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A randomized placebo-controlled pilot study of the efficacy and safety of D-cycloserine in people with chronic back pain

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Abstract

Background: Few effective pharmacological treatment options exist for chronic back pain, the leading cause of disability in the US, and all are associated with significant adverse effects.

Objective: To determine the efficacy and safety of D-cycloserine, a partial agonist to the N-methyl-D-aspartate receptor, in the treatment of chronic low back pain.

Methods: A total of 41 participants with chronic back pain who met all inclusion and exclusion criteria were enrolled in a double-blind, placebo-controlled randomized pilot trial of D-cycloserine. Treatment was administered orally for six weeks at escalating daily doses of 100 mg, 200 mg, and 400 mg, each for two weeks. The primary outcome measure was back pain intensity using the Numeric Rating Scale (0–10). Secondary measures were back pain-related questionnaires: McGill Pain Questionnaire short form, painDETECT, PANAS, and BDI. The pre-specified analysis was a two-way repeated measures analysis of variance.

Results: A treatment difference was observed between groups treated with D-cycloserine and placebo at six weeks of 1.05 ± 3.1 units on the Numeric Rating Scale, with an effect size of 0.4 and $p = 0.14$. This trend of better chronic back pain relief with D-cycloserine was also observed in the secondary measures. No safety issues were seen.

Conclusion: The difference in mean pain between the D-cycloserine and placebo groups did not reach statistical significance. However, a clinically meaningful effect size in the magnitude of pain relief was observed with a consistent pattern across multiple outcome measures with good safety, supporting further research into the effectiveness of D-cycloserine for chronic back pain.

Keywords

D-cycloserine, chronic back pain, randomized, clinical trial, N-methyl-D-aspartate agonist

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Background

Chronic pain remains a huge medical and societal burden. Its incidence rate continues to rise, and chronic back pain (CBP) remains the most prevalent chronic pain condition. Recent epidemiological studies indicate that the CBP is the leading source of disability in the US and the seventh leading source worldwide.¹ Despite a long list of available pharmacological and management strategies, a significant percentage of CBP patients remains dissatisfied with their levels of pain relief, and

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the World Health Organization states that no available treatments are superior to each other.² Moreover, the most commonly used pharmacological options (nonsteroidal anti-inflammatory drugs [NSAIDs], gabapentin, duloxetine, and opiates) have important adverse effects and are not tolerated for long periods of use.³ Thus, there is an urgent need to develop novel pain management options especially for CBP.

D-cycloserine (DCS) is an established, FDA-approved antimicrobial agent, recommended to be used at doses up to 1000 mg/day for the treatment of tuberculosis in the US and widely used throughout the world as a second-line agent for that disease.⁴ In addition, it is a partial agonist to the N-methyl-D-aspartate receptor in the central nervous system and at high doses can lead to drowsiness, dizziness, and convulsions.⁵ In rodents, oral DCS has been shown to decrease pain-like behaviors in multiple models of chronic pain (spared nerve injury, and chemotherapy-induced neuropathy), in a dose dependent manner, with efficacy increasing with longer duration use.⁶ Moreover, animals already treated with DCS, when re-treated showed larger alleviation and longer duration persistence of alleviation of neuropathic pain, and when treated for about 30 days, post-treatment alleviation of symptoms persists for more than an additional 30 days.⁶ Although at the doses tested, DCS in neuropathic rats relieved pain-like symptoms by only about 50%, the emotional impact of the neuropathic condition seemed completely eliminated (i.e., animals behaved as if the remaining pain does not bother them). It seems that in neuropathic rodents DCS does not change stimulus sensitivity for body parts outside of the injury, and acute or single doses of DCS do not alleviate neuropathic pain. Therefore, in the rodent DCS does not act as a short-term analgesic; instead, it reduces neuropathic pain and seems to largely eliminate associated negative affect.

