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Enhancing Cognition with Citicoline ^[6]

An interview with Deborah Yurgelun-Todd, PhD, and Perry Renshaw, MD, PhD

By Natural Medicine Journal



MAY 2018 SUPPLEMENT

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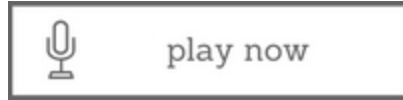
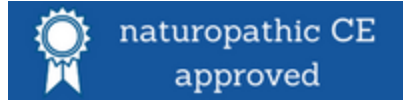
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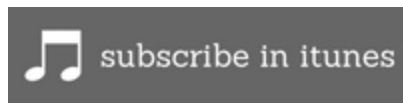
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Natural Medicine Journal's publisher interviews Deborah Yurgelun-Todd, PhD, and Perry Renshaw, MD, PhD, about the research they are conducting at The University of Utah in the Neuroscience Department. They specifically describe research associated with the safety and efficacy of supplemental citicoline, as well as evaluate emerging research in this area.



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About the Experts



Deborah Yurgelun-Todd, PhD, is director of the Neuroscience Initiative and a USTAR Professor of Psychiatry at the University of Utah School of Medicine. Her research focus is on identifying the neuropsychological and neurobiological bases of human behavior. Yurgelun-Todd is an expert in the application of structural and functional magnetic resonance imaging, the administration and analysis of neurocognitive tests, and the integration of the results obtained by these multiple modalities. She has examined the etiologic bases of neural models of dysfunction in psychiatric disorders including depression, bipolar illness, substance misuse, and schizophrenia. She is also recognized for applying imaging techniques to study cortical changes during development in healthy children and adolescents, and during treatment intervention in adult patients.



Perry Renshaw, MD, PhD, MBA, is a USTAR Professor of Psychiatry at the University of Utah School of Medicine and a Medical Director of the VISN 19 Mental Illness Research, Education and Clinical Center (MIRECC) at the Salt Lake City Veterans Affairs Medical Center. His training as a biophysicist and psychiatrist has led to a primary research interest in the use of multinuclear magnetic resonance spectroscopy (MRS) neuroimaging to identify changes in brain chemistry associated with psychiatric disorders and substance abuse. Current clinical trials are focused on the use of citicoline as a treatment for methamphetamine dependence, creatine as a treatment for depression, and uridine as a treatment for bipolar disorder. Renshaw's recent work focuses on brain chemistry changes that may increase depression and suicide for people living at high altitudes.

Transcript

Karolyn Gazella: Hello, I'm Karolyn Gazella, the publisher of the *Natural Medicine Journal*. Today, I'm thrilled to be joined by two highly respected brain researchers from the University of Utah Neuroscience Department, Dr. Deborah Yurgelun-Todd and Dr. Perry Renshaw. Now, before we begin and dig into today's topic, I'd like to have each of you describe the focus of your research. So let's start with you, Dr. Yurgelun-Todd.

Deborah Yurgelun-Todd: Yeah. Well, my research is initially started to focus on cognitive function and the neuropsychological, or brain, pathways that mediate how we think and how we feel. And then I became very interested in the application of brain-imaging to help us understand exactly how those pathways worked and give us some insights into how the brain does things well, and how it does things less well.

Gazella: Perfect. Now, Dr. Renshaw, how about you? Can you please describe your

research focus?

Renshaw: Well, sure. Well, I'm sort of confused soul. I'm a psychiatrist/biophysicist, and the way in which I merged these techniques together is to do brain-imaging studies that focus on, how is brain chemistry altered in, particularly, diseased states that psychiatrists might be interested in. And based on identifying unusual patterns in brain chemistry, my research group likes to focus on identification and development of novel treatment strategies. One of which is a molecule, I guess we'll be talking about today, CDP-choline or Cognizin.

Gazella: Perfect. And you're absolutely correct, I'd like to talk about citicoline in a lot more detail. Now, Dr. Yurgelun-Todd, why did you become interested in citicoline for the brain, and why did it catch your attention?

