Chromium Potentiation of Antidepressant Pharmacotherapy for Dysthymic Disorder in 5 Patients

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Background: Dysthymic disorder is a relatively common illness that is often treated with antidepressants. Compared with the study of major depression, there has been little systematic study of potentiation strategies for antidepressant-refractory dysthymic disorder.

Method: Following a patient's report of dramatic response to the addition of chromium supplementation to sertraline pharmacotherapy for dysthymic disorder (DSM-IV), the authors initiated a series of single-blind and open-label trials of chromium picolinate or chromium polynicotinate in the treatment of antidepressant-refractory dysthymic disorder.

Results: In a series of 5 patients, chromium supplementation led to remission of dysthymic symptoms. Single-blind substitution of other dietary supplements in each of the patients demonstrated specificity of response to chromium supplementation.

Conclusion: Preliminary observations suggest that chromium may potentiate antidepressant pharmacotherapy for dysthymic disorder. Controlled studies are indicated to test the validity of these initial observations.

(J Clin Psychiatry 1999;60:237–240)

Received March 5, 1998; accepted July 20, 1998. From the Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill.

The patents for the discoveries described within this report have been filed by Malcolm N. McLeod, M.D., 901 Willow Dr., Suite 3, Chapel Hill, NC 27514, and are pending.

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Dysthymic disorder is a common illness with an estimated point prevalence in the community of approximately 3%.[1] While dysthymia appears to respond to a variety of antidepressant medications, the response rate may be low compared with the treatment response for major depression.[2] There is a surprising relative paucity of controlled clinical trials for this illness,[3] and to date, no medication has been recognized by the Food and Drug Administration (FDA) as safe and effective in the treatment of dysthymic disorder.

The need for pharmacologic potentiation strategies for this common and relatively refractory mood disorder is clear, yet there are few reports of augmentation trials in dysthymic disorder. We report here a series of patients who responded dramatically to the addition of chromium supplementation to antidepressant treatment of dysthymic disorder. While the effects of chromium on glucose utilization and lipid metabolism have been described,[4] to our knowledge, this is the first report of apparent antidepressant potentiation activity and the first report of the use of chromium in the pharmacotherapy of a psychiatric disorder.

CASE REPORTS

Case 1

Mr. A is a 50-year-old married white man with a 25-year history of dysthymic disorder (DSM-IV), characterized by depressed mood, overeating, and fatigue. His symptoms had caused marked distress, and the patient believed his illness contributed to ongoing marital discord. During his illness, he never met criteria for major depressive episode, manic or hypomanic episode, or other Axis I disorders. Past treatment included both individual and group psychotherapy that had limited success.

Pharmacotherapy with sertraline was titrated to a dosage of 100 mg/day. Mr. A experienced a partial response, with persistence of all of his symptoms, but to an attenuated degree. Following an increase in the sertraline dosage to 150 mg/day, his symptoms improved further, but he complained of constipation, tinnitus, and a "sluggish, drugged-like feeling" that was intolerable. Following a reduction in dosage to 125 mg/day, the side effects improved, but there was an exacerbation in his dysthymic symptoms.

Mr. A began to take a daily vitamin and mineral preparation without informing his psychiatrist. Four weeks later, he added a second dietary supplement preparation, which included 300 μg of chromium picolinate, to his daily regimen, and within a few days, he experienced a dramatic, complete resolution of all dysthymic symptoms. At this point, he informed his psychiatrist about the vitamin-mineral preparations and his rapid remission following the addition of the second dietary supplement preparation. Ex-

amination revealed an apparent complete remission of his dysthymia and no indication of hypomania.

Mr. A agreed to his psychiatrist's suggestion that he discontinue both dietary supplements and, if his symptoms should return, begin a series of 1-week, single-blind trials of each of the 5 major ingredients in the latter compound, so that any putative "active" ingredient could be identified. He continued to take sertraline, 125 mg/day, and after a 1-week washout from the dietary supplements, his dysthymic symptoms returned.

The single-blind addition of vitamin C (500 mg/day) to sertraline treatment produced no clinical improvement. At that point, he scored 10 points on the Beck Depression Inventory (BDI).[5] In the second single-blind trial, chromium picolinate (200 μg/day) led to complete resolution of dysthymic symptoms, as documented by a score of 0 on the BDI. Discontinuation of chromium picolinate resulted in a return of dysthymic symptoms that did not respond to subsequent trials of the remaining ingredients, including guarana (300 mg with 45 mg of caffeine/day), ginseng (100 mg/day), and selenium (50 μg/day).

