CDP-Choline as a Biological Supplement During Neurorecovery: A Focused Review

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Abstract: Cytidine 5′-diphosphocholine (CDP-choline or citicoline) is a highly bioavailable compound with potential benefits for aiding neural repair and increasing acetylcholine levels in the central and peripheral nervous system. As a result, many researchers have investigated the use of CDP-choline for various types of neurological insult or conditions, including stroke, traumatic brain injury, and Alzheimer disease. Despite the fact that the safety of the compound has been verified across multiple international studies, evidence for efficacy remains less clear. This may be attributable, at least in part, to several issues, including a lack of randomized clinical trials, a lack of availability of the compound in the United States, and statistical power issues in reported trials. In addition, the fact that CDP-choline has multiple potential points of therapeutic impact makes it an exciting treatment option in theory but also complicates the analysis of efficacy in the sense that multiple mechanisms and time points must be evaluated. Although some clinical conditions do not appear to benefit from CDP-choline treatment, the majority of findings to date have suggested at least minor benefits of treatment. In this review we will examine the evidence in the published literature pertaining to use of CDP-choline in rehabilitation populations and briefly consider the work yet to be done.

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INTRODUCTION

Choline is an essential nutrient with known functions that are of potential significance in the treatment of rehabilitation populations. It is an intermediary in the formulation of acetylcholine, a neurotransmitter that is key to many operations of the central and peripheral nervous systems, including arousal, motor and cognitive functioning [1], and, in particular, memory. Disruption of the cholinergic system is a known result of both injury and degenerative diseases of the central nervous system (CNS), such as stroke [2], traumatic brain injury (TBI) [3], and Alzheimer disease [4,5], all of which result in significant impairment and often chronic disability.

Choline is of additional interest for rehabilitation because it is a primary building block for the phospholipids essential for cellular structure and cellular signaling. This mechanism of action suggests possible utility in neural stabilization and repair after injury to the CNS, because disruption of neurochemical signaling, cellular metabolism, and cell membrane integrity also are common sequelae associated with stroke, brain injury, and other CNS insults [6,7] . This understanding of how choline affects the nervous system suggests that, theoretically, in addition to improving cholinergic system functioning, supplementation with an exogenous source of choline actually has the potential to aid in neuroprotection during the secondary injury phases of acute neurological insult or injury and to promote and aid in neurorepair. The suggestion of both neuroprotective and neurofacilitative mechanisms of impact suggests that treatment with a choline biologic supplement has the potential to benefit multiple diagnostic groups treated by rehabilitation specialists and at multiple time points over the course of the recovery process.

Cytidine 5′-diphosphocholine (CDP-choline or citicoline) is a naturally occurring compound that is a viable source of choline supplementation. As will be explored in this review, studies have suggested that treatment with CDP-choline may provide neuroprotection and

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repair, as theoretically postulated, and may ameliorate cognitive symptoms even months to years after injury. Available studies worldwide also suggest that CDP-choline is relatively safe and causes few adverse effects or interactional effects compared with many other agents used in neurorecovery. For these reasons, CDP-choline has drawn the attention of researchers and clinicians interested in the possibility of improving patient outcomes while providing safe clinical care for persons with neurological diagnoses who can require complex treatment regimens and chronic care. The purpose of this focused review is to summarize research pertinent to the clinical use of CDP-choline in rehabilitation populations. In doing so, we will discuss the state of the current literature and directions for the additional study needed to more fully elucidate the efficacy of this compound.

