A Double-Blind, Placebo-Controlled, Exploratory Trial of Chromium Picolinate in Atypical Depression: Effect on Carbohydrate Craving

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Background: **In a small pilot trial, patients with atypical depression demonstrated significant positive therapeutic response to chromium picolinate. This finding is of interest because of the demonstrated link between depression, decreased insulin sensitivity, and subsequent diabetes and chromium picolinate's insulin enhancing effect.** ***Methods:*** **In this double-blind, multicenter, 8-week replication study, 113 adult outpatients with atypical depression were randomized 2:1 to receive 600 μg/day of elemental chromium, as provided by chromium picolinate (CrPic), or placebo. Primary efficacy measures were the 29-item Hamilton Depression Rating Scale (HAM-D-29) and the Clinical Global Impressions Improvement Scale (CGI-I).** ***Results:*** **Of the 113 randomized patients, 110 (70 CrPic, 40 placebo) constituted the intent-to-treat (ITT) population (i.e., received at least one dose of study medication and completed at least one efficacy evaluation) and 75 (50 CrPic, 25 placebo) were evaluable (i.e., took at least 80% of study drug with no significant protocol deviations). In the evaluable population, mean age was 46 years, 69% were female, 81% were Caucasian, and mean body mass index (BMI) was 29.7. There was no significant difference between the CrPic and placebo groups in both the ITT and evaluable populations on the primary efficacy measures, with both groups showing significant improvement from baseline on total HAM-D-29 scores during the course of treatment ($p < 0.0001$). However, in the evaluable population, the CrPic group showed significant improvements from baseline compared with the placebo group on 4 HAM-D-29 items: appetite increase, increased eating, carbohydrate craving, and diurnal variation of feelings. A supplemental analysis of data from the subset of 41 patients in the ITT population with high carbohydrate craving (26 CrPic, 15 placebo; mean BMI = 31.1) showed that the CrPic patients had significantly greater response on total HAM-D-29 scores than the placebo group (65% vs. 33%; $p < 0.05$) as well as significantly greater improvements on the following HAM-D-29 items: appetite increase, increased eating, carbohydrate craving, and genital symptoms (e.g., level of libido). Chromium treatment was well-tolerated.** ***Limitations:*** **The study did not include a placebo run-in period, did not require minimum duration or severity of depression, and enrolled patients with major depression, dysthymia, or depression NOS.** ***Conclusions:*** **In a population of adults with atypical depression, most of whom were overweight or obese, CrPic produced improvement on the following HAM-D-29 items: appetite increase, increased eating, carbohydrate craving, and diurnal variation of feelings. In a subpopulation of patients with high carbohydrate craving, overall HAM-D-29 scores improved significantly in patients treated with CrPic compared with placebo. The results of this study suggest that the main effect of chromium was on carbohydrate craving and appetite regulation in depressed patients and that 600 μg of elemental chromium may be beneficial for patients with atypical depression who also have severe carbohydrate craving. Further studies are needed to evaluate chromium in depressed patients specifically selected for symptoms of increased appetite and carbohydrate craving as well as to determine whether a higher dose of chromium would have an effect on mood.** *(Journal of Psychiatric Practice* **2005;11:302–314)**

KEY WORDS: chromium picolinate, atypical depression, carbohydrate craving, appetite, eating, weight gain, metabolic syndrome

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INTRODUCTION

Depression as a Metabolic Disorder

Emerging findings suggest that depression is a systemic metabolic disorder that, in addition to abnormalities of mood, involves dysregulation of a variety of bodily systems. Depression is associated with increased rates of a number of serious medical disorders, including hypertension, ischemic heart disease, stroke, osteoporosis, and diabetes.[1–8] Depression has been found to increase the risk of cardiovascular disease (CVD) in healthy individuals and to increase the risk of cardiac morbidity and mortality in patients with existing CVD.[9,10] A well established reciprocal relationship also exists between depression and diabetes, with depression predicting subsequent onset of diabetes and vice versa.[7,8]

Dysregulation of Appetite in Atypical Depression

Changes in appetite, food intake, carbohydrate consumption, and food preferences are also prominent symptoms in depressive states, with some types of depression (e.g., melancholic) associated with decreased appetite, while others types of depression (e.g., atypical) are associated with increased appetite.[11] Atypical depression, as defined in the DSM-IV-TR, is a subtype of major depressive disorder (MDD) that is characterized by mood reactivity and the presence of two or more of the following: increased appetite or weight gain, hypersomnia, leaden paralysis, or a long-standing pattern of extreme sensitivity to interpersonal rejection (Table 1). Despite the use of the term "atypical" to describe this subtype of depression, it has been reported that (depending on the specific criteria used to define the syndrome) 22%–83% of all patients with major depression exhibit these symptoms.[12–16] Although the DSM-IV-TR criteria give precedence to mood reactivity in diagnosing atypical depression, other investigators are focusing on validating a syndrome characterized primarily by overeating and oversleeping.[17–23]

Table 1. Criteria for Atypical Features Specifier for a Major Depressive Episode

Specify if:

With Atypical Features (can be applied when these features predominate during the most recent 2 weeks of a current Major Depressive Episode in Major Depressive Disorder or in Bipolar I or Bipolar II Disorder when a current Major Depressive Episode is the most recent type of mood episode, or when these features predominate during the most recent 2 years of Dysthymic Disorder; if the Major Depressive Episode is not current, it applies if the feature predominates during any 2-week period)

A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events)

B. Two (or more) of the following features:

1. significant weight gain or increase in appetite
2. hypersomnia
3. leaden paralysis (i.e., heavy, leaden feelings in arms or legs)
4. long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment

