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Possible Benefit and Validity of Supplements for Alcohol Use Disorder

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Considering the complex nature of alcohol use disorder (AUD) and the limitations of the three US Food and Drug Administration (FDA) approved medications, clinical trials for diverse treatment options are required. During the last decade, several interesting clinical trials with over-the-counter (OTC) supplements have been conducted for AUD by taking advantage of less vulnerable nature in regard to toxicity and side effects. In this commentary, we discuss the article describing “A randomized, double-blind, placebo-controlled trial of citicoline in patients with alcohol use disorder” (Brown et al., 2018). The authors concisely describe the effects of oral citicoline, an OTC supplement, which has been suggested as a therapeutic candidate in neurological disorders, cocaine addiction and AUD (Wignall and Brown, 2014). Although this article fails to show a significant effect of citicoline on the AUD and cognitive function compared with placebo group, this clinical trial provides us with several interesting factors to consider for AUD clinical trials in the future. This commentary will discuss potential advantages of using OTC for comorbidity in AUD as well as importance of accumulating all the negative and positive information toward individual precise medications in AUD.

CLINICAL AND PRECLINICAL OUTCOMES OF CITICOLINE TREATMENTS

Citicoline, one of the OTC supplements, is known to intervene with neurological and addictive disorders including stroke (Cho and Kim, 2009, Davalos et al., 2012, Warach et al., 2000), memory deficits (Spiers et al., 1996), and cocaine addiction (Renshaw et al., 1999, Licata et al., 2011, Bracken et al., 2011, Brown et al., 2007). Thus, this article has a strong rationale to investigate whether citicoline is effective for AUD. The current options for its pharmacotherapy are limited in their efficacy and scope of use and only subpopulations of patients with AUD achieve remission after an adequate trial with the present agents. Accumulating evidence indicates that OTC supplements can be the better therapeutic option

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CONFLICT OF INTEREST

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because of the significant benefits in safety and favorable side effects profile. Particularly, the previous clinical trials performed by the author group have shown promise of citicoline in studies on comorbid bipolar disorder and cocaine use disorder (Brown et al., 2007).

Citicoline is a nucleotide compound that consists of cytosine, choline, ribose and pyrophosphate, and it is rapidly metabolized to cytidine and choline after oral administration (Wignall and Brown, 2014). It affects neuronal conditions *via* multiple mechanisms; 1) increases incorporation of phospholipids into membranes, enhancing structural phospholipid synthesis (Silveri et al., 2008), 2) regulates neurotransmitter levels primarily through modulation of catecholamine (Secades and Frontera, 1995) and indirectly increases norepinephrine, dopamine and serotonin in the brain regions (D'Orlando and Sandage, 1995, Fioravanti and Yanagi, 2005, Secades and Frontera, 1995), 3) may also reduce brain glutamatergic excitability by increasing astrocytic scavenger role via increase in excitatory amino acid transporter-2 (EAAT2, as known as GLT1) (Hurtado et al., 2005). In preclinical and clinical trials, citicoline appears to improve cognitive impairments (Zhao et al., 2006, Gareri et al., 2015). Therefore, this study aimed to determine whether citicoline treatment 1) reduces alcohol use in individuals with AUD and 2) improves cognition including executive functioning and declarative memory. Notably, while no statistical significance was found between citicoline and placebo group with AUD, the authors reported a significant reduction in alcohol use and craving within the citicoline treated group over the 12-week treatment. Having noticed this, the placebo has a strong effect as well. Despite a negative finding, the result provides important information for the future approach in the development of AUD intervention in terms of the rationale and strategy for OTC treatments for AUD. For example, as is evident from the discussion, there are several limitations to this study that preclude a definitive conclusion about the efficacy of citicoline in AUD, such as the modest sample size, relatively short observation period, and missing data. More importantly, there is a possibility that the heterogeneity in AUD and lack of multiple drinking outcomes such as heavy drinking days and length of abstinence periods may lead to the negative results. Although they used similar cohorts' size and dose in the trial similar to those used in cocaine trials which had shown the significantly positive effects of citicoline in cocaine use, the unique characteristics in AUD including its very various behavioral patterns and outcomes should have been considered. In addition, given that previous clinical trials with citicoline examined its effects as an "add-on" therapy for comorbid cocaine use and bipolar disorder, the efficacy of this supplement as an "add-on" therapy in AUD with or without comorbid disorders may be different. Thus, with careful dissections about the heterogeneous characteristics in AUD, the appropriate sample size with well categorized cohorts with detailed AUD patterns should be considered to design further trials. In addition, future research will need to investigate more closely how citicoline administration interacts with several neurotransmitter systems given specific circumstances and conditions. How might citicoline differentially act on cocaine or alcohol addiction? How might citicoline affect alcoholics with or without comorbid disorders? A more detailed understanding of the mechanisms of action underlying the effects of citicoline in different contexts will lead to a better understanding of its potential efficacy as therapeutic options for AUD.