BASIC PHARMACOLOGY AND DOSING SAFETY

CDP-choline is composed of ribose, pyrophosphate, cytosine, and choline. It is classified as an acetylcholine precursor. When taken orally, it is hydrolyzed in the intestine and absorbed as choline and cytidine. It is distributed through the body and efficiently crosses the blood−brain barrier into the CNS [8]. When administered orally, intravenously (IV), or intramuscularly, the necessary components of CDP-choline have been shown to be well absorbed and to have greater than 90% bioavailability for processes necessary for efficient functioning of the cholinergic and related systems [9]. The potential adverse effects of CDP-choline are similar to those of other cholinomimetic agents. The most common, although infrequent, adverse effects reported with CDP-choline have been mild gastrointestinal symptoms [10]. Other reported infrequent or rare adverse effects have included headache, tinnitus, insomnia, vision problems, anxiety, restless legs, leg edema, and dizziness. Overall, however, at common doses of 1000 mg orally or intramuscularly and IV doses of 250 to 1000 mg daily, this supplement has been considered to be well tolerated and safe. In fact, the authors of previous studies of patients who have had a stroke or head injury indicate that doses up to 4000 mg per day are generally well tolerated [1,11]. In our review of the literature, dosing was quite inconsistent across studies, ranging from 500 mg per day to 6000 mg per day, with higher dosing (ie, 2000 mg per day) appearing to show increased efficacy compared with lower doses.

In comparison with the safety profile, the efficacy of CDP-choline in treating neurologically based issues has been less clear. Although some early animal and human studies demonstrated positive results, others have been less conclusive. Many factors may affect efficacy and interpretation of findings in the literature up to this point. Significant reviews of the clinical literature relating to CDP-choline have been provided by Secades and Frontera [12] and Secades and Lorenzo [1]. We refer the reader to these reviews for full coverage of this topic outside of studies with particular relevance to rehabilitation.

Regarding factors that may affect the findings in the literature, it is worth noting that most of the clinical studies of CDP-choline have been conducted in Europe, Japan, and other countries, where CDP-choline is considered to be a pharmaceutical drug and is prescribed clinically. In the United States, CDP-choline is considered to be a supplement at this time and, until recently, has generally been available only in nutrition stores, with the preparations lacking regulated consistency regarding the active ingredient per dose. As a result of these differences, one challenge in conducting studies with CDP-choline in the United States has been a limitation in the availability of pharmaceutical-grade capsules or solutions. The use of nonstandardized doses may introduce variability into studies of this drug and make findings difficult to interpret.

Of note, however, is that the major manufacturer of CDP-choline in Europe has recently opened offices in the United States and is making and marketing a pharmaceutical-grade supplement that is now more widely available in the United States, with the goal of obtaining Food and Drug Administration approval. This development may make the clinical study of CDP-choline more feasible and practical under U.S. clinical trial guidelines.

BRIEF OVERVIEW OF RELEVANT NONHUMAN STUDIES

Studies in animals suggest benefits from CDP-choline treatment that are of potential significance for the rehabilitation population. For example, Dempsey and Raghavendra Rao [13] used a rat model of TBI in which groups of animals were injected with various doses of CDP-choline or saline solution at 1 and 6 hours after injury or sham. These animals were evaluated with a battery of neurological tests (ie, bilateral resistance to forced lateral pulsion and bilateral forelimb contraflexion while being suspended by the tail, and position maintenance on a vertical inclined plane) before injury and then at 1, 4, and 7 days after injury. After 7 days, findings indicated improvement in recovery of neurological functioning with administration of CDP-choline, and histopathological evaluation showed significantly decreased volume of cortical contusion and prevention of neuronal loss in the hippocampus [13]. In a rat model of cerebrovascular disorders producing cerebral white matter lesions (ie, stroke and vascular dementia), a chronic hypoperfusion condition was surgically induced and followed by treatment with CDP-choline or placebo in both immediate and delayed conditions. The goal of this study was to see whether CDP-choline could aid in the prevention of white matter damage under conditions of chronic hypoperfusion as well as improve cognitive functioning after injury. Cognition was measured

via animal performance in an 8-arm radial maze. White matter changes were completed through histopathologic investigation. White matter findings suggested that CDP-choline provided some neuroprotection for the immediate treatment group but not the delayed treatment group. In addition, improved cognitive performance was indicated for both the immediate and delayed groups receiving CDP-choline treatment compared with the group that received saline solution as a control [14]. The authors concluded that treatment with CDP-choline may be effective in treatment of acute ischemic stroke and also may assist with cognitive impairment in more chronic phases.