C. Criteria are not met for With Melancholic Features or With Catatonic Features during the same episode.

Reprinted with permission from DSM-IV-TR, p. 422[11]

Treatment Options for Atypical Depression

A variety of antidepressant agents have been evaluated in atypical depression. Studies have found that patients with atypical depression appear to be less responsive to tricyclic antidepressants, but may respond preferentially to monoamine oxidase inhibitors (MAOIs).[24–27] However, given the dietary restrictions that complicate the use of MAOIs, especially in patients with increased appetite, studies have investigated the use of selective serotonin reuptake inhibitors (SSRIs) in atypical depression. Unfortunately, response rates to SSRIs have not generally been equal to those seen with the MAOIs. McGrath et al.[28] found that fluoxetine and imipramine had similar therapeutic effectiveness in atypical depression and that both were superior to placebo, but that the response rates of approximately 55% in both groups were lower than previously observed in studies with MAOIs. In contrast, a study by Pande et al.[29] found that fluoxetine was as efficacious as phenelzine in atypical depression and was better tolerated. However, a recent study by Papakostas et al.[30] found that greater body weight in patients with major depression was a predictor of nonresponse to fluoxetine, and patients with atypical depression are likely to have higher body weight, possibly related to overeating.[31]

Studies with Chromium Picolinate

In light of the prevalence of increased appetite, hyperphagia, and carbohydrate craving in patients with atypical depression, this syndrome appears to be a potentially useful target for evaluating the possible antidepressant activity of compounds that exert a normalizing effect on insulin sensitivity and appetite. One such compound is chromium, an essential trace element involved in the metabolism of carbohydrates, lipids, and proteins that acts by increasing the efficiency of insulin action. Trivalent chromium is a co-factor necessary for proper insulin function and plays a major role in cellular insulin sensitivity and insulin-regulating activities.[32,33] Chromium picolinate supplementation enhances insulin sensitivity and glucose transport in genetically obese hyperinsulinemic rats.[34] It has also been found that insulin-resistant hyperglycemia in chromium-deficient patients receiving total parenteral nutrition can be reversed with chromium supplementation.[35,36] Reviews have found that chromium picolinate supplementation at doses containing $\geqslant$ 200 μg/day of elemental chromium produced a significant benefit in patients with diabetes mellitus, as evidenced by lower fasting and 2 hour postprandial glucose levels and lower fasting insulin values.[33,37] Of particular relevance to depression, Ravina et al.[38] found that corticosteroid-induced diabetes was associated with accelerated chromium losses, and this loss was successfully reversed by chromium supplementation. In rodent models, chromium picolinate has been shown to decrease the sensitivity of the 5HT2A receptors, a neuronal system important in the regulation of both mood and appetite.[39]

The first reports of the use of chromium in depression were published by McLeod in 1999[40] and 2000.[41] The first report involved five patients with previously treatment-refractory dysthmic disorder in whom chromium supplementation of antidepressant pharmacotherapy led to remission of dysthymic symptoms, and single-blind substitution of other dietary supplements in each of the patients demonstrated specificity of response to chromium supplementation.[40] The second report involved eight patients with treatment-refractory mood disorders who described dramatic reductions in their symptoms and improvement in their functioning when they received monotherapy with chromium supplements.[41] Again, in several instances, single-blind trials confirmed specificity of the response to chromium. The first author of this article (JPD) interviewed the subjects treated in the McLeod studies and found that, although the patients' diagnoses involved a varied range of psychopathology, response to chromium was strongly associated with the presence of carbohydrate craving.

Based on the case reports by McLeod, Davidson et al.[42] conducted a small, placebo-controlled, double-blind pilot study in 15 patients with DSM-IV major depressive disorder, atypical type. Ten patients received chromium picolinate (CrPic) (initial dose of 400 μg/day of elemental chromium which was then increased to 600 μg/day after 2 weeks) and 5 patients received matching placebo for 8 weeks. Using the criteria of a 66% reduction in symptoms as measured by the 29-item modified Hamilton Depression Scale (HAM-D-29) (Thase et al. 1996[43], as developed by Williams and Rosenthal, unpublished data) and a Clinical Global Impression-Improvement (CGI-I)[44] score of 1 (very much improved) to indicate response, the Davidson et al. study found that 70% (7 of 10) of the subjects treated with CrPic responded to treatment, while none (0 of 5) of the placebo group responded ($p = 0.02$). Treatment with CrPic was well tolerated. The investigators postulated that these antidepressant effects in atypical depression might be related to 5HT2A downregulation, increased insulin sensitivity, or other effects.

Objective of This Study

The multicenter, controlled clinical trial described here was undertaken to attempt to confirm and extend the preliminary results from the pilot trial by Davidson et al.,[42] which suggested a possible antidepressant effect of CrPic in atypical depression, and to gather more information about the precise nature of chromium's effect.

METHODS

Inclusion and Exclusion Criteria

The current trial was a double-blind, randomized, placebo-controlled, multi-center 8-week treatment study in which adult outpatients were randomized in a 2:1 ratio to either chromium picolinate (CrPic; Chromax supplied by Nutrition 21, Inc., Purchase, NY) or placebo. In order to replicate and facilitate comparison with the earlier pilot study by Davidson et al.,[42] the methodology used in that study was duplicated as closely as possible in this larger double-blind trial (e.g., use of 2:1 randomization, inclusion and exclusion criteria, outcome measures). The 10 sites at which the study was conducted were commercial research centers.

