Creatine Supplement Speeds Antidepressant Response

In a randomized, proof-of-concept trial in women with major depression, augmentation with creatine resulted in rapid response to SSRI therapy.

**Background:** Creatine monohydrate is available as an oral dietary supplement. Preclinical animal studies showed that creatine produced an antidepressant-like response, but only in female rodents. It may also improve the abnormal brain bioenergetics observed in patients with depression. Abnormal cerebral metabolism is more common in depressed women than men, which suggests creatine supplementation may be more effective in women.

**Methods:** Study subjects were 52 medication-free women, aged 19–65 years, with major depressive disorder. All patients were treated with flexibly-dosed 10–20 mg/day escitalopram (Lexapro) plus double-blind randomly assigned creatine or placebo for 8 weeks. Creatine was added at 3 g/day for the first week, and then increased to 5 g/day afterward. The primary outcome measure was the Hamilton Rating Scale for Depression (HAM-D). Response (>50% decrease in symptoms) within 4 weeks was considered early.

**Results:** Forty-five of the women were experiencing their first depressive episode, and 41 were medication-naive. The rest had been medication-free for ≥2 months before enrollment. A total of 39 women (75%) completed the trial.

In an intent-to-treat analysis, creatine augmentation resulted in significantly greater improvement in depression, beginning at week 2 and continuing at the 4- and 8-week evaluations. (See table, next page.) Effect sizes* for HAM-D improvement with creatine were 1.3 at week 2, 1.2 at week 4, and 1.1 at week 8. Early response (by week 4) was evident in 68% of the creatine group, compared with 30% of the placebo group (p=0.001). The difference remained statistically significant at week 4, but not at week 8. Remissions occurred by week 8 in 52% of creatine-treated
women and in 26% of the placebo group (p=0.008). Creatine augmentation was also superior to placebo on secondary outcome measures including the Montgomery-Asberg Depression Rating Scale and the Clinical Global Impressions–Severity subscale.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean HAM-D Score</th>
<th>P Value</th>
<th>Effect Size</th>
<th>Odds Ratio* for creatine response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Creatine (n=25)</td>
<td>Placebo (n=27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27</td>
<td>27</td>
<td>p=ns</td>
<td>N/A</td>
</tr>
<tr>
<td>Week 1</td>
<td>23</td>
<td>24</td>
<td>p=ns</td>
<td>0.33</td>
</tr>
<tr>
<td>Week 2</td>
<td>15</td>
<td>20</td>
<td>p&lt;0.001</td>
<td>1.28</td>
</tr>
<tr>
<td>Week 4</td>
<td>9</td>
<td>15</td>
<td>p&lt;0.001</td>
<td>1.20</td>
</tr>
<tr>
<td>Week 8</td>
<td>5</td>
<td>10</td>
<td>p&lt;0.001</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Mean escitalopram dosage (15 mg/day) did not differ between the groups, and adverse events were similar in the 2 groups and typical of SSRI therapy. There were no differences in laboratory measures or BMI between the 2 groups.

Discussion: Results of this proof-of-concept study suggest creatine augmentation of SSRI therapy may result in greater improvement in depression and in earlier response. In addition to normalizing energy metabolism in the brain, emerging evidence suggests creatine has neuroprotective effects via antioxidant and antiapoptotic properties.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.


*See Reference Guide.

**Tolcapone Attenuates Impulsive Decision-Making**

In a laboratory experiment, the antiparkinsonian drug tolcapone (*Tasmar*) reduced impulsive behavior in healthy subjects. If these results translate to "real-world" impulsive behaviors, tolcapone may have potential as an adjunct to other treatments for impulse-control disorders.

Background