Alkan and colleagues [15] also suggested that CDP-choline treatment reduced mortality and provided neuroprotective benefits (on the basis of histology and edema infarct volume) in a rat model of subarachnoid hemorrhage with secondary cerebral ischemia. Başkaya and colleagues [16] also studied brain edema as well as blood−brain barrier breakdown after experimental TBI in rodents. When evaluating these secondary injury factors, they found dose-dependent neuroprotective effects with CDP-choline treatment, with higher doses significantly decreasing edema and blood−brain barrier breakdown compared with lower doses. As a final example, Dixon and colleagues [17] at the University of Pittsburgh used the controlled cortical impact model of TBI and found that, compared with injured animals treated with a saline solution, those treated with CDP-choline showed significant improvements in performance on skilled motor tasks and on spatial memory cognition in the Morris water maze. In addition, they demonstrated that a single dose of CDP-choline could increase extracellular levels of acetylcholine in the dorsal hippocampus and neocortex in noninjured animals [17].

STUDIES OF SPECIFIC REHABILITATION POPULATIONS

Stroke

A stroke occurs when blood flow in the brain is interrupted by (1) blockage of a blood vessel by a thrombosis or emboli or (2) the bursting of a weakened blood vessel with bleeding into surrounding brain tissue. In either case, injury to the brain may occur at the site of blockage or hemorrhage and at other areas that are not supplied with blood because of the injury. Although the actions of CDP-choline as applied to stroke are not fully known, theoretical science, basic science, and clinical findings suggest that it may be a beneficial complementary treatment when added to current clinical treatment guidelines. As described previously, studies in animals have shown that CDP-choline can aid in the repair of neuronal membranes and lead to an increase in the amount of acetylcholine in the brain.

Theoretically, these neuroprotective mechanisms are likely to occur in humans as well, although studies are limited at this time. Functionally, studies in humans have implicated CDP-choline in decreasing neurological deficits, aiding the recovery of daily activities, motor function, and even memory, and reducing the size of infarction. However, the evidence for these claims has been suggestive but not overwhelming. In addition, biomarker measurements are notably absent from the designs of studies reviewed here, making it difficult to relate the basic science definitively to the clinical findings.

Although early studies of human stroke populations from Europe and Japan were quite promising (see Clark [11]), recent studies have demonstrated only minor benefits. Three of the four U.S. studies on CDP-choline after stroke did not meet their primary objectives. Clark and colleagues [18] completed a randomized, double-blind, vehicle-controlled trial of persons with acute ischemic stroke. Patients were enrolled in this study within 24 hours of the onset of symptoms that were consistent with middle cerebral artery ischemia and with baseline computed tomography findings also consistent with this diagnosis. Treatment consisted of a 6-week trial of 1 of 3 oral doses of CDP-choline (500, 1000, or 2000 mg divided into 2 daily doses) or placebo, with an additional 6 weeks of follow-up. The authors found differences in functional outcome as measured by the Barthel Index [19] in support of CDP-choline (with doses of 500 and 2000 mg per day orally outperforming the 1000-mg dose). In a second study [20], the same investigators were unable to replicate that result with 500 mg; however, secondary analysis suggested benefit for a subgroup of subjects in the moderate-to-severe category (National Institutes of Health [NIH] Stroke Scale score of $\geq$8).

Clark and colleagues [21] also reported the findings of a third large, 118-center, phase 3 trial (n = 899) comparing placebo with a 2000 mg per day oral dose of CDP-choline. As in their previous studies, the authors studied patients who had sustained an acute ischemic stroke within 24 hours of the onset of symptoms that were consistent with middle cerebral artery stroke. Also, consistent with their previous trials, the treatment period was 6 weeks, followed by a 6-week follow-up period. In their primary analysis, the authors found no differences in the percentage of patients with a $\geq$7 point change on the NIH Stroke Scale [22] who had received CDP-choline compared with patients who had received a placebo. However, post-hoc analysis suggested a "moderate" treatment effect when the authors used measures of global outcome and examined differences in the percentage of groups reaching levels associated with "excellent" recovery (ie, Modified Rankin Scale score of $\leq$1 or 2, a Barthel Index Score of $\geq$95, and an NIH Stroke Scale score of $\leq$1) and when they used statistical methods of combining these index scores (ie, generalized estimating equations analysis) to evaluate efficacy differences between groups. The authors suggested that the use of these types of different primary outcome measures would have indicated at least some benefit

with CDP-choline treatment. They also suggested that a longer treatment period may have had a positive effect on outcome measures.