Mr. A terminated the trial on his own initiative at week 6 because he was convinced that the compound that he received during the second single-blind trial (chromium picolinate) was responsible for the dramatic remission of his chronic dysthymia, and he insisted on learning what that compound was. He then added chromium picolinate, 200 μg b.i.d., to his sertraline pharmacotherapy and reported an immediate response. The only side effect that he reported was initial insomnia and increased dreaming. After the timing of his second chromium dose was shifted to midafternoon, his sleep returned to normal. He discontinued sertraline and reported that chromium picolinate alone maintained the remission of dysthymic symptoms. He attempted to discontinue chromium picolinate on 3 occasions, but on each occasion experienced a return of symptoms of dysthymia, which again went into remission following the reinstitution of chromium picolinate. The patient reported that while the combination of chromium picolinate and sertraline produced the greatest antidepressant response, he felt better while receiving chromium picolinate alone than he ever had during his many years of dysthymia, and better than he had while receiving sertraline alone.

After 5 months of treatment with chromium picolinate, he switched to the same dose of chromium polynicotinate. He remains in remission after 15 months of treatment with chromium polynicotinate alone.

Case 2

Ms. B, the 24-year-old daughter of Mr. A, also met DSM-IV criteria for dysthymic disorder, with persistent symptoms despite a 2-year course of treatment with sertraline, 50 to 100 mg/day. When her father informed her of his dramatic response to the addition of chromium picolinate to his sertraline pharmacotherapy, she insisted on a trial for herself. Under single-blind conditions, she was given consecutive trials of 6 different dietary supplements, with 5 days of exposure to each followed by a 2-day washout. Her dysthymic symptoms resolved within 3 to 4 days of the addition to sertraline therapy of chromium picolinate, 200 μg/per day (BDI scores: 12 on sertraline alone, 2 at the end of the chromium picolinate trial), and returned within days after its discontinuation. The addition of vitamin C (500 mg/day), guarana (300 mg with 45 mg of caffeine/day), ginseng (100 mg/day), and selenium (50 μg/day) failed to produce any clinical response.

Following completion of this series of single-blind trials, the patient received open-label treatment with sertraline, 100 mg/day, and continued to take chromium picolinate, 200 μg b.i.d. The reinstitution of this regimen again led to resolution of Ms. B's dysthymic symptoms. When the patient discontinued the chromium picolinate, dysthymic symptoms returned; while receiving chromium picolinate alone, she also experienced a return of symptoms. The third exposure to sertraline and chromium picolinate again resulted in remission of her dysthymia.

Case 3

Mr. C is a 42-year-old white man with dysthymic disorder and major depressive episode (DSM-IV) who experienced partial remission of both conditions while receiving bupropion, 200 mg/day, and lithium, 900 mg/day. An increase in the dose of either medication was associated with intolerable side effects (including akathisia and difficulty with fine motor movements). Both of these medications were discontinued, and following a thorough discussion of the experimental nature of chromium picolinate augmentation, the patient agreed to an open-label trial of sertraline, 100 mg/day, and chromium picolinate, 200 μg b.i.d. Start of therapy was followed by resolution of symptoms within 1 week. Three subsequent open-label trials were completed: sertraline alone (150 mg/day) led to relapse within 1 month; the addition of chromium picolinate, 200 μg b.i.d., for 2 weeks again led to remission, which was maintained for 6 weeks on treatment with chromium picolinate alone.

The patient then agreed to a single-blind substitution of a dietary supplement (vitamin B_{12}) for chromium. His psychiatrist gave him, on a weekly basis, envelopes containing either chromium picolinate or a vitamin B_{12} formulation that was nearly identical in appearance to chromium picolinate. After receiving vitamin B_{12}, 250 mg/day, for 1 month, Mr. C's dysthymic symptoms returned. A few days after substituting chromium picolinate, 400 μg/day, for vitamin B_{12}, his dysthymic symptoms resolved. The only side effect that the patient reported while receiving the chromium picolinate was increased dreaming, which remitted within 2 weeks.

Case 4

Ms. D is a 46-year-old white woman who presented with DSM-IV dysthymic disorder, a major depressive episode, and a history of mild-to-moderate response to 4 years of treatment with nortriptyline, 100 to 150 mg/day. In a single-blind trial, vitamin B_{12} tablets were added to her ongoing treatment with nortriptyline, 100 mg/day. After 3 weeks, her dysthymic symptoms had become more intense, with a worsening in her mood, insomnia, concentration, and energy. She was then given chromium picolinate tablets, which were nearly identical in appearance to the vitamin B_{12} tablets. Within 4 days, she began to feel an improvement in her symptoms, and within 2 weeks, she felt "better than I have in my adult life." Ms. D also reported an increase in dreaming shortly after the initiation of chromium picolinate treatment, which resolved within 2 weeks. Following the substitution of an oyster shell preparation in place of chromium picolinate, her symptoms returned, but again went into remission when chromium polynicotinate replaced the oyster shell preparation.