Yurgelun-Todd: Well, they've done some work looking at why the brain was not working very well in mood disorders, and why attention, in particular, was a problem in individuals who had depression and other mood disorders. And when citicoline was brought to my attention, there seemed to be interesting potential for that to alter attentional systems. So I became very excited at the possibility of that becoming a treatment for individuals who may not have optimal brain functioning.

Gazella: Perfect. I love the fact that attention actually is what caught your attention, so that's brilliant. That's brilliant. Now, Dr. Renshaw, what does the scientific literature tell us about the safety of citicoline, and are there any contrary indications or risks associated with its use orally?

Renshaw: You know, that's a great question because we have a really well established answer that citicoline has been used millions of times around the world. In some countries, particularly where they use it as an intravenous administration as a drug. In other countries like the US and Canada, it's a nutritional supplement.

We've done studies, or rather, Dr. Yurgelun-Todd has done studies looking at the effects of citicoline on adolescents and she can describe what she saw. But, by and large, you have to take a whole lot of citicoline before you notice anything adverse. And in the few instances where we've seen that, it's been people feeling like they've had too much Starbucks coffee and that goes away over about a half an hour.

Gazella: Yeah, and I would like to hear about the studies on children, Dr. Yurgelun-Todd. What does your research tell you about safety, especially in that population?

Yurgelun-Todd: It's very interesting because we, as I mentioned, I was interested in potential ways to improve thinking and so we decided we would look at the developing brain in individuals who were adolescent. And we found that when we supplemented with citicoline, they actually improved their attentional span and could do—and had some improvement in their psychomotor function as well. So this was in healthy adolescence, rather than anyone who actually had a documented impairment. The fact that you could see improvement in cognitive functioning and psychomotor functioning in healthy individuals without a documented impairment was actually quite remarkable.

The other thing that was remarkable was that the dosing was very low, and in fact, this was a new area to explore. How low could we dose and still see an effect on the brain? So

we were quite enthusiastic about those findings and think they have important implications. With regard to safety, we also were very rigorous in the documenting potential side effects associated with the administration of citicoline and we really saw essentially no side effects in the side effects profile that we did document. Looked very similar to the placebo, in fact, was not statistically different between placebo and the treatment arm. So we were really reassured that even with the rigorous assessment for side effects, there was nothing that was documented in this trial.

What's really compelling, however, is that most treatments for cognitive changes or for any neurologic disorder, neuropsychiatric disorder do end up having side effect issues, some of them being more visceral, like stomach or headache or things like that, but also some of them actually diminishing your cognitive functioning. So this was rather remarkable that we could enhance cognitive functioning with no side effects.

Gazella: Yeah. I mean, it's good to hear that the safety profile is good. And I may want to come back on that topic of children, but Dr. Yurgelun-Todd, I'm going to stick with you here. There's a wide variety of brain functions and cognitive issues that have been researched associated with the use of citicoline, like focus, attention, dementia, and other issues. Which area, presently, has the strongest, and most compelling research?

Yurgelun-Todd: Well, that's a very interesting question because there's a bias based on what science you happen to love. I think some of the most compelling research has been associated with the fact that there's a repair mechanism associated with the administration of citicoline, that is, cellular biochemistry is actually altered and phospholipid synthesis is improved when you have an administration of citicoline, therefore, individuals who have neurological insults, such as strokes or mild traumatic brain injury, things like that can see rapid repair in their cells with citicoline administration. That is the area that's more involved in the patient or the real neurological insult area.

Within the healthy individual, I think the most compelling research really falls on two ends of the lifespan, that is the elderly or middle-age and above, and also then some of the work we talked about in adolescence, where both when your brain is growing rapidly and also when your brain is aging, it seems as if the supplement with Citicoline can make a substantial difference.

Gazella: Yeah, that's interesting. Now, Dr. Renshaw, there's preliminary research demonstrating that citicoline may be able to help with cocaine dependence and addictions. I find that pretty fascinating. How promising is that research, and do you see that as a viable application in the future?

Renshaw: Yeah. No, that's a great question. Citicoline, broadly speaking, has 2 effects. One that Dr. Yurgelun-Todd just touched on. Brain repairs is probably more well established and been investigated for probably 30 or 40 years. Our work, to a first approximation, looks at the effects of citicoline in terms of increasing the levels, brain levels, of neurotransmitters, particularly dopamine and norepinephrine in the brain.