We enrolled patients aged 18–65 years who met the following criteria:

1. DSM-IV-TR criteria for a major depressive episode or dysthymia, as determined by the Mini International Neuropsychiatric Interview (MINI),[45] and
2. Criteria for atypical depression as measured by the Columbia Atypical Depression Diagnostic Scale (ADDS)[46] based on exhibiting 50% mood reactivity plus two of the following additional atypical features: increased appetite or weight gain, hypersomnia, leaden paralysis, or rejection sensitivity.

Females of child-bearing potential were required to test negative on a serum pregnancy test at screening and to use adequate contraception throughout the trial.

Patients were excluded if they:

- Met DSM-IV-TR criteria for any other Axis I psychiatric condition, including substance abuse within the last year (based on the MINI);
- Had a concurrent clinically significant medical condition;
- Had a significant abnormality on the electrocardiogram (ECG);
- Had attempted suicide within the last year or were at risk for suicide based on the investigator's assessment;
- Were taking any psychotropic drugs;
- Had a history of nonresponse to three adequate trials of antidepressants;
- Had taken any form of chromium $\geqslant$ 100 μg/day for the 21 days preceding study entrance.

A 2-week washout for antidepressants and herbal supplements was required except in the case of fluoxetine, for which a 5-week washout was required.

Schedule of Assessments

Patients were seen for 6 visits, beginning with a screening visit (Visit 1) at which those who met entrance criteria for the study were randomized. The period between screening and the baseline visit at which treatment was begun was a minimum of 1 week and a maximum of 5 weeks to allow for necessary washout from previous treatments. The 4 subsequent treatment visits, Visits 3–6, occurred at 2-week intervals. Patients in the CrPic group received 400 μg/day elemental chromium, as provided by CrPic, for the first 2 weeks and 600 μg/day for the remaining 6 weeks of treatment. Study drug was to be taken once daily in the morning 30 minutes before or 1 hour after a meal.

At Visit 2 (the baseline visit) and succeeding visits, patients rated tolerability using the self-rated Severity of Symptoms Scale[47,48] for adverse events. Investigators then rated the adverse events in terms of their relation to treatment as "probable," "possible," or "unlikely." Additional information was gathered concerning any adverse events that patients reported as being severe in intensity. Investigators reported any serious or unexpected adverse events to the study coordinating center. Vital signs and concomitant medications were assessed at each visit. Safety assessments, which consisted of physical examinations, laboratory evaluations (complete blood count, blood chemistry, and urinalysis), and ECGs, were performed at the screening visit and at study termination. The population on which safety data was gathered included all patients who took any dose of the study drug.

Efficacy assessments were completed at each of the 6 visits and included 1) the 29-item modified Hamilton Depression Scale (HAM-D-29) which contains the 8-item Seasonal Affective Disorder (SAD-8) Scale;[49] 2) the Clinical Global Impression-Severity (CGI-S) scale; and 3) the 90-item Symptom Checklist (SCL-90).[50] The CGI-I scale was also administered at Visit 3 (the first treatment visit) and succeeding visits. The ADDS was administered at the final visit in addition to the screening visit. The ratings were completed by experienced, well trained personnel with at least 2 years of experience in performing ratings in other trials of depression. Raters also participated in a full HAM-D-29 training session in which they received instructions on how to score the HAM-D-29 based on a video example.

Primary and Secondary Efficacy Measures

To mirror the pilot study by Davidson et al.,[42] the primary efficacy measure prospectively selected for this trial was response rate to chromium picolinate versus placebo, with clinical response defined as $\geqslant$ 66% decrease in HAM-D-29 score between baseline and final visit and CGI-I = 1. To facilitate comparison between results of this trial and other atypical depression trials,[12,13,26–29,51–54] clinical response was also defined more conventionally in a supplemental analysis as $\geqslant$ 50% reduction from baseline on HAM-D-29 scores and a CGI-I = 1 or 2 (very much or much improved). Prospective secondary outcome measures were reductions from baseline on the total HAM-D-29, the SAD-8 score, SCL-90 total and subscale scores, ADDS total and individual symptom scores, and patient's weight.

Efficacy was evaluated in two populations, the intent-to-treat (ITT) and evaluable groups. The intent-to-treat population included all randomized study patients who received at least one dose of chromium picolinate or placebo and who completed at least one efficacy evaluation. The evaluable population was predefined as those patients in the ITT population who took at least 80% of

study drug and who were without significant post-enrollment protocol deviations. Although the evaluable population lacked true randomization, we analyzed results from this population since all patients in the evaluable group had received sufficient drug to allow investigators to perceive a clinical effect if present and thus these subjects provided a sample that may be more clinically meaningful than the ITT sample.

IRB Approval and Informed Consent

This study was conducted in accordance with the "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Patients" contained in the Declaration of Helsinki of 1975, as revised in 1983, and in compliance with current Good Clinical Practices and Title 21 Part 56 of the Code of Federal Regulations pertaining to institutional review boards. Institutional Review Board oversight was provided by Biomedical Research Institute of America, San Diego, CA. All study participants provided consent after being informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

Statistical Analyses

Fisher's exact test was used to determine statistical significance in rate of response between chromium picolinate and placebo groups. The Fisher's test was used instead of chi-square analysis since it is appropriate no matter what size samples are involved. Two-way analysis of variance (ANOVA) (treatment, time) was used to evaluate change in severity as measured by the HAM-D-29. T-tests with Bonferroni correction for multiple comparisons were performed on the individual HAM-D-29 items. We used the Bonferroni correction method because multiple variables were involved and we wanted to take the most conservative approach; it should be noted, however, that the Bonferroni method may sometimes overcorrect so that some important associations may be missed. The Bonferroni Pearson correlation was used to evaluate the relationship between carbohydrate craving and clinical response. A linear regression was run to evaluate the relationship between change from baseline in HAM-D-29 scores and baseline carbohydrate craving scores in both the CrPic and placebo groups. The strength of the relationship was assessed using the r-squared fit statistic and the fitted coefficients of the regression relationship. Site was taken into account in the models for all continuous responses that were statistically analyzed. A site-by-treatment interaction term was not included in the models nor were treatment differences plotted graphically by site.