The initial study of DCS in the rat described above was in fact a reverse translational effort, as it was based on the evidence that brain imaging studies in CBP patients had shown that chronic pain preferentially activates the medial prefrontal cortex (mPFC) and the amygdala,⁷ and DCS administration systemically or centrally (within mPFC or amygdala) in the rodent facilitates fear extinction,⁸ and that mPFC is critical in the rodent extinction of fear.^{9,10} More recent studies provide strong additional evidence regarding the role of mPFC in human chronic pain^{11–16} and its interaction with subcortical limbic structures most notably hippocampus, amygdala, and nucleus accumbens,^{14–18} as well as rodent evidence showing that direct manipulation of components of this circuitry either disrupts or modulates persistent pain behavior.^{18–23} We have hypothesized that chronification of pain critically depends on brain memory circuitry²⁴ and DCS enhances cognitive and

memory processes and especially fear extinction^{10,25,26} through prefrontal limbic circuitry and reduces persistent pain in the rodent.⁶ We therefore undertook the present forward translational pilot study to specifically test the efficacy and safety of DCS in reducing back pain in CBP, utilizing dosages that were well below those resulting in significant clinical side effects.

Methods

This study was a pilot trial of DCS in subjects with chronic low back pain, designed as a double-blind, parallel-group randomized clinical trial. The study was conducted in compliance with the Declaration of Helsinki and registered at clinicaltrials.gov (NCT00125528). The protocol and informed consent documentation were reviewed and approved by the Northwestern University Institutional Review Board. Subjects provided written informed consent before protocol-specified procedure initiation. No external funding was provided for this study.

Study population

Eligible subjects had to be between the ages of 18 and 75 years, have low back pain for a minimum of six months, with or without radiation of pain to buttocks or legs, and be in stable medical health. Subjects had to rate their back pain at baseline as ≥ 5 out of 10 on the Numeric Rating Scale (NRS; 0–10 scale) and be willing to abstain from alcohol consumption during the course of the study. Females had to be post-menopausal or, if of child-bearing potential, use a highly effective method of contraception or abstinence and plan to continue during the course of the study. Exclusion criteria included low back pain associated with any systemic signs or symptoms; evidence of rheumatoid arthritis, ankylosing spondylitis, acute vertebral fractures, fibromyalgia, history of surgery or tumor in the back; involvement in litigation regarding their back pain or having a disability claim or receiving workman's compensation or seeking either; neurologic or major psychiatric disorder; history of, or current, substance abuse/dependence including alcohol; significantly abnormal laboratory values; known sensitivity to DCS; currently taking any of the following medications: ethionamide, dilantin, isoniazid (INH), pyridoxine (vitamin B₆); any change in medication for back pain in the last 30 days.

Study design

This was a parallel group, randomized, double-blind, placebo-controlled, dose-escalation clinical trial that aimed to enroll 40 participants with low back pain. There were five study visits overall: a screening visit, a

baseline assessment and visits every two weeks thereafter for six weeks after initiation of study medication. Randomization occurred at the baseline visit in a 1:1 ratio with assignment to either DCS 50 mg bid or matching placebo, respectively. The randomization sequence was generated by computer-generated program, and participants received the next available number and numbered container(s) when they qualified. No study staff had access to the randomization sequence, and medication assignment and labeling were done by non-study staff. All study staff and participants were blinded to medication assignment until database lock. Participants were required to continue their current medications for low back pain throughout the course of the study. After two weeks of study medication, all participants received an increase in their assigned study medication to DCS 100 mg bid or matching placebo. All study medication was identical in appearance and formulated by the University of Charleston School of Pharmacy from commercially available DCS (Chao Center for Industrial Pharmacy and Contact Manufacturing, West Lafayette, IN) under IND 71528. This medication regime was continued for two weeks when assigned study medication was again increased to either DCS 200 mg or placebo to be taken twice daily. These dosages were based on the preclinical rat studies which demonstrated efficacy at low overall doses of DCS. Dose escalation was undertaken after two weeks as that was felt as an adequate length of time to reach a new steady-state and observe efficacy; continued escalation was designed in an attempt to maximize the chances of detecting efficacy while limiting side effects. Study capsules were all identical in appearance. Randomization was in blocks of four by use of a computer-generated list that was accessible to study staff only in case of drug-related study emergency. Efficacy and safety were assessed at baseline and at each subsequent study visit. Acetaminophen rescue medication was allowed and limited to 500 mg qid. All visits and data collection took place at Northwestern University Feinberg School of Medicine between July 2012 and April 2014.

