Can Citicoline Cause Depression?: A review of the clinical literature

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Abstract

Citicoline, also known as CDP-Choline (or less frequently Cognizin in its branded form) is a widely-used nootropic substance known for its ability to acutely increase acetylcholine availability in the brain. As it stands, citicoline is one of the most commonly used ingredients in pre-made natural nootropic supplements. Owing to the commonality of its use, people have become increasingly concerned about the safety of citicoline use, particularly when it is used on a daily basis for prolonged periods. Specifically, many people have become concerned that citicoline may cause lethargy, loss of motivation, and depression. In this article, we examine the available clinical literature on citicoline use as it related to mental illness, with a particular focus on depression.

Keywords: Citicoline, CDP-Choline, nootropics, depression

1. About Citicoline

Citicoline is a naturally-occurring compound found in the cells of humans and select plant tissues. It is an intermediary in the synthesis of phosphatidylcholine from choline. This is a very common biological process carried out in the cell membrane of most cells; as such, citicoline is found in relatively large quantities in human cell membranes, particularly in the liver and brain.

In terms of use as a nootropic and cognitive enhancer, citicoline serves a very particular purpose: increasing acetylcholine synthesis in the brain. Citicoline has been found to be readily absorbed in the human gut, and it is able to easily cross the blood-brain barrier. This makes it markedly different from choline, which is neither well absorbed nor able to easily enter the brain from the blood stream. Once consumed, citicoline enters the brain where it acts as raw material for the formation of acetylcholine; a key neurotransmitter involved in executive cognitive functions. It also provides some of the raw materials for the formation of phosphatidylcholine, which is a primary structural component of brain cell membranes.

Citicoline has so-called “peripheral benefits” owing to its cytidine content. Cytidine is component of RNA. RNA is the messenger which decodes DNA and instructs the body on how to build proteins. It is thought that consuming cytidine promotes RNA synthesis, which in turn promotes cell maintenance and/or generation. This has by no means been established as a clinical fact, but it is one of the main reasons people use citicoline as a supplement (although the primary reason is the increased actylcholine synthesis leading to enhanced cognitive capacity).

1.1 What does Citicoline do?

The primary effect of citicoline supplementation on humans is heightened focus, although the effects can be quite broad and touch on most measures of executive cognitive function.

There are several robust clinical trials showing that citicoline improves executive cognitive function. In one trial, researchers gave a group of healthy women aged 40-60 either a potent citicoline supplement or placebo for 28 days. The treatment group scored significantly higher in cognitive tests after the 28 days compared to the placebo group (particularly

in the area of commission errors in memory tests) [1]. It seems that the subjects were better able to commit a list to memory and repeat it at a later date without errors.

As well as enhancing executive cognitive performance in the short-term, citicoline has been found to be a useful substance for the treatment of pathological memory impairment. At least one study has shown that citicoline is effective for improving memory function in people with cerebrovascular pathogenesis [2].

One interesting study suggests a novel mechanism of action of citicoline. It is worth quoting the authors here in full:

"These data show that citicoline improves frontal lobe bioenergetics and alters phospholipid membrane turnover. Citicoline supplementation may therefore help to mitigate cognitive declines associated with aging by increasing energy reserves and utilization, as well as increasing the amount of essential phospholipid membrane components needed to synthesize and maintain cell membranes." [3]

This is extremely interesting, as it raises the possibility that citicoline may directly increase energy levels in the frontal lobe, which is where so-called "higher-order" cognitive function is thought to originate. This mechanism would go some way to explaining the benefits of citicoline as reported by subjective user reports: greater motivation, increased concentration, heightened focus, and better work-centric discipline.

The focus of this paper is not the efficacy of citicoline as a nootropic cognitive enhancer. This section has only served to provide background and an explanation of why citicoline is so widely used. We will not move on to discussing citicoline's supposed effect on mental health.

1.2 Does Citicoline cause depression?

There is a growing concern that the misuse of nootropics can cause adverse long-term effects. More specifically, there is some evidence to suggest that the use of certain nootropics, including citicoline, may trigger adverse psychiatric events and long-term mental health issues such as anxiety and depression.

Much of the discussion about citicoline and depression emanates from a case review published in 2015. In that paper, researchers outlined specific cases in which natural nootropics have caused unsuspected and serious adverse effects in users. One of the cases involves a man who presented with a sudden onset of psychosis and paranoia; the man had been taking citicoline regularly leading up to the incident [4]. It is worth quoting the case here in full:

"A 19-year-old male college student with a history of depression and attention deficit hyperactivity disorder (ADHD) presented to the emergency department with psychosis and paranoia resulting in self-injurious behavior. His current medication was bupropion, and historically he had been prescribed methylphenidate but was no longer taking that medication. His parents reported a history of cannabis abuse but he had been abstinent for the past year. No history of psychosis was reported. Previously, the patient was functioning well, in a euthymic state, and was attending his classes. He denied any substance abuse, and urine toxicology was negative. On further questioning, the patient revealed that he was taking a supplement to treat his ADHD. He reported purchasing it online. The supplement was found to be citicoline, and he had been consuming 2 to 3 tablets three times a day for several weeks. The family had noticed some insomnia and irritability early on, but no other concerning behaviors until now. The patient was admitted to the psychiatry department, and his symptoms resolved with olanzapine. He was discharged home in a stable condition and instructed to continue taking olanzapine for one month and to stop using all supplements."

This is the primary source of concern with regards to citicoline and depression. But it is important to note that in this case, citicoline was not identified as the cause of the psychotic/paranoid behavior. The doctors treating the man advised the cessation of all supplements alongside the administration of anti-psychotic drugs. The man did not present symptoms of depression, although he did have a history of depression.

More importantly, there is no obvious mechanism by which citicoline would cause such a psychotic or paranoid episode. Elevated levels of phosphatidylcholine or acetylcholine cannot explain the onset of psychosis. Similarly, increased energy metabolism in the frontal lobe should not result in psychotic episodes of any severity; quite the opposite, increased frontal lobe activity should reduce emotional instability, paranoia, and the inability to regulate thoughts.

In fact, one study found that citicoline has potential antidepressant properties [5]. Instead of causing depression, citicoline may actually improve outcomes for patients with depression.

1.3 Conclusion

The only reasonable conclusion to draw from the cited case study is that citicoline may exacerbate or hasten the onset of psychiatric problems due to increases in overall brain activity. It seems highly unlikely that citicoline has any effect on depression, anxiety, or any other mood disturbance. Not only are there no recorded cases of citicoline causing depression in anybody, regardless of medical or psychiatric history. If anything, the clinical evidence suggests that citicoline may have antidepressant properties.

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None of the work presented here would exist without the tireless work of the nootropics community. Together, bio-hackers are paving the way toward better cognitive function. It is through their research and their experimentation that we yield improvements in focus, memory, and productivity.

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