations of treatment. In some case reports, cyproheptadine was found to be effective in the treatment of tardive dyskinesia.¹⁸

CYPROHEPTADINE IN NIGHTMARES OF PATIENTS WITH POSTTRAUMATIC STRESS DISORDER

Cyproheptadine is effective in reducing nightmares of patients with post traumatic stress disorder. Moreover, the sedative property of cyproheptadine makes it a good choice for such patients.

Cyproheptadine can improve sleep architecture and REM sleep pattern. Cyproheptadine causes rapid eye movement (REM) suppression due to its antagonistic effect on serotonin autoreceptor (5-HT_{1A}), which results in increased serotonin outflow at the midbrain raphe. The anticholinergic property of cyproheptadine is also responsible for the reduction of REM sleep. Commonly used dose of cyproheptadine in such cases is 4–24 mg/day.^{19–23} However, a few studies have shown conflicting results too.

CYPROHEPTADINE IN HIV POSITIVE PATIENTS FOR NEUROPSYCHIATRIC ADVERSE EFFECTS OF EFAVIRENZ

Efavirenz belongs to non-nucleoside reverse transcriptase inhibitors (NNRTIs) group of antiretroviral drug, used in the treatment of HIV infection. Neuropsychiatric adverse reactions are common following efavirenz therapy (up to 50%) and more common within the first 2 weeks of treatment. These adverse effects can lead to poor compliance to treatment. Dizziness, headache, nightmares, sleep disturbance, concentration difficulty, mild cognitive impairment, anxiety disorders, depressive disorders, mania, emotional lability, poor impulse control, hallucination, delusion, aggressive behavior, and catatonia are the most commonly reported adverse reactions. The neuropsychiatric effects of efavirenz appear to be dose-dependent and mediated by the 5-HT_{2A} receptor.

Cyproheptadine helps in improving these adverse effects. Moreover, some of the adverse effects of cyproheptadine such as increased appetite and weight gain are beneficial for HIV patients with weight loss and poor appetite.^{24–27}

CYPROHEPTADINE AS AUGMENTATION AGENT IN SCHIZOPHRENIA

Typical antipsychotics block mainly D₂ receptors. 5-HT receptor plays an important role in the negative symptoms of schizophrenia. Atypical antipsychotics act better than typical antipsychotics in the treatment of negative symptoms due to their action on 5-HT receptors.

Clozapine exhibits higher serotonin (5-HT₂) than dopamine (D₂) blockade *in vivo*, which contributes to clozapine's greater efficacy and lower propensity for extrapyramidal adverse effects. High 5-HT₂ blockade and moderate D₂ blockade can also be obtained by combining two medications: one with prominent 5-HT₂ antagonism (in sufficient amount) and another with D₂ antagonism (in less amount). One such optimum combination can be made by combining cyproheptadine (4–6 mg three times daily (TDS)) with a low dose of a typical antipsychotic (D₂ antagonist).

Therefore, it can be said that cyproheptadine, due to 5-HT antagonistic action, can be used as an augmentation agent in treating chronic schizophrenia patients to reduce extrapyramidal

adverse effects of conventional antipsychotics such as haloperidol and to counteract the negative symptoms.^{28–30}

CYPROHEPTADINE IN TREATMENT OF MIGRAINE TYPE HEADACHE

Trigeminal-vascular system plays an important role in the pathogenesis of migraine. Release of serotonin from platelets results in vasoconstriction (serotonin 1B and 1D receptors are implicated) and resulting in decreased cerebral blood flow. This is followed by the depletion of serotonin leading to cerebral vasodilatation and trigeminal nerve stimulation. These changes induce neurogenic inflammation and result in migraine headache.

Cyproheptadine inhibits the release of vasoactive peptides, including calcitonin gene-related peptides, with simultaneous inhibition of both serotonin 1B and 1D receptors and prevents neurogenic inflammation. Cyproheptadine in the dose of 4–8 mg/day can be used in migraine type headache in both children and adult population.^{31–33}

CONCLUSION

Cyproheptadine has been found to be effective in many psychiatric conditions such as various functional gastrointestinal disorders, serotonin syndrome, akathisia, tardive dyskinesia, anorexia nervosa, stimulant induced weight loss, antidepressant-induced sexual dysfunction, neuropsychiatric adverse effects associated with efavirenz therapy in HIV positive patients, migraine type headache, and augmentation agent in schizophrenia. It is very interesting that a single molecule is effective in so many psychiatric conditions. There are so many drug treatment options for those conditions. However, most of them appear costly to poor patients. Cyproheptadine can be a cheaper treatment option for these conditions and so may be cost-effective in developing countries. But unfortunately the number of studies on cyproheptadine in such situations are limited. Therefore, the molecule should be studied for those conditions in different parts of the world to get a cheaper alternative treatment option.

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