Efficacy evaluation

At each visit, the following instruments were completed by each subject: NRS (0–10 mm scale; no pain to worst possible pain); McGill Pain Questionnaire (short-form, MPQ); Neuropathy Pain Scale (NPS); Pain Detect Questionnaire; and Positive and Negative Affect Schedule (PANAS).

Safety evaluation

At each visit, participants were asked about changes in health status and medications. Adverse events were

recorded and evaluated. The Beck Depression Inventory (BDI) was administered at each visit.

Statistical methods

Sample size calculation. With 20 participants in the active group and 20 in the placebo group, there will be 88% power to detect an effect size of 1.0, reflecting a difference of 1.5 units on the NRS scale between the mean pain in the active and placebo groups, with an alpha of 0.05 and a standard deviation in both groups of 1.5 units, using a two-sided test. With a smaller difference of 1.0 units on the NRS scale (effect size = 0.7), which is still clinically meaningful, and with an alpha of 0.10 for this pilot study and the remaining parameters remaining unchanged, the power is reduced to 68%. The sample size was limited by the availability of funding.

Outcome measures. The primary outcome measure was the difference between the mean change from baseline in the NRS pain score at week 6 in the active group compared to the placebo group. Secondary outcome measures included similar paired comparisons of each of the efficacy instruments (BPI, Roland-Morris Disability Scale, SF-36, PANAS, BDI, MPQ, NPS, Pain Detect Questionnaire) at the six-week time point as well as at all other times measured.

Analysis. The pre-specified analysis was a two-way repeated measures analysis of variance (two-way rm-ANOVA) for the primary outcome measure NRS, with repeated measure of time and treatment type (DCS or placebo) as the independent factor, and with planned post-hoc comparison between baseline and end of treatment, contrasting between treatment types. All secondary outcome measures were also pre-specified to undergo the same type of analysis.

Imputation. NRS and all questionnaires were collected at visits 1–5. We averaged for visits 1 and 2 outcomes whenever available, otherwise we used visit 2 outcomes. In the questionnaire, outcomes less than 5% of individual queries were left unanswered. We replaced these missing values by the same subject's values from the previous visit (imputation was performed for 57 of a total of 957 entries). The procedure enabled performing a repeated-measures analysis of variance, and only minimally changed group averages.

Results

Demographics

There were initially 41 subjects enrolled into the study, 21 assigned to the placebo group, and 20 to DCS