In the fourth U.S. study [23], Warach and colleagues used radiological methods (magnetic resonance imaging and diffusion-weighted magnetic resonance imaging) and the same basic inclusion criteria and design as the Clark studies. Primary statistical analysis failed to show significance in an analysis of differences in the "distribution of changes in lesion volume" during the 12-week period for the group receiving 500 mg/day of CDP-choline compared with the placebo group. The authors stated that significant variance in the size and, therefore, the percentage of change may have played a role in the lack of statistically significant findings.

Despite a lack of primary findings, planned secondary analysis found significant benefit with CDP-choline treatment during the first 6 weeks in terms of lesion volume reduction when evaluated from baseline to 12 weeks. Although clinical outcome was not directly measured, the authors asserted that lesion volume measurements may be useful biomarkers of clinical benefit for acute stroke treatments. These findings also raise the question of whether the reduction of tissue injury early after injury may contribute to improved outcomes in the longer term and suggest that further study is needed to evaluate such potential effects.

A meta-analysis in which the authors pooled participants from all 4 of the aforementioned studies also was conducted [24]. The authors used generalized estimating equations analysis to statistically combine the 3 commonly used indices (the NIH Stroke Scale, the modified Rankin Scale [25], and the Barthel Index) to obtain a global measure of recovery. For this analysis, they used only subjects from these studies with a diagnosis of moderate to severe stroke (NIH Stroke Score of $\geq$8) and excluded those with mild stroke because previous investigators had suggested significantly increased benefit for persons in the moderate-to-severe range. Other exclusionary factors included a therapeutic window $>$24 hours and a Rankin Scale score before stroke $>$1, which resulted in a combined subject pool of 1372 persons, 789 of whom received CDP-choline and 583 of whom received placebo.

With use of these methods, the authors found that 25.2% of patients in the CDP-choline group achieved "full" recovery, whereas 20.2% of those receiving placebo attained the same level of recovery (odds ratio 1.33; 95% confidence interval 1.10-1.62; $P = .0034$). Thus CDP-choline treatment was associated with a greater probability of complete recovery at the 3-month mark after stroke [24]. The dose showing the largest difference was the highest one used among the studies (ie, 2000 mg) [24]; 29.7% of patients receiving that dose were classified as making a complete recovery (odds ratio, 1.38; 95% confidence interval 1.10-1.72; $P = .0043$). Safety analysis indicated the profile of CDP-choline to be similar to that of placebo. The authors asserted that this evidence suggests that the individual studies may have been hampered by a lack of power. They concluded that treatment with CDP-choline within 24 hours of symptom onset may provide significant benefit 3 months after the stroke.

Along the same lines, the authors of an observational study from Korea [10] followed nearly 4200 cases of acute ischemic stroke and used the same outcome measures as the meta-analysis just described. Consistent with the findings and suggestions of these previous studies, this group found statistically increased functional gains for patients who received the drug for longer than 12 weeks compared with those who stopped taking the drug at 6 weeks. Patients who received a higher dose of CDP-choline ($\geq$2000 mg/day) performed better on those functional scales, and some positive differences were found between patients who did and did not receive the first dose within 24 hours of the stroke [10].

In summary, although CDP-choline appears promising for the treatment of ischemic stroke in humans, some factors require further evaluation. Current findings suggest that beginning administration of the compound within the first 24 hours seems to be useful. Interestingly, this treatment initiation window is longer than that used for most other available stroke treatments (eg, tissue plasminogen activator), which suggests that CDP-choline may be an option for treatment in situations in which the window has closed for the use of other agents or when other treatments are contraindicated.