RESULTS

Study Population

Between December 2002 and August 2003, 157 outpatients, recruited by advertisement or clinical referral, were screened by telephone. Of these, 113 met entrance criteria for the study and were randomized at 10 study sites in the United States (72 CrPic, 41 placebo). Of these 113 patients, 93 completed the study and 20 dropped out (there was no statistically significant difference in drop out rates in the two groups, which were 22% in the CrPic group and 21% in the placebo group). Three patients (2 CrPic, 1 placebo) were lost to follow-up after the screening visit, so that 110 patients (70 CrPic, 40 placebo) were qualified for safety and ITT analysis (i.e., received at least one dose of study medication and completed at least one efficacy evaluation). Of these 110 patients, 75 (50 CrPic, 25 placebo) met the predetermined criteria to be considered evaluable (i.e., took at least 80% of study drug and had no significant post-enrollment protocol deviations). Of the 35 ITT patients who were disqualified from the evaluable population, 7 missed two or more study visits, 6 took less than 80% of dispensed study drug, and the remaining 22 were disqualified for protocol entrance violations or post enrollment deviations; rates of these deviations were similar in the two groups. The evaluable population had a mean age of 46 years and was predominantly female (69%), Caucasian (81%), and overweight or obese (mean body mass index [BMI] 29.8). No statistical differences were found at baseline between the CrPic and placebo groups with regard to demography or any clinical characteristics (Table 2). Screening results on the ADDS are shown in Table 3. Although site was taken into account in the models for all continuous responses that were analyzed, no site effects were shown to be significant.

Primary Efficacy Measures

Using Davidson et al.'s definition of "responder" ($\geq$ 66% reduction in HAM-D-29 from baseline and a CGI-I = 1),[42] rates of responders in this trial were 20% CrPic vs. 30% placebo in the ITT population (p = 0.92) and 24% Cr Pic vs. 32% placebo in the evaluable population (p = 0.85). A two-way analysis of variance (treatment, time) revealed significant improvement in HAM-D-29 scores over time

Table 2. Disposition, demographics, and baseline clinical characteristics of patients in intent-to-treat (ITT), evaluable, and high carbohydrate-craving populations

Variable	ITT population			Evaluable population			ITT patients with high carbohydrate craving*		
	CrPic (*N* = 70)	Placebo (*N* = 40)	Total (*N* = 110)	CrPic (*N* = 50)	Placebo (*N* = 25)	Total (*N* = 75)	CrPic (*N* = 26)	Placebo (*N* = 15)	Total (*N* = 41)
Age, mean (SD)	46.4 (11.7)	45.5 (10.2)	46.1 (11.1)	46.1 (12.2)	44.5 (9.9)	45.6 (11.4)	51.3 (8.9)	47.8 (7.9)	50.0 (8.6)
Gender, n (%)									
Female	54 (77%)	24 (60%)	78 (71%)	37 (74%)	15 (60%)	52 (69%)	22 (85%)	9 (60%)	31 (76%)
Male	16 (23%)	16 (40%)	32 (29%)	13 (26%)	10 (40%)	23 (31%)	4 (15%)	6 (40%)	10 (24%)
Race, n (%)									
Caucasian	60 (86%)	29 (73%)	89 (81%)	43 (86%)	18 (72%)	61 (81%)	20 (77%)	10 (67%)	30 (73%)
Black	6 (8%)	4 (10%)	10 (9%)	4 (8%)	2 (8%)	6 (8%)	4 (15%)	3 (20%)	7 (17%)
Hispanic	3 (4%)	3 (7%)	6 (6%)	2 (4%)	2 (8%)	4 (5%)	2 (8%)	1 (7%)	3 (7%)
Asian	1 (1%)	3 (7%)	4 (4%)	1 (2%)	2 (8%)	3 (4%)	0	1 (7%)	1 (2%)
Other	0	1 (3%)	1 (1%)	0	1 (4%)	1 (1%)	0	0	0
BMI, mean (SD)†									
Females	30.8 (7.7)	27.9 (6.5)	29.9 (7.5)	30.3 (7.8)	28.6 (7.2)	29.8 (7.6)	32.6 (7.8)	28.9 (7.6)	31.5 (7.8)
Males	29.6 (7.1)	29.5 (5.9)	29.5 (6.4)	28.6 (6.6)	30.4 (7.0)	29.4 (6.7)	28.3 (4.9)	30.9 (2.4)	29.8 (3.6)
DSM-IV diagnosis, n (%)									
Major depressive disorder, single episode	10 (14%)	3 (8%)	13 (12%)	8 (16%)	1 (4%)	9 (12%)	5 (19%)	1 (7%)	6 (15%)
Major depressive disorder, recurrent	55 (79%)	35 (88%)	90 (82%)	40 (80%)	23 (92%)	63 (84%)	19 (73%)	12 (80%)	31 (76%)
Dysthymic disorder	1 (1%)	0	1 (1%)	1 (2%)	0	1 (1%)	1 (4%)	0	1 (2%)
Depressive disorder NOS	4 (6%)	2 (5%)	6 (6%)	1 (2%)	1 (4%)	2 (2%)	1 (4%)	2 (13%)	3 (7%)
HAM-D-29 total score, mean (SE)	35.3 (1.2)	33.6 (1.2)	34.7 (0.9)	35.0 (1.4)	33.5 (1.5)	34.5 (1.1)	37.7 (2.4)	35.6 (2.0)	37.0 (1.7)
SAD-8 total score, mean (SE)	13.3 (0.6)	12.1 (0.7)	12.8 (0.5)	13.1 (0.7)	12.1 (0.9)	12.8 (0.5)	14.9 (1.2)	13.9 (1.2)	14.5 (0.9)
HAM-D-29 carbohydrate craving score, mean (SE)	1.7 (0.1)	1.3 (0.2)	1.6 (0.1)	1.8 (0.1)	1.2 (0.2)	1.6 (0.1)	2.3 (0.2)	2.3 (0.3)	2.3 (0.2)