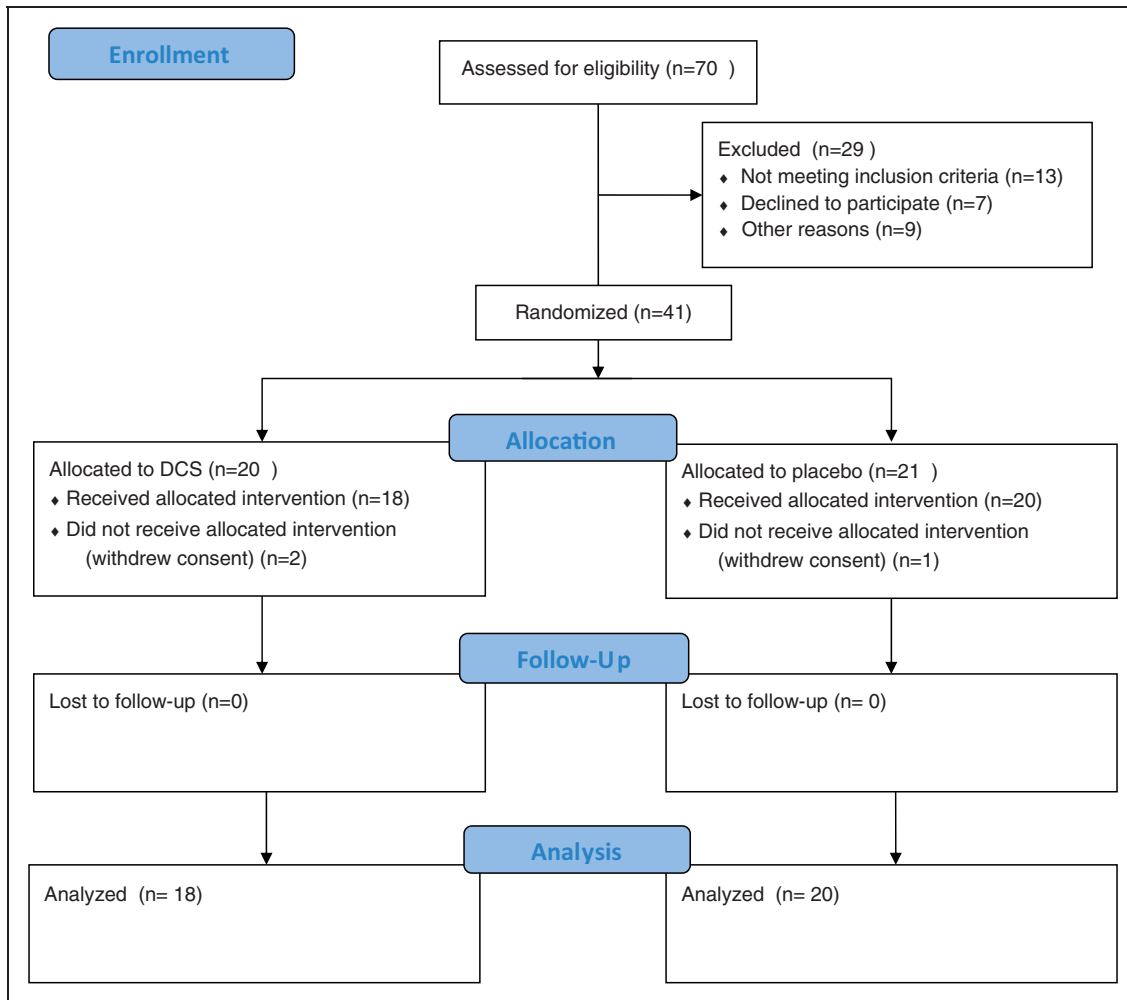


Figure 1. Consort diagram.

treatment (See Consort Flow Chart, Figure 1). The demographics of the two groups were similar with a mean age at baseline of 53.2 ± 11.4 years versus 53.3 ± 10.7 years in the DCS and placebo groups, respectively. Fourteen subjects in the DCS group and 11 subjects in the placebo group were female. There was no significant difference in racial or ethnic backgrounds in the two groups, and no statistically significant differences in any of the other measures (Table 1). Three subjects withdrew consent prior to receiving study medication; all other subjects completed the study.

Primary outcome

Both groups showed a reduction in pain magnitude over the course of the study, but the difference between groups did not reach statistical significance. The absolute measure of NRS was not different between treatment groups (two-way rm-ANOVA; Time effect $F_{3,108} = 10.1$, $p < 0.01$, but no time-by-treatment interaction $F_{3,108} = 0.61$, $p > 0.60$)

(Figure 2(a)). We obtained a similar result when we compared within subject change in NRS scores (current NRS score – baseline NRS score) over time (Figure 2(b)). However, the post-hoc test indicates a significant decrease in NRS for DCS treatment between baseline and six-week treatment (Fisher LSD test, $p < 0.01$), but not for placebo treatment.

Secondary measures

For the MPQ affective score (Figure 3(a)), there was a large time effect ($F_{3,108} = 6.9$, $p < 0.01$) and borderline time-by-treatment interaction effect ($F_{3,108} = 1.5$, $p < 0.20$). Post-hoc analysis showed a significant decrease in MPQ affective score for DCS treatment between baseline and six-week treatment (Fisher LSD test, $p < 0.01$), but not for placebo treatment. A similar but slightly smaller effect was observed for MPQ sensory outcome (Figure 3(b)). The MPQ sensory outcome showed a time effect ($F_{3,108} = 2.96$, $p < 0.04$) but no treatment-by-time

Table 1. Participant demographics.