When someone is using cocaine or methamphetamine, they often have a depletion of dopamine within their brain, as well as, in the case of methamphetamine, some damage related to decreases in blood flow. From that perspective, citicoline is almost a perfect fit in terms of what it can do an active user, increasing the level of dopamine in the brain, makes them feel, I think, more intact and, perhaps, less inclined to continue using drugs.

And the brain repair mechanism because the mechanism on which stimulants cause brain damage is often related to ischemia. It's just a really good fit.

Where we're going now in this research, is that we've broadened our scope from cocaine to methamphetamine to stimulants that are used to treat ADHD. In fact, we are in the middle of finding a study supported by the National Institutes on Drug Abuse, we're working with in Salt Lake City and Seoul, South Korea. And what we're looking at is adolescents who are using stimulants, not necessarily as a drug of abuse, as a way to approve their attention, focus, and do better on very rigorous South Korean college entrance exams. Some estimates suggest that close to a quarter of all high school students in South Korea are taking stimulants, which is probably not good or the long-term outcome of which is not good. We think citicoline may be a way to help people feel better and get off the use of stimulants. Which is better avoided, unless you have a really good reason for continuing treatment with that class of medication.

Gazella: Yeah. That's actually one of the questions I was going to ask. When you're talking about using citicoline in healthy children, I was curious ... and Dr. Renshaw, I'll stick with you on this one ... I was curious, I have not read any studies using citicoline for children with ADHD, but I think what you're saying is you're evaluating whether or not this could be a viable alternative to the pharmaceuticals that are being used for ADHD. Is that what I'm hearing?

Renshaw: There's a real divide, at least in the United States, between things that are approved as natural products, nutritional supplements, and pharmaceutical agents. The natural product industry lives in fear of having their products considered to be drugs because the amount of testing, and safety monitoring, and efficacy, and evaluation that goes into getting something onto the market as a drug is really very expensive and onerous.

So for us, any research that we do, we have to have it paid for itself. It's been a lot easier to look at the use of citicoline in healthy populations, and certainly the sponsors of the work that we've done, which have been certain large natural product companies, who are much, much happier without us in approach. That's said, if I take off my sort of business man's hat and put on the scientific garb, what we believe is that, in fact, citicoline would likely have good effects for treating ADHD.

In Europe, it's been used as a drug to treat Parkinson's disease with good outcomes, and Parkinson's disease is, as you may know, is also a disorder associated with decreased dopamine in the brain. The ability to increase focus and attention is generally quite good. The difference between citicoline and the stimulant per se, is the effect of citicoline is to increase the brain's concentration of dopamine, that you're encouraging the brain to make dopamine when it otherwise might not do so. Stimulants just release dopamine from the brain and tend to deplete it, so they are very different mechanisms, and there's every reason to think that they'd both be affective. They probably have different safety profiles.

Gazella: That's fascinating. And Dr. Renshaw, I'm going to stay with you one more time. What about autism, autism spectrum? There's numerous conditions that are in that category. Any preliminary research in that or are we pretty much leaving that alone for now?

Renshaw: We haven't been involved in that research. There was a company we did some

research with in the Boston area, that was very interested in a related compound from the treatment of autism. They got involved in a big patent dispute with the University of California in San Diego that was resolved in UCSD's favor. So I don't think there's ever been a trial. But, there certainly is a suggestion in the autism literature to treat with pyrimidines, as the effect of either cytidine or uridine on the brain might help some individuals with autism spectrum disorders, but I think in fairness, it's really quite preliminary and that we'd have to do studies to understand what the effects were likely to really be to a population.

Gazella: Yeah. That makes a lot of sense. Now, Dr. Yurgelun-Todd, I'd like to stay on this topic of exciting new research in the area of citicoline use. Another area of research that's pretty interesting, and could be significant, is the use of citicoline for appetite control. I mean, obviously we have an issue with obesity in this country. Is it too early to tell is this may be a promising application of citicoline in the future?