**Patients with a score of 3 on Question 10 of the HAM-D ("irresistible craving for sweets and starches")*
†The American Diabetes Association defines BMI scores as follows for both males and females: underweight, < 18.5; normal weight, 18.5–24.9; overweight, 25.0–29.9; and obese, ⩾ 30.0.

in both groups ($p < 0.0001$) but no difference between active and placebo conditions. Thus, these results failed to show any difference between CrPic and placebo in effects on atypical depression as measured by scores on the HAM-D-29 and CGI-I.

While the analysis of responders found fewer responders to CrPic than did the study by Davidson et al.,[42] the overall absolute reduction in severity of depression with CrPic treatment as measured by mean HAM-D-29 scores was similar between the two studies, with a drop of 17.7 points in this study and 18.2 points in the Davidson et al. study. However, since mean baseline HAM-D-29 scores were higher in this study (CrPic 35.0, placebo 33.5) than in the Davidson et al. study (CrPic 30.9, placebo 29.8), the percent of reduction in overall HAM-D-29 scores with CrPic treatment was lower in this trial (51%) than in the Davidson et al. study (59%). There was also a higher absolute and relative placebo response in this study, with a drop of 15.9 points (47% decrease) compared with a drop of 10.8 points (36% decrease) in the Davidson et al. study.

Both the CrPic and placebo groups in this study improved significantly from baseline, but few patients achieved complete remission, and neither group showed the magnitude of remission observed with CrPic in the study by Davidson et al. In order to be able to compare

Table 3. Number (*n*) and percent (%) of subjects with positive results on the Atypical Depression Diagnostic Scale (ADDS) at screening

	ITT population			Evaluable population			ITT patients with high carbohydrate craving		
Positive rating on	**CrPic (*N* = 70)**	**Placebo (*N* = 40)**	**Total (*N* = 110)**	**CrPic (*N* = 50)**	**Placebo (*N* = 25)**	**Total (*N* = 75)**	**CrPic (*N* = 26)**	**Placebo (*N* = 15)**	**Total (*N* = 41)**
Overall ADDS*	69 (99%)	39 (98%)	108 (98%)	50 (100%)	24 (96%)	74 (99%)	25 (96%)	15 (100%)	40 (98%)
⩾ 50% mood reactivity	70 (100%)	39 (98%)	109 (99%)	50 (100%)	24 (96%)	74 (99%)	26 (100%)	15 (100%)	41 (100%)
Increased appetite or weight gain	57 (81%)	26 (65%)	83 (76%)	42 (84%)	15 (60%)	57 (76%)	21 (81%)	13 (87%)	34 (83%)
Hypersomnia	33 (47%)	21 (53%)	54 (49%)	22 (44%)	15 (60%)	37 (49%)	13 (50%)	6 (40%)	19 (46%)
Leaden paralysis	52 (74%)	31 (78%)	83 (76%)	37 (74%)	20 (80%)	57 (76%)	19 (73%)	12 (80%)	31 (76%)
Rejection sensitivity	62 (89%)	29 (73%)	91 (83%)	44 (88%)	16 (64%)	60 (80%)	23 (89%)	12 (80%)	35 (85%)

**Met diagnostic criteria for atypical depression. To be included in the study, patients were required to exhibit atypical features, defined as ⩾ 50% mood reactivity and two of the following: increased appetite or weight gain, hypersomnia, leaden paralysis, and rejection sensitivity.*

our results with those of other studies of atypical depression which used other criteria, we performed a supplemental analysis defining "responder" in the more usual fashion as a reduction from baseline of at least 50% in HAM-D-29 scores and a CGI-I scores of 1 or 2. Using these criteria, we observed responder rates of 46% for CrPic compared with 43% for placebo in the ITT group; $p = 0.82$) and 54% for CrPic compared with 36% for placebo in the evaluable group; $p = 0.18$) (Figure 1); neither difference was statistically significant.

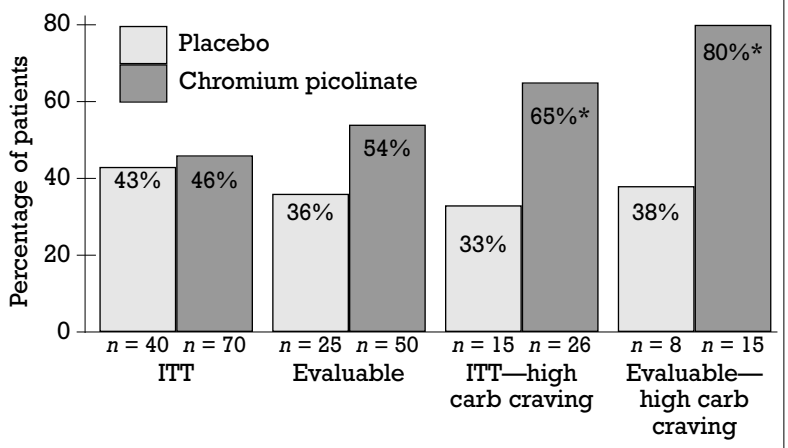
Secondary Efficacy Measures

There were no statistically significant differences noted between the CrPic and placebo groups in changes in patient weight (the CrPic group showed a mean decrease from baseline of 0.18 kg compared with a mean increase of 0.08 kg in the placebo group; $p = 0.85$). There were also no statistically significant differences between the CrPic and placebo groups in total HAM-D-29 scores, in total SAD-8 scores, on individual items in the SAD-8, or in total scores on the SCL-90 and the ADDS (data not shown).