	DCS	Placebo
Age (years)	53.2 ± 11.4	53.3 ± 10.7
Gender (%Female)	70.0%	52.4%
Race		
African-American	50.0%	66.7%
Caucasian	50.0%	28.6%
Other	0.0%	4.8%
Ethnicity		
Non-Hispanic	85.0%	95.2%
Hispanic	15.0%	4.8%
BMI	33.9 ± 11.8	30.1 ± 6.2
Back pain duration (years)	10.7 ± 7.8	8.7 ± 9.0
Educational level		
Through high school	45.0%	33.3%
Beyond high school	55.0%	66.7%
Employed	70.0%	42.9%
Smoker	40.0%	38.1%
Hypertension	35.0%	38.1%
Medications		
APAP	30.0%	33.3%
NSAID	65.0%	38.1%
Opioids	20.0%	19.0%
None	5.0%	19.0%

DCS: D-cycloserine; BMI: body mass index; APAP: acetaminopen; NSAID: nonsteroidal anti-inflammatory drug.

interaction ($F_{3,108} = 0.5$, $p > 0.60$). However post-hoc analysis showed a significant decrease in score for DCS treatment between baseline and six-week treatment (Fisher LSD test, $p < 0.01$), but not for placebo treatment.

We observed a similar but stronger DCS effect with the painDETECT outcome measure (Figure 3(c)). There was a large time effect ($F_{3,108} = 7.8$, $p < 0.01$) and borderline time-by-treatment interaction effect ($F_{3,108} = 1.9$, $p < 0.14$), and for post-hoc there was a significant decrease in painDETECT score for DCS treatment between baseline and six-week treatment (Fisher LSD test, $p < 0.01$), but not for placebo treatment. The PANAS positive scale (Figure 3(d)) showed an overall time effect ($F_{3,108} = 3.61$, $p < 0.02$) and a borderline treatment-by-time interaction effect ($F_{3,108} = 1.5$, $p = 0.20$). Post-hoc analysis indicated that DCS treatment improved outcome at six weeks relative to baseline (Fisher LSD $p < 0.01$) but not for placebo. In contrast, PANAS negative showed no modulation (no effect of treatment, time or their interaction $F_{3,108} = 0.79$, $p > 0.45$). Similarly, treatment over six weeks did not modulate BDI scores (no effect of treatment, time or their interaction $F_{3,108} = 0.65$, $p > 0.50$).

Adverse effects

No serious adverse effects were reported during the trial in either group. The most common adverse events were