Some evidence also suggests that higher doses and longer treatment times appear to provide increased benefits, as mentioned previously. In short, although it is still under investigation, CDP-choline appears to represent only minimal risk while having potential advantages for use in treatment after stroke. Additional study is needed to more fully elucidate efficacy. Ideally, direct replication and elaboration of some of the earlier European and Japanese studies should be conducted to evaluate safe use and efficacy in the United States and to attempt to clarify some of the complexity of timing, dosage, and outcomes. The inclusion of biomarker measurements should be incorporated to gain additional understanding regarding the mechanisms of action and to learn more about subgroup and individual characteristics that may play a role in the determination of efficacy. Biomarker methods also may be useful as proxy measures of short-term and long-term outcome and for comparison with other measures of recovery. As pharmaceutical-grade CDP-choline supplements become more readily available and further studies are completed, randomized clinical trials using U.S. clinical trial guidelines should be conducted to evaluate efficacy in the stroke population.

Traumatic Brain Injury

TBI refers to any injury to the brain caused by external mechanical forces, such as a blow to the head, abrupt deceleration, or a penetrating injury to the brain. As with stroke, repair of the primary injury and further minimization of

secondary injury damage is critical to recovery and eventual outcome. On the basis of animal studies and theory, cholinergic systems are believed to be involved in these processes. Initially, the biochemical cascade that occurs during the acute postinjury phases includes a significant increase in cholinergic activity [2,26]. After the acute phases, it has been shown that a long-term hypocholinergic state results from TBI [2,26]. In addition, areas of the brain known to have significant roles in memory and learning (such as the hippocampus and limbic system) are both rich in cholinergic receptors and particularly susceptible to TBI-related disruption as a result of the location of these structures in areas vulnerable to rotational forces that occur during the primary injury.

As a result, treatments aimed at improving cholinergic system function after TBI are theoretically promising. Studies in which investigators evaluated CDP-choline use during the acute phases of recovery from TBI have been conducted over many years in Japan and Europe. Secades and Lorenzo [1] have provided an excellent review of these studies. They report that, as early as 1967, Moriyama and colleagues evaluated 25 patients with acute cranial trauma and impaired cognition and found that treatment with CDP-choline was associated with improvement in acute neurological clinical symptoms and level of consciousness. Secades and Lorenzo [1] also describe several other studies that indicate more rapid regaining of consciousness with CDP-choline compared with standard care or placebo.

Studies in which the investigators compared CDP-choline with other medications also have been conducted. For example, as reported by Secades and Lorenzo in their review of European studies [1], the authors of 2 French studies found that treatment with CDP-choline promoted improved acute outcomes (ie, duration of coma, changes in electroencephalographic measures, and functional recovery) when directly compared with 2 other European CNS-stimulant medications (meclofenoxate and piracetam).

Additional reviews and comparison of cholinergic agents for the treatment of neurocognitive impairments after TBI have been contributed to the literature [27-29]. These reviews have reported positive findings with CDP-choline based on many of the studies included here, but they also provide a review of other cholinergic agents and recommendations for additional areas for research. For example, in 2008, Poole and Agrawal [29] conducted a systematic review of cholinomimetic agents used for the improvement of neurocognitive issues after head injury. They found that clinical evidence for donezepil (Aricept, manufactured by Eisai, Inc, Tokyo, Japan) was greater than that for physostigmine for persons with TBI. These investigators stated that studies of CDP-choline were promising, with positive findings noted in available studies of mild TBI, as well as one study of moderate to severely injured individuals. Across the board, however, the authors called for additional well-designed clinical trials to further study use of all of these compounds in persons with TBI. The need for further study was echoed in the other reviews as well. Studies combining CDP-choline with other medications also may be beneficial.