Due to the exploratory nature of this investigation, we conducted supplemental t-tests on the individual HAM-D-29 items for the evaluable population. The CrPic group showed significant improvements (i.e., change from baseline values) on four items where placebo did not ($p < 0.00167$, with Bonferroni correction): appetite increase (change from baseline values of –1.18 with CrPic vs. –0.64 with placebo), increased eating (–1.22 CrPic vs. –0.56 placebo), carbohydrate craving (–1.00 CrPic vs. –0.48 placebo), and diurnal variation of feelings (–0.48 CrPic vs. 0.16 placebo). There were no differences in individual HAM-D-29 items favoring placebo. There was also a significant correlation between baseline severity of carbohydrate craving and improvement on the overall HAM-D-29 in the group treated with CrPic but not in the placebo group (ITT population, $p = 0.004$; evaluable population, $p = 0.0006$; Figure 2).

Given these observations and the relationship between carbohydrate metabolism and chromium picolinate, we then assessed overall response rate and changes in HAM-D-29 items in the subpopulation of 41 ITT patients who had high carbohydrate craving (i.e., patients who scored 3 on item 10 of the HAM-D-29 ("irresistible craving for sweets and starches"). Compared to the overall evaluable population, this group was slightly older (mean age of 50 years), had a preponderance of females (76%), a higher percentage of black patients (17% vs. 8% in the overall evaluable population), and was more likely to be obese (mean BMI 31.5) (Table 2). Patients with high carbohydrate craving showed a significantly greater response to CrPic than to placebo in both the ITT (65% vs. 33%; $p < 0.05$; $n = 41$) and evaluable (80% vs. 38%; $p < 0.05$; $n = 23$) populations (Figure 1). In the subgroup of high carbohydrate cravers in the ITT population, patients treated with CrPic showed significant improvements on four HAM-D-29 items whereas high carbohydrate cravers treated with placebo did

Figure 1. Percentage of patients classified as treatment responders (≥ 50% reduction on HAM-D-29 and CGI-I rating of 1 or 2)



not ($p < 0.00167$, with Bonferroni correction): genital symptoms (e.g., level of libido; change from baseline –0.69 with CrPic vs. –0.13 with placebo), appetite increase (–1.23 CrPic vs. –0.53 placebo), increased eating (–1.19 CrPic vs. –0.53 placebo), and carbohydrate craving (–1.54 CrPic vs. –0.93 placebo). Three of the four items—appetite increase, increased eating, and carbohydrate craving—were the same items that differentiated between response to CrPic and placebo in the overall evaluable population. In the ITT subpopulation with high carbohydrate craving, 21 of the individual HAM-D-29 items showed greater change in patients treated with CrPic, while none showed greater change in those who received placebo. Similar patterns were observed in the evaluable subpopulation with high carbohydrate craving.

Safety and Tolerability

Chromium picolinate was well-tolerated. Safety data were obtained on 110 patients, 71 (65%) of whom experienced at least one adverse event (61% [43/70] in the CrPic group and 73% [29/40] in the placebo group). Seventeen patients (11 CrPic, 6 placebo) experienced clinically significant adverse events, none of which was judged to be related to treatment. Only 2 patients (1 CrPic, 1 placebo) discontinued treatment due to adverse events.

In total, 193 adverse events were reported by the placebo group, 20 of which (10%) were considered clinically significant and 327 adverse events were reported by the CrPic group, 36 of which (11%) were considered clinically significant. However, relatively few of the adverse events—19% (61/327) in the CrPic group and 8% (15/193) in the placebo group—were considered to be treatment related (i.e., events the investigators rated as probably or possibly related to treatment). In addition, none of the adverse events rated as probably or possibly related to treatment in either group was considered clinically significant. There were also no differences between patients treated with CrPic and those who received placebo in any clinically significant adverse event, including weight gain and sexual dysfunction. The most frequently occurring treatment-related events are listed in Table 4.

With respect to laboratory data, both groups exhibited a decrease in mean red blood cell count and hemoglobin and an increase in mean corpuscular volume. Patients treated with placebo exhibited a significant decrease in absolute lymphocytes and percent neutrophils and an increase in mean corpuscular hemoglobin concentration, platelet volume, and mean percent eosinophils, whereas patients treated with CrPic did not. None of these changes was deemed to be clinically meaningful.