Case 5

Ms. E is a 50-year-old white woman who met DSM-IV criteria for dysthymic disorder and major depressive episode in partial remission after 5 years of treatment, first with fluoxetine, 20 mg/day, and then with sertraline, 100 mg/day. She also had a 30-year history of premenstrual dysphoric disorder. In addition to residual depressive symptoms, the patient was concerned about decreased libido, which had emerged with sertraline pharmacotherapy. After her referring physician told her about another patient's response to chromium picolinate, Ms. E began taking chromium picolinate on her own. After consultation with one of us (M.N.M.) a few days later, she agreed to stop the chromium picolinate and to begin a single-blind trial comparing chromium picolinate to another dietary supplement in combination with sertraline. Within 3 weeks, she experienced a dramatic improvement in her mood disorders as well as a striking absence of her usual premenstrual symptoms. For the next month, vitamin B_{12} was substituted for chromium picolinate, and the patient described a return of symptoms of decreased energy and irritability. When chromium picolinate replaced the vitamin B_{12} in the following month, the patient again experienced a remission in her mood and premenstrual symptoms.

DISCUSSION

This series of 5 patients is the first report of antidepressant potentiation activity of chromium in the treatment of dysthymia. As with any initial anecdotal report of clinical efficacy in a new treatment, 2 key questions must be considered: Is the treatment safe and effective? If so, what is the mechanism of action?

The safety of chromium supplements, especially in oral formulations within the dosage range described here, appears to be well established.[6] Although an anecdotal report describes cognitive and perceptual changes in a single patient taking 200–400 μg/day of chromium picolinate,[7] there have been no documented reports of chromium toxicity in any of the past 3 decades of chromium supplementation studies, which have used trivalent chromium at doses up to 1 mg/day.[8] The addition of chromium picolinate to the diet of rats at doses greater than a thousand times the usual human intake is not associated with toxicity.[8]

In terms of efficacy, there is a clear limit to the conclusions that can be drawn from these initial observations. In fact, one hypothesis that must be considered, and which links the 2 key questions, is that the dramatic clinical effects observed in these 5 patients were placebo responses. Several factors argue against this explanation, however. First, the placebo response rate in dysthymic disorder and double depression is relatively low compared with placebo response in acute major depression.[9] Each of these patients had failed to respond to chronic treatments with adequate doses of antidepressants for periods ranging from months to years. Furthermore, in all of the cases, the results from the single-blind substitutions of other nutrient supplements, including vitamin B_{12} in tablets that were nearly identical in appearance to the chromium picolinate, strongly suggest that a placebo response does not underlie the clinical remissions induced by chromium potentiation. Also, the sustained improvement of patients argues against a placebo response.

Alternative explanations of the observed efficacy include pharmacokinetic interactions between chromium and the antidepressants. This seems unlikely for several reasons. Chromium is excreted via the kidney, and the possibility that it affects the hepatic metabolism of antidepressants seems remote. Furthermore, several of the patients who responded to the addition of chromium supplementation had previously failed to respond to substantially higher doses of the antidepressant alone, suggesting that even if chromium increased antidepressant blood levels, this increase alone would be unlikely to induce clinical remissions in these patients.

The rapidity of response to chromium supplementation, along with the rapid return of symptoms following discontinuation, suggests that the compound may exert mood-elevating effects independent of any underlying mood disorder. Such an effect has been described for another trace element, selenium.[10] There is considerable experience in the use of chromium as an adjunct in the treatment of diabetes, but to our knowledge, mood elevation has not been reported as a frequent side effect.[6] Another possibility involves a deficiency in dietary intake of chromium in these patients, which could theoretically produce a syndrome with symptoms of chronic depression.

This hypothesis is difficult to test, as there are currently no reliable analytical methods to determine the nutritional chromium status of patients.[4] While chromium deficiency in patients receiving total parenteral nutrition results in gross disorientation and a syndrome similar to hepatic encephalopathy,[6] chronic depression has not been observed.

Another potential mechanism for the putative antidepressant activity of chromium involves enhancement of glucose utilization in the central nervous system. Chromium is known to enhance the efficiency of glucose utilization in peripheral tissues,[11,12] and similar activity in the brain might be linked to the behavioral effects observed in these patients. Finally, chromium may indirectly enhance monoaminergic neurotransmission. A recent report suggests that chromium compounds can induce catecholamine secretion.[13] Enhancement of norepinephrine release may be induced by chromium via interference with intracellular functions of calcium in the cytoplasm.[13] This is consistent with caffeine-like activating effects described by some of our patients. Serotonin synthesis may also be enhanced by chromium. Insulin increases the relative availability of tryptophan for transport across the blood-brain barrier by stimulating muscle uptake of competing branched chain amino acids, and since chromium enhances the peripheral effects of insulin, it may thereby increase serotonin synthesis via increased central tryptophan availability.[14]

We believe that these observations, while clearly preliminary and limited in scope, suggest the value of a prospective controlled trial. We are mindful of at least one instance in which serendipity played an important role in the discovery of the clinical efficacy of a trace element—lithium—in the treatment of mood disorders.[15]

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), nortriptyline (Pamelor and others), sertraline (Zoloft).

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