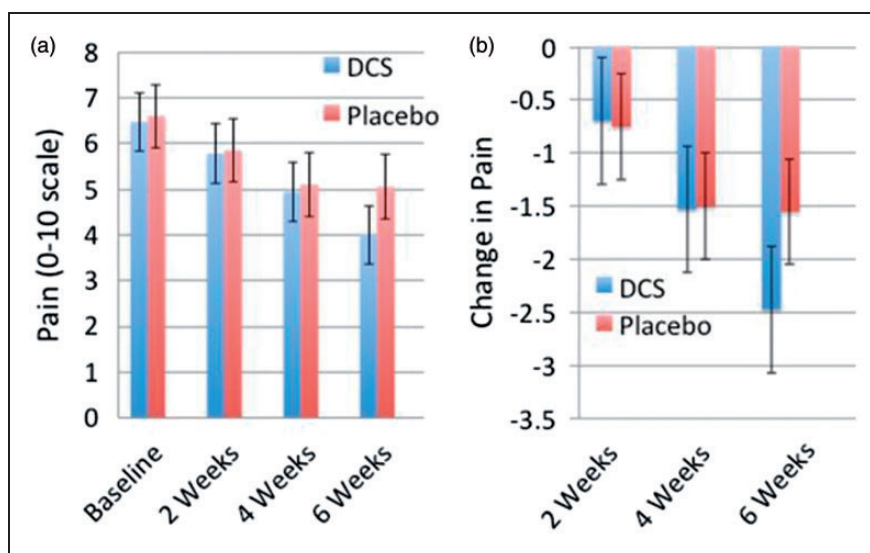


Figure 2. Back pain intensity ratings over a six-week, dose escalating, placebo or DCS treatment in CBP. (a) Across subject average back pain, assessed on the primary outcome measure of 0–10 numeric rating scale. (b) Within subject change in pain, relative to baseline, using the 0–10 numeric rating scale. Error bars are SEMs.

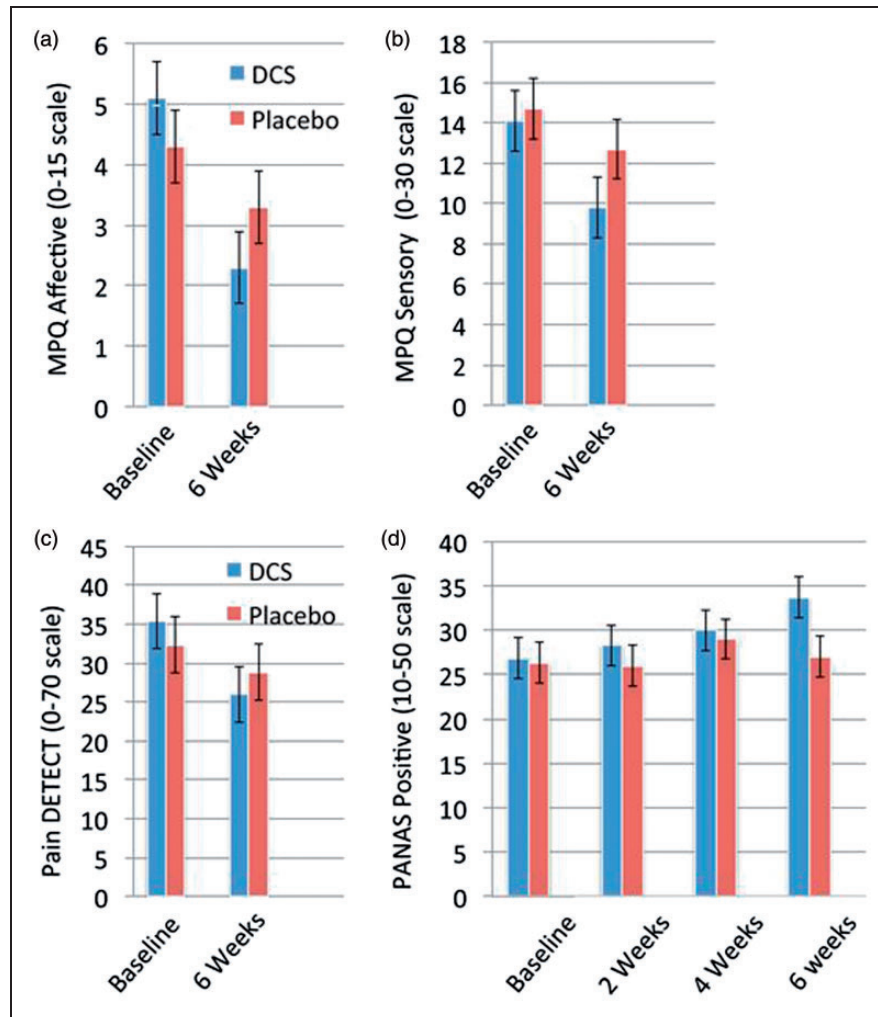


Figure 3. Back pain related secondary outcome measures showing improved back pain with six-week DCS treatment. (a) Affective score of McGill Pain Questionnaire short form (sf-MPQ). (b) sf-MPQ sensory score. (c) Pain DETECT. (d) PANAS positive affect score. All measures indicate a trend or significant improvement with DCS in comparison to placebo. Error bars are SEMs.

headache (3/21 in the placebo group; 1/20 in the DCS group), numbness and/or tingling (3/20 in the DCS group and 0/21 in the placebo group), and lower extremity edema (2/21 in the placebo group, 0/20 in the DCS group). All adverse effects were rated mild in severity.