Regarding the use of CDP-choline in persons with TBI, some researchers also have evaluated clinical and functional recovery beyond recovery of consciousness and acute trauma care. For example, in a clinical study of 60 persons with severe head injury [30], treatment with CDP-choline was associated with an accelerated overall rate of recovery. Dosing for this study was as follows: patients received 750 mg/day of CDP-choline intravenously for the first 6 days, and the same dose was delivered intramuscularly for an additional 20 days. Patients underwent follow-up for a period of 6 months. Differences were statistically significant between the placebo and treated groups at 15 days in terms of recovery of response to painful stimuli and regaining consciousness. At 120 days, persons in the CDP-choline group were more likely to be walking unaided compared with those in the control group.

In another example, Lozano [31] evaluated changes in posttraumatic edema in 78 severely injured individuals by using computed tomography. He also included evaluation of the length of hospital stay and level of independence at the time of hospital discharge. In this study, 39 patients received intravenous dosing for the initial 2 weeks (dose ranging from 3-6 g/day). At the end of the 14-day treatment period, those who received CDP-choline were more likely to have decreased or normalized cerebral edema and a reduction in the required length of hospitalization. At the time of discharge, Glasgow Outcome Scale differences were not significant between groups; however, this finding was judged to be attributable to the limited number of participants, as well as individual characteristics of the subjects who participated. Nonetheless, a trend toward improved functional outcomes for those treated with CDP-choline was noted.

The review by Secades and Lorenzo [1] reports 2 larger European studies with positive findings for improved functional recovery after acute care treatment with CDP-choline. The first study is a French survey of 921 cases of head injury in which those treated with CDP-choline (n = 219) were concluded to have increased "quality of survival," including more functional family interaction and greater likelihood of return to work or school. Calatayud Maldonado and colleagues [32] completed a study of 216 patients with moderate to severe injury. Of these patients, 115 were treated with a mean dose of 4 g/day. The investigators found reductions in the length of both inpatient and outpatient care, improvement in motor, cognitive and personality changes associated with injury, and improved global outcome. Finally, in a small study of patients with a concussion, Levin [33] found, at 1 month, a decrease in postconcussion symptoms and improvement in visual recognition memory with CDP-choline treatment (1 g delivered orally) compared with placebo.

Leon-Carrion and colleagues [34] also conducted 2 CDP-choline studies that focused on cognition after TBI . In each of these studies, at least 6 months had passed since patients had sustained a TBI and they had severe memory deficits. The first study used a measure of cerebral blood flow at baseline and 1 hour after administration of 1 g of CDP-choline. At baseline, the investigators found initial hypoperfusion in areas known to be involved in memory and noted subsequent normalization during the second neuroimaging session after administration of the CDP-choline [34] . In the second study, 2 groups underwent an ecological neuropsychological memory rehabilitation program with one group receiving placebo and the second group receiving CDP-choline treatment (1 g/day) for a 30-day period. When baseline and follow-up neuropsychological testing results were compared, the authors found that the placebo group showed no significant improvement, whereas those in the treatment group showed general improvements in cognition, with significant improvements in performance on a task of verbal fluency and on the Luria Memory Words-R test [34].

Overall, studies of TBI suggest that CDP-choline has the potential to be beneficial both as a neuroprotective compound for reducing the impact of the secondary injury cascade and as a neurofacilitating compound for improving recovery over the course of rehabilitation. The studies reviewed suggest positive findings both early and during the more chronic phases of recovery, although a true understanding of efficacy remains unclear. In part, this situation may be attributable to the complicated nature of studying a compound with multiple potential mechanisms for impact.

Additional studies of dosing and timing of treatment for optimal impact and well-designed randomized clinical trials are still needed at this time. Pairing functional outcomes with biomarker measures may assist with evaluation of efficacy at various time points or with particular subgroups of the TBI population. The use of neuroimaging techniques, such as functional magnetic resonance imaging and magnetic resonance spectroscopy (MRS), also may help to further inform us about the mechanisms of recovery when CDP-choline is administered after TBI.