In summary, there were no statistically or clinically significant differences between the treatment groups on adverse effects, laboratory results, vital signs, or other safety parameters.[55]

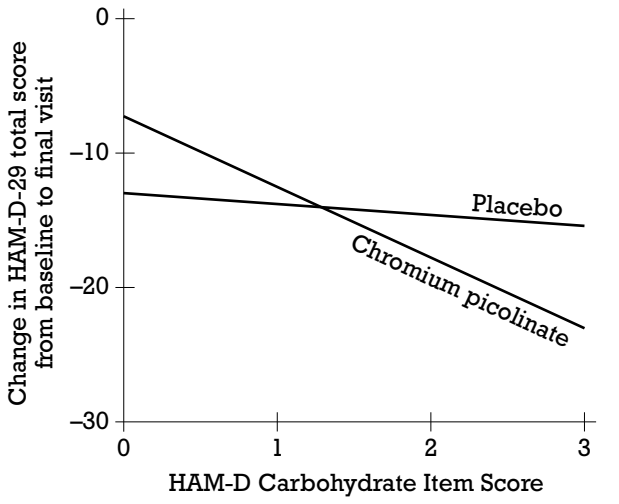
DISCUSSION

The beneficial effect of chromium in patients with atypical depression, a subtype of depressive disorder characterized by lethargy, hyperphagia, and carbohydrate craving, had been suggested by case reports[40,41] and a small double-blind pilot trial by Davidson et al.[42] The multi-center replication study described here used the same enrollment criteria, recruitment methods, and assessments as the trial by Davidson et al.

Findings in the Treatment Groups as a Whole

A two-way ANOVA of HAM-D-29 scores revealed a significant effect for time but no significant differences between the CrPic and placebo treatment groups. An analysis of the proportion of responders in the two

Figure 2. Relationship between change in mean HAM-D-29 score from baseline to final visit and HAM-D-29 carbohydrate item score at baseline for CrPic patients in ITT population ($p = 0.004$, R = 0.117)
(evaluable population: $p = 0.0006$, R = 0.217 [not shown])



groups, which used the Davidson et al. response criteria of ⩾ 66% reduction from baseline on HAM-D-29 total score and a CGI-I = 1, also failed to reveal a difference between CrPic and placebo. The magnitude of improvement with CrPic treatment as measured by the change in mean HAM-D-29 scores was similar in the current study and in the Davidson et al. trial (–17.7 points vs. –18.2 points). The failure to find a difference in treatment effect between the two groups appears to be due largely to the high rate of placebo response observed in this trial (–15.9 points) compared with the lower placebo response rate in the Davidson et al. study (–10.8 points). Another factor that may have been involved is the loss of sensitivity that accompanies expansion from a single site study to a multicenter trial. It should also be noted that 50% or more of contemporary studies of known antidepressants fail to observe significant drug-placebo differences.[56–60]

Given the exploratory nature of this study, we conducted supplemental analyses of the individual HAM-D-29 items to identify specific symptoms that may have responded differentially to the two treatments. We found that patients treated with CrPic showed a greater reduction on four HAM-D-29 items—appetite increase, increased eating, carbohydrate craving, and diurnal variation of feelings—than the placebo group, whereas no HAM-D-29 items favored placebo.

Table 4. Number (*n*) and percent (%) of treatment-related adverse events (those occurring in ⩾ 2% of either treatment group)

	Safety population		
Adverse Event (MedDRA terms)	***CrPic (N = 70)***	***Placebo (N = 40)***	***Total (N = 110)***
Dry mouth	5 (7%)	3 (8%)	8 (7%)
Disturbance in attention	4 (6%)	1 (3%)	5 (5%)
Insomnia	2 (3%)	2 (5%)	4 (4%)
Nightmare	3 (4%)	1 (3%)	4 (4%)
Constipation	3 (4%)	0	3 (3%)
Thirst	3 (4%)	0	3 (3%)
Pollakiuria	2 (3%)	1 (3%)	3 (3%)
Headache	2 (3%)	1 (3%)	3 (3%)
Blurred vision	3 (4%)	0	3 (3%)
Dysgeusia	2 (3%)	0	2 (2%)
Peripheral edema	2 (3%)	0	2 (2%)
Increased sweating	0	1 (3%)	1 (1%)

Note: Investigators graded the treatment-relatedness of patient-reported adverse events as "probable," "possible," or "unlikely." Events graded "probable" or "possible" were considered to have been treatment-related.

Findings in the Subpopulation with Marked Carbohydrate Craving

In contrast to the findings for the treatment groups as a whole, within the subpopulation of patients with marked carbohydrate craving, we found that significantly more patients responded to chromium than to placebo. Furthermore, in the patients treated with CrPic, the magnitude of change on the HAM-D-29 correlated with severity of carbohydrate craving at baseline. A similar sensitivity to CrPic among those with appetite-related symptoms was noted by Davidson et al.,[42] who observed that, of the 8 patients treated with CrPic who were overeating at baseline, 4 experienced complete disappearance of this symptom compared with only 1 of the 5 overeaters who were on placebo. While these findings require replication in a prospective trial, they suggest that CrPic may be beneficial for patients with atypical depression who are also high carbohydrate cravers.

Since we hypothesized that marked carbohydrate craving may be a clinical marker for insulin resistance, we

predicted that chromium's effect would be greatest in this population. The greater improvement observed in patients with marked carbohydrate craving was due to improvements in the following HAM-D-29 items: appetite increase, increased eating, carbohydrate craving, and genital symptoms. Although the supplemental nature of these analyses limits their interpretation, the pattern of response to CrPic in this group is highly consistent and is also consistent with the known effects of CrPic on carbohydrate metabolism.

Safety Data

Treatment-associated adverse events were minimal and not statistically or clinically different from those seen in the placebo group. The treatment safety profile contrasts markedly with that of the MAOIs and other drugs demonstrated to be effective in treating patients with atypical depression, which can produce side effects that are intolerable to some patients.