Yurgelun-Todd: You know, I don't think it is. We've noticed some years ago that in looking at the response to food cues, individuals who had received the supplementation of citicoline actually showed significant decreases in appetite and that this was related to dose of citicoline that they'd received. And the thing that was interesting about that data, was it wasn't just that the individual said, "Oh, I feel like I have a reduced appetite." They actually showed differences in the way their brain responded to the cues, such as food items, ice cream, donuts, things like that when they viewed them in the magnet.

So we had documentation that neural activation was altered in food-processing related areas of the brain, as well as having a decrease in appetite, which really suggests that there is some mediation of brain responses to appetitive cues, which is really one of the problems with obesity. And within weight control, that's just sort of having an over-reaction to these kinds of cues.

And thinking about it further, it didn't really surprise us because it goes back to what Dr. Renshaw just mentioned about the dopamine system, the dopamine system in addiction are part of the reward system in the brain and the ... although we initially focused on the impact of citicoline on cellular function and phospholipid metabolism, we recognized as we thought about it further, that the concentration of dopamine is being changed with the supplementation of citicoline as well. So we're changing neurotransmitter balance in the brain and that had a really positive affect in terms of response to food items. I don't know if Dr. Renshaw wants to comment.

Renshaw: No, I think that's right. When stimulants have been used for this purpose, in fact, that's why many of them were developed initially, but they sort of force the brain to release all the dopamine that it's already made. What we really like about citicoline or pyrimidines as a strategy for increasing brain dopamine is that A, it's really encouraging the brain to speed up synthesis, which is sort of what you'd like to do, and again from a safety perspective the latter approach should be much safer for individuals taking a supplement or another medication over time.

Yurgelun-Todd: To go back to your question on is it too soon. I don't think so because I think most studies that we hear about are really just using self-report and don't have the documentation of a brain response. You couldn't really fake a brain response in terms of metabolic activations, so that is a really, I think, robust piece of research that will support this as an appetite moderator.

Gazella: That's fascinating. Now, I want to stick with you, Dr. Yurgelun-Todd because I do want to go into dosage. But specific to appetite control, what was the dosage used?

Yurgelun-Todd: 2,000 milligrams in the study that we did. Although, we did not ... we've not had the opportunity to see how low we can go to have this effect. And this was in middle-aged individuals. So we were looking at people, 40 to 60 years old, and they were looking at the extent to which having a 6-week supplementation could impact the brain. And that's what we saw.

Gazella: And 2,000 milligrams, is that divided doses?

Yurgelun-Todd: Yes, it was. It was morning and evening.

Gazella: Okay, perfect. Now, Dr. Renshaw, I want to dig a little bit deeper into this issue of dose. Now, does the dose of citicoline vary depending on the application or is there a consistent dosage range that is affective across most conditions?

Renshaw: That's a great question, and citicoline has a funny history that was used most extensively first in Europe. And there, after an injection of citicoline, they had a lot of trouble showing that there was any citicoline or cytidine in the bloodstream. When they went to oral ingestion, that became an even bigger problem. And it turns out, that the stomach plays tricks with citicoline, it turns the cytidine, that's part of it, into a molecule called uridine, which is the predominate pyrimidine in the human central nervous system. Because of that, it's been a wide spectrum on the views on how bioavailable, that is how much citicoline gets used by the body. It turns out that if you measure uridine, essentially all the citicoline is absorbed and gets distributed across the body, but it took a long time to figure that out. This was sorted out by a scientist at MIT, Richard Berkman, who's also studied citicoline extensively.

If you look at the clinical indications, a lot of the ones we look at, mood disorders, attention-deficit disorder, probably require lower doses. In the United States, the most recent trials have really looked at serious brain injury conditions, like stroke, and so there have been trials that are conducted with oral administration of citicoline to treat stroke. The problem there is that in the context of someone who's found out a real metabolic stress affecting the brain and the body, it just sort of absorbs things effectively from your stomach, plus you've got a problem with the area you want to impact has got decreased blood supply due to the stroke. And doses went up to something like four grams a day in those instances.