Other Populations

As a cholinomimetic agent, CDP-choline has potential benefit in other conditions associated with aging, such as Alzheimer disease, vascular dementia, and age-related (degenerative) changes in the brain. Changes in hippocampal volume and disturbances in cholinergic transmission are known to be associated with neurodegenerative disorders and with Alzheimer disease in particular [4,35,36]. A few studies published in the 1990s evaluated CDP-choline in Alzheimer disease, with limited but slightly positive results. In one early study, Cacabelos and colleagues [37] examined changes in patients with early- or late-onset Alzheimer disease who had received oral CDP-choline at a dosage of 1000 mg/day for 1 month. Results showed minor gains in mental performance on the Mini Mental State Examination, as well as increases in blood flow velocity and changes in blood chemistry for participants with the early-onset form of the disease. The latter of these included reductions in histamine and interleukin-1 levels and an increase in tumor necrosis factor–α [37].

In contrast to Alzheimer disease, at least one randomized, double-blind, placebo-controlled study [38] of CDP-choline treatment efficacy for vascular dementia found no benefits in either neuropsychological performance or neuroimaging measures with administration of 1000 mg a day orally for 12 months, although the study had small patient groups (15 per group before dropout). It is possible that differences in hippocampal and cholinergic system involvement between Alzheimer disease and vascular dementia, or the more diverse presentation of vascular dementia, may account for differences in response to CDP-choline. In an additional study of changes in normal aging conducted by Babb and colleagues [39], older participants treated with CDP-choline for a period of 6 weeks showed a 7.3% increase from baseline levels in brain phosphodiesters, which correlated with improvement on a neuropsychological test of verbal learning. The conclusion of this study was that 6 weeks of 500 mg/day orally administered CDP-choline stimulated phospholipid synthesis and turnover in a group of older participants, suggesting that CDP-choline may be a useful agent for reversing age-related biochemical changes in the brain [39]. Similar memory gains were also noted by Spiers et al [40].

Additional studies of neurological disorders also have had mixed results or are very limited at this time. For example, CDP-choline has been used in combination with levodopa for the treatment of Parkinson disease symptoms. Because a gradual loss of efficacy of levodopa my occur with chronic treatment and significant adverse effects may become an issue, the development of additional treatments is of interest. The rationale for use of CDP-choline is that it may provide some neuroprotective benefits, increase the availability of dopamine in the striatum, and act as dopamine agonist. Some minor benefits have been demonstrated for CDP-choline use in Parkinson disease [41], and there was some suggestion in the early 1990s that the use of CDP-choline in combination with levodopa may allow for the reduction of levodopa dosing, resulting in prolonged efficacy and reduced adverse effects [42]. Further large-scale randomized controlled trials appear to be lacking since that time and would be needed for further efficacy evaluation. A single animal study of Huntington disease produced no positive results, and the authors concluded that the substance would not be useful as a treatment [43].

CDP-choline treatment after spinal cord injury is just beginning to be examined experimentally, but it has shown promise in animal studies. In a rat model of spinal cord injury, neurobehavioral recovery rates after surgi-

cally induced spinal cord injury in rats treated with CDP-choline and methylprednisolone [44] (which is standard treatment immediately after spinal cord injury) were equivalent, and both rates were statistically better than placebo. In addition, both agents were also equivalent to each other and superior to placebo in histopathological findings, indicating reductions in malondialdehyde levels, nitric oxide levels, and trauma size ratios. Furthermore, both agents produced greater reductions in glutathione levels compared with placebo. The authors concluded that CDP-choline was equivalent to treatment with methylprednisolone but that a combination of the 2 agents did not provide additional efficacy [44].