Discussion

In subjects with chronic low back pain in this study, we observed a consistent pattern of the effect of DCS, in contrast to placebo, on a number of clinically important outcome measures. Although neither the primary outcome nor secondary outcomes showed an overall statistically significant time by treatment effect, they all showed trends, and the primary outcome measure as well as the four secondary outcomes indicated significant

post-hoc effect of DCS at six weeks relative to baseline with no effect of placebo. Given the limited number of subjects included in the studied, these results are stronger than we had expected. Moreover, we observed that at six weeks at a dose of 200 mg DCS treatment, the effect size of pain relief was 0.4, a magnitude at least comparable to efficacy of NSAIDs reported for chronic low back pain.²⁷ For two outcome measures, placebo and DCS effects were not different at two weeks and at four weeks of treatment, but all five outcomes showed at six weeks a larger effect in the DCS group than in the placebo group. As the trial was a dose escalating regimen, with stepwise increases every two weeks, and given that rodent results indicated that continued treatment with DCS over many weeks potentiates its efficacy for analgesia in neuropathic animals,⁶ these results cannot differentiate whether the observed efficacy of DCS is due to

dose escalation or simply a reflection of continued drug consumption. Yet, taking into consideration the earlier rodent results,⁶ we expect that continuation of DCS treatment for longer periods should result in even larger effect sizes. As expected from a recent review of the DCS literature,²⁸ we observed minimal side effects of DCS consumption across all three doses and for up to six weeks of treatment. Therefore, the present results suggest that DCS may be a viable treatment for CBP, as it demonstrates minimal side effects and suggestive evidence that it might be efficacious in ameliorating back pain intensity in low back pain patients. However, larger population and longer duration treatment trials are the next necessary steps that remain to be done.

The original study where DCS was demonstrated to be effective in ameliorating neuropathic pain in rodents⁶ demonstrated not only that DCS reduces tactile sensitivity for the paw with neuropathic injury but also showed complete reversal of place avoidance, when paw mechanical stimulation was competed with the aversiveness of a white compartment. This result suggests that DCS diminishes the negative emotional load of neuropathic pain much more than its sensory component. Somewhat consistent with this observation, the current study showed an increase in PANAS positive scores at six weeks of DCS treatment (with no change in PANAS negative scores), which suggests improvement in positive emotional affect, reflecting higher energy, more pleasurable engagement, and increased extroversion. Thus, improved mood accompanied with decreased pain seem to also have been observed in the chronic low back pain patients.

The original study of DCS reducing neuropathic pain also showed that the primary site of action of DCS was through the glycine partial agonist site on the N-methyl-D-aspartate receptor localized specifically in the pre-limbic portion of the mPFC, with no effects on multiple other regions most importantly within the spinal cord.⁶ An observation that is important to consider given that three recent studies show that manipulating activity or excitability of pre-limbic neurons can completely reverse neuropathic pain-like behavior in rodents.^{23,29,30} Thus, we surmise that in the current trial as well DCS effects for relieving back pain were being mediated through the same mechanism and brain pathway as observed in the rodent.

Limitations of this study include the small sample size, and the relatively short follow-up period available. In a condition such as CBP, longer follow up would be ideal to evaluate maintenance of pain-relief benefit, and a larger number of subjects would allow evaluation of whether there were subgroups of individuals with CBP who might respond in a differential manner to DCS. Additionally, because of the dose-titration design, it was not possible to differentiate a dosage from time effect.

Conclusion

Although the current study remains preliminary and exploratory in nature, the obtained results imply further studies of DCS as a treatment option for chronic pain are warranted. Future studies should consider longer duration treatments as well as assess post-treatment cessation persistence of pain relief.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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