We've been ... most of our indications using somewhere between 500 and 2,000 milligrams of citicoline. The effects of citicoline last for about two, or three, or four hours just depending on the individual. So taking it twice a day works reasonably well. There is, for many normal people, a self-correcting mechanism, which if you're taking more than your body needs, you will feel anxious and jittery. That's relatively uncommon. Anyone taking less than 2,000 milligrams a day is unlikely to have side effects. This is obviously important in figuring out what to do. Studies in children, for example, as Dr. Yurgelun-Todd has done. Children come in a variety of shapes, sizes, and weights. It's probably going to be important to adjust the dose to reflect the weight of the child.

Gazella: Yeah. I think one of the fascinating things for me with citicoline, is that it does, in fact, have efficacy at what could be considered a fairly low dose, even as low as 250

milligrams. But even at 500 milligrams, that's a pretty low dose, and it's still showing affect, correct?

Renshaw: That's right. From that perspective, it's really important to recognize that one of the most established effects of citicoline is to speed up membrane synthesis, and this is true in every cell in the body, and we all travel around with CDP-choline in our cells. For that reason, because it's highly important in controlling this fundamental process, the body tends to keep the concentration of CDP-choline low. So that relatively low doses, especially for natural product, work much more effectively than is true of almost any other type of natural product. And again, we think that that has a lot to do with the fact that it's a really important regulatory control molecule within the body.

Gazella: Right. Now, Dr. Yurgelun-Todd, we've talked about a lot of different conditions, and application, and some pretty exciting emerging research associated with the oral use of citicoline. Out of all of that, what do you feel shows the most promise?

Yurgelun-Todd: I think I'm going to relate that to where I think there's a great deal of need. And that is in our children, and our adolescents, and young adults. And specifically, I think the fact that we can provide a very safe, minimally, essentially no side effect treatment to improve attention, and you touched on this earlier, I think is very significant. We've not done studies in ADHD or populations, such as a diagnosed ADHD population, but I'm quite sure that this would be a supplement that would make a significant difference for many of those and not have any long-term or short-term side effects. So I think that's a very important point.

The other thing that hasn't been as well explored, but I think is important, is the area of concussion or sports injury. Where, I believe, because of the data that we've seen in stroke, and in other neurologic disorders there's every reason to believe that citicoline could actually provide a preventative capacity, like in a sports drink or a bar, something to that effect, prior to concussion. And then also supplementation during the season could be very helpful. So I think that ... well, that hasn't been an area that we've focused on so much. I think given the attention now in the sports of our children and college students, that this would be an area that could be really important.

And then, of course, my original reason for wanting to get into this work, which is mood disorders. I think that we hadn't really capitalized on the impact of Cognizin on improving mood disorders. And I think there are many individual, particularly, in the perimenopausal age group who have found that this has been a very important supplement in their life and has helped them significantly in feeling that they can think more clearly and feel better overall. So those are my favorite areas to think about.

Gazella: Yeah. That concussion, that is really fascinating and it would be great if there could be some studies done there. Dr Renshaw, do you agree? Anything to add to that list?

Renshaw: Yeah. There's a substance abuse investigator at the University of Texas Southwestern in Dallas, Sherwood Brown, who did a study of the individuals who had both, cocaine dependence and bipolar disorder. And what he found was citicoline was actually much more effective in treating the bipolar disorder than the cocaine dependence in the patients that he was working with.

We have a colleague here in Utah, Doug Hondo, who looked at that and said, "Why would something like citicoline be effective in treating bipolar disorder?" And he's developed a theory that suggests that citicoline may have a really potent antisuicidal effect. And it shares, to an unbelievable degree, many of the same effects on the human brain that both lithium, which is known to be antisuicidal and ketamine, which is the antidepressant for those of us in psychiatry. So he's about to begin a study looking at whether or not, and this has been funded by the Veterans Administration, Citicoline reduces suicidality with treatment for only the first week. This is very exciting, and is something that will get underway, it's a 4-year study, in a couple of weeks. And if that's really true, and you could get the same protective effect without having to take Lithium or Ketamine, both of which have pretty significant side effects, that would be a real advance. The compound that Doug will be using in the study is uridine, which is the major metabolite that citicoline provides through the body in [inaudible 00:25:19].