NEUROIMAGING AND BIOMARKER STUDIES WITH CDP-CHOLINE

The bioavailability of CDP-choline has been demonstrated through clinical studies in which the authors evaluated serum levels and through animal studies, some of which have been presented in this article. Perhaps of particular relevance to neurorehabilitation populations, however, are biomarker studies, as well as those that use neuroimaging techniques with human subjects. Additional serum and cerebrospinal fluid biomarker studies may provide biochemical information about mechanisms of action and subgroup characteristics that contribute to efficacy of CDP-choline. In addition, some neuroimaging techniques allow for "real-time" measurement of changes occurring in the brain as a result of treatment with CDP-choline and may help increase our understanding of the mechanisms of action of this supplement, as well as the neural substrates of recovery from neurological injury. MRS is particularly interesting because MRS techniques allow for the detection of distinct magnetic profiles of biomarkers, including choline-associated compounds in the brain. Studies in healthy human control subjects have yielded some interesting results, including evidence of increased choline-related compounds in the brain after ingestion of CDP-choline [45]. In addition, evidence of increased phospholipid turnover in the frontal lobes suggests that CDP-choline may be useful for increasing energy reserves and improving the ability to maintain cell membranes [46] .

Perhaps most interesting, however, are studies in which the authors combine and correlate biomarker and neuroimaging techniques together or with other measures. For example, in the normal aging study by Babb and colleagues [39], discussed previously, MRS techniques were used in combination with neuropsychological tests of verbal learning. Positive correlations were found between increased brain phosphodiesters in persons treated with CDP-choline and improvements in neuropsychological testing performance. Also, as previously mentioned, Leon-Carrion and colleagues [34] used measures of regional cerebral blood flow to show normalization in regions of hypoperfusion after treatment with CDP-choline in persons with a history of TBI, and these areas were noted to be specifically associated with memory (ie, inferior left temporal area). In a separate study, these investigators found that persons with a history of TBI and memory issues who were treated with CDP-choline over the course of a 6-week memory neurorehabilitation program had improved outcomes in terms of memory, learning processes, and verbal fluency compared with persons treated with placebo.

Taken together, these results suggest that CDP-choline may target areas of the brain specifically associated with memory functioning and may assist in rehabilitation of cognitive functioning. It is our assessment that additional studies in which biomarker data and neuroimaging data are gathered simultaneously with cognitive data would be even more powerful. For example, functional magnetic resonance imaging and MRS studies conducted during the same session could yield virtually simultaneous measures of hemodynamics and biochemical compounds in the brain, both at baseline and after a period of treatment with CDP-choline. Similar studies combining neuroimaging with serum measures and/or additional neuropsychological and biological measures could be conducted.

SUMMARY

A review of the available literature shows that CDP-choline has some promise for use within rehabilitation populations during both the acute phase and longer term phases of recovery. CDP-choline use is relatively safe, and it has the potential to affect multiple neuroprotective and neurofacilitative targets in the CNS that may influence outcome. Studies to date have indicated that risks for adverse effects or complications are low, and at least some benefit may be gained. Although its multiple potential mechanisms of action make CDP-choline a promising treatment option, they also complicate the approach to efficacy studies in that multiple time points and systems must be carefully evaluated.

As a result, the current research suggests that many questions about CDP-choline still need to be answered. For example, in the stroke literature, it has been suggested that the amount of time that elapses after a stroke before CDP-choline is administered, the method of CDP-choline delivery, and the dosage may all be important factors that influence the efficacy of CDP-choline, whereas the choice of outcome measures (eg, the use of global versus functional outcome measures) may affect whether study authors are able to report positive results [47]. In addition, sample size, magnitude of change, and analysis of efficacy with subgroup populations may be important.

Similar issues are indicated in the TBI literature and are likely applicable across other rehabilitation populations. Certainly these issues require more study, and further clinical trials that are designed to address these complexities are

needed. It is our sense that, in the future, research designs that include multimodal and cross-disciplinary methods of exploration used in concert are likely to yield a greater understanding of the complex problems associated with determining the efficacy of medications and therapies.

Additional studies that combine CDP-choline with other medications or treatments also may be of interest. Incorporating biomarkers into the research design may significantly advance our progress in utilizing clinical trials to study treatment efficacy. This step may be particularly true in rehabilitation populations, in which multiple injuries and multiple systems may be involved in the process of recovery. In our opinion, "Rehabilomic"-focused studies [48] are critical to bridging the gap between (1) what is known in basic science regarding CDP-choline and other rehabilitation treatments and (2) the efficacy and comparative effectiveness studies that inform clinical care of persons with neurological deficits.

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