HOW TO PRIOTIZE THE DRUG DEVELOPMENT?

As we mentioned above, few medications such as acamprosate, naltrexone, disulfiram are currently approved by the FDA for the treatment of AUD (Willenbring et al., 2009). Apparently, three medications show a limited efficacy for heterogenous AUD patients (Jonas et al., 2014). Therefore, the search for novel therapeutic options for AUD is currently a research priority and targeting a broad spectrum of new candidates including both novel and repurposed compounds (Oliveros and Choi, 2017). Particularly, development of effective pharmacologic treatments for individuals with co-occurring psychiatric disorders such as post-traumatic stress disorder (PTSD), is getting more attention compared with non-comorbid individuals. People with comorbid disorders tend to have a severe clinical impairment, higher utilization of mental health service, higher rate of suicide attempts, and lower quality of life (Kessler et al., 1997, Helzer and Pryzbeck, 1988).

Because of unmet needs for the development of AUD therapeutics, we have to consider at least two essential strategies. First, investigators have to carefully select new pharmacological agents, including supplements considering the potential benefits and risk of failures. Perhaps, the continued exploration of various supplements will result in optimal use of a drug for AUD. For example, while acamprosate is more efficacious in maintaining abstinence than naltrexone and shows a higher effect in patients having undergone detoxification, naltrexone is more efficacious in reducing heavy drinking than acamprosate and especially has a better effect in patients entering treatment after a lead-in period of abstinence (Maisel et al., 2013). Given the distinguishable mechanisms of acamprosate and naltrexone, majorly targeting GABA/glutamatergic and opioid system, respectively (Hinton et al., 2017, Niciu and Arias, 2013, De Sousa, 2010), the development of various agents and several supplements could be a direct benefit for sub-phenotypes of AUD. Second, investigators should reveal molecular and cellular mechanisms of how the supplements could be effective for certain AUD sub-phenotypes, which will lead to proper use of supplements for off-labeling treatments. When we know the precise mechanism leading to possible synergistic combinations of supplements for targeting specific symptoms, we may suggest the compatible medications to reduce the side effects or improve the efficacy with relatively low side effects and costs. OTC supplements generally have a good safety and low side effects profile, thus there is the potential to use these supplements as “add-on” therapies to improve the efficacy of FDA-approved AUD medications. In this case, the study with this negative outcome is also very valuable for drug development because it will provide information in a way to improve clinical studies. For example, we could investigate the precise mechanisms why a certain dose of OTC is working well with cocaine but was not working with AUD patients.

FUTURE OUTLOOK

The use of OTC drugs including citicoline in the management of AUD remains at investigational stages. How research in this treatment modality for AUD should continue and improve from this point represents a meaningful challenge for both researchers and physicians. The benefits of OTC supplements lie in their general safety and favorable side effects profile, even at higher doses. Although this study reported negative results, given that

the cocaine study finding the strongest positive results enrolled a very narrow patient cohorts (Brown et al., 2007) and AUD is highly heterogeneous in comparison to the narrow cohort studied in the cocaine trials, it should be considered that future studies ought to proceed with those factors carefully in order to ensure adequate power to detect significant effects. Further work will aim at studying the impact of various treatment of OTC supplements and will also aim at investigating the detailed mechanisms of the OTC supplements in the reward related brain activities. In this view, this study reminds us of the importance of collecting all negative and positive information regarding the treatment of OTC supplements in AUD. It is certain that accumulation of multiple clinical trials with OTC will assist in improving the therapeutic options in AUD and other related comorbidities.

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