Gazella: Dr. Yurgelun-Todd, because we're talking about bi-polar mood disorders, a lot of these folks are on some heavy duty medications as Dr. Renshaw just mentioned. Do we know anything about interactions? I don't know that there's been any studies, but if somebody is on a Prozac, or an antidepressant, or some of these other, Lithium and whatnot, can citicoline be taken with that or is that a no-no?

Yurgelun-Todd: Thus far, I don't know of a clinical trial that examined that specific question, however, everything that we know about citicoline would suggest that because this is found in normal diets and is a part of the human body, that it would not have any interaction effect with the treatments that have been provided. So it should be perfectly safe.

Gazella: Yeah. That makes some logical sense.

Yurgelun-Todd: But with the caveat that we don't have that empirical data.

Gazella: Right. You're basing that on logic and mechanisms of action and ...

Yurgelun-Todd: Exactly.

Gazella: Now, Dr. Renshaw, I'm going to put you on the spot here, but this is your area of expertise, your background is with addiction. I would love to hear your thoughts on our present opioid epidemic. I realize that this is a huge topic. This might be an unfair question, but can you give us a snapshot from your perspective as a researcher with this type of expertise, what needs to happen to get this issue, this opioid epidemic under control?

Renshaw: Boy, if I knew the answer to that question, I'd have a really high profile job. We're very interested in addiction as you know, we live in the Rocky Mountain states, and so one of the things we study is, what happens when someone moves from a lower altitude to higher altitude, and what we find is that people often get more depressed and more anxious and, curiously, use more different kinds of drugs of abuse. So I guess you could say, flatten out the Rocky Mountain states, but that's not actually our strategy. We're looking for molecules like citicoline that may have an effect in changing brain chemistry in ways that are effective in treating some of these high altitude related conditions.

The fact that this is something you can do that changes the use of drugs across a broad variety of categories suggests that these may be molecules that are really valuable in treating a range of different addictive disorders, but clearly you've figured out by now, that I'm sort of waving my hands because I think there are a lot of very smart people who are struggling with the question of how do you prove the problems of opiate dependence in this country. And it's really shocking how we have a problem that's occurred over a short period of time.

Gazella: Right. We've covered it in the *Natural Medicine Journal*, so it's definitely in our radar as well. Now, I think we covered everything, but Dr. Yurgelun-Todd, is there any final thoughts that you'd like to add on this subject?

Yurgelun-Todd: Yeah, just one final thought, which is that I think that the impact of citicoline and particularly Cognizin citicoline has not been fully appreciated yet. It's come a long way since we began working with it and I think we've appreciated that it has multiple types of impact on the human brain and body, but I think we have even more potential to see it improve the quality of our lives. So I'm excited to continue working with it.

Gazella: Yeah. That's kind of why I wanted to focus on the emerging research because I think that that's very exciting, and I think that this can be a really positive clinical tool for healthcare practitioners. Dr. Renshaw, anything else to add to that?

Renshaw: Just one comment and then a tantalizing tidbit if you will, we can edit this out, I guess. But one of the things that we think is going to be an important trend, is the combination of citicoline with other natural products as a way to boost its efficacy. And that's something that hasn't happened yet, but we have some combinations that we're exploring now. One of the things that Dr. Yurgelun-Todd didn't share with you, is she has, across 3 different studies, evidence that citicoline also improves complexion. It has effects on skin tone, which makes some sense when you think that both the brain and the skin are rapidly turning over cells. So that's an area that's a little bit outside our area of clinical expertise that merits investigation as well.

Gazella: Wow. Yeah, that is pretty interesting because that could then ... it could be a topical ingredient.

Yurgelun-Todd: Right. Exactly.

Renshaw: Exactly.

Gazella: Yeah. Wow. That's pretty interesting. Well, I want to thank you both for joining me. This has been fascinating and information-packed. I'm so pleased that you took time out of your schedule to join me today. And I hope you have an awesome day.

Yurgelun-Todd: Well, thank you so much. We were delighted to join you.


Renshaw: Yeah, you too, Carolyn.

About the Author



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