Directions for Future Research

Placebo response. In light of the robust improvement observed in this study in both placebo and CrPic groups, further studies assessing the antidepressant efficacy of CrPic that better control for placebo-related variables appear warranted. The high placebo response rate in this study confounds interpretation of the results. Several aspects of the experimental design used in this study have been associated with a high rate of placebo response in other controlled trials of depression.[58–61] These include absence of a placebo run-in period, no specified minimum duration or severity of depression, and inclusion of a diagnostically heterogeneous population. There is, however, controversy as to whether a placebo run-in lowers the placebo response rate or increases the drug-placebo difference in acute phase efficacy trials.[62,63]

Optimum dosing. Another potentially confounding variable in this study is that optimal dosing of CrPic for health and disease states has not been fully characterized[33,64] and the doses used here may not have been sufficient to maximize treatment effect. One study of chromium in diabetes found that the response to chromium was dose dependent up to 1000 μg/day.[37] Published studies suggest that the metabolic effects of CrPic may be mediated through an increase of insulin activity via a number of sensitivity enhancing effects. These include phosphoinositide kinase-3 (PI3K) activity, enhanced protein kinase B (Akt) phosphorylation, and increased rates of insulin-responsive glucose transporter (GLUT-4) vesicle translocation to the cell surface.[34,64–66] In turn, this increased sensitivity may increase central noradrenergic[67] and serotonergic[39] activity. This suggests the possibility that a higher dose of chromium picolinate might be able to reverse mood-related components of the atypical depressive syndrome, in addition to its effects on symptoms of increased appetite and eating and carbohydrate craving.

Seasonal affective disorder. Neither this study nor the Davidson et al. pilot study[42] ruled out patients with SAD and it is possible that, due to overlapping symptoms, patients with SAD may have been included in the samples, although no data are available to evaluate the possible influence this may have had on the results. To improve specificity of findings in future studies, study samples should be screened for SAD and this variable should be taken into account in the analyses of results. In addition, given the similarity in symptomatic profiles between atypical depression and SAD, which, as noted in DSM-IV-TR,[11] is often characterized by "prominent anergy, hypersomnia, overeating, weight gain, and a craving for carbohydrates" (p. 426), it may be useful to conduct studies examining the use of chromium in the treatment of patients with SAD.

Relationship between depression, diabetes, and the metabolic syndrome. As noted in the introduction to this article, a well established relationship exists between depression, cardiovascular disease, and diabetes.[7–10] While the mechanism for these associations is not clear, research has increasingly focused on changes in insulin activity as a possible mediator.[8] For example, studies have found that patients with depression appear to have a higher prevalence of insulin resistance (a condition in which the body cannot use insulin efficiently) and the metabolic syndrome compared with the general population.[68–78] It has been hypothesized that insulin resistance may underlie symptoms such as hyperphagia, carbohydrate craving, and weight gain that occur in some depressive syndromes. The metabolic syndrome, estimated to occur in 47 million U.S. adults, is characterized by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) Guidelines[79] as the co-occurrence of a group of risk factors: central/abdominal obesity (waist size > 40 inches for men and > 35 inches for women), elevated triglycerides (TG > 150 mg/dL), low HDL (men < 40 mg/dL; women< 35 mg/dL), high blood pressure (> 130/85), and impaired fasting glucose (> 110 mg/dL). The American Heart Association also includes

insulin resistance in its criteria for metabolic syndrome, which is therefore sometimes called the insulin resistance syndrome.[80] Patients with insulin resistance have abnormally elevated levels of fasting insulin due to hyperexcretion by the pancreatic beta cells as the body attempts to maintain glucose homeostasis. As insulin resistance progresses over time, these elevated insulin levels are not sufficient to maintain normal glucose levels, thus leading to chronic hyperglycemia. Additional vascular, metabolic, and neurological complications arise as the chronic hyperinsulinemia reciprocally gives rise to concomitant chronic hypercortisolemia. Underlying causes of metabolic syndrome are excessive weight, physical inactivity, and genetic factors.[80] People with metabolic syndrome are at increased risk for CVD, strokes, and type 2 diabetes.

Okamura et al.[81] observed that resistance to insulin in major depression appears to be state dependent and is reversible with symptomatic improvement. A study by Raikkonen et al.[82] found that women with high levels of depression had an elevated risk for developing the metabolic syndrome and that the metabolic syndrome in turn predicted an increased incidence of later mood problems. Studies suggest that the increased state-dependent insulin resistance found in depressive syndromes may account for the linkage between depression and cardiovascular disease.[83] A recent study by Rasgon and Jarvik also suggested that insulin resistance may be one factor involved in the link between affective disorders and Alzheimer's disease.[84]

It has been hypothesized that hyperactivity of the hypothalamic-pituitary-adrenocortical axis (HPA-axis) may be associated with the insulin resistance and abnormalities in the regulation of blood glucose found in both depression and type 2 diabetes mellitus[85] and that cognitive and depressive disorders in patients with diabetes mellitus may be associated with this hyperactivity of the HPA-axis and concomitant hypercortisolemia.[86] Depression has also been found to be associated with diminished glycemic control, insulin resistance, and poorer overall functioning in depressed diabetics.[87–91]

Given the effects of chromium on insulin regulation and the association between depression and dysregulation of the insulin system described above, further research on chromium in depressive disorders should include monitoring and evaluation of insulin function and metabolic parameters.

Summary. A study or set of prospective studies to determine if chromium picolinate has a beneficial effect on carbohydrate craving and related symptoms of appetite increase/increased eating in patients with atypical depression and other psychiatric disorders appears warranted. Carbohydrate craving is highly prevalent and can have potentially serious consequences, which are often exacerbated by treatment with psychotropic medications, including antidepressants, mood stabilizers, and antipsychotics. A treatment that effectively reduces carbohydrate craving and has a favorable tolerability and side-effect profile would be a very useful contribution to improve overall health outcomes. Such studies could also evaluate the effects of varying dosages of chromium on other symptoms associated with affective disorders and might help elucidate the relationship between insulin resistance, the metabolic syndrome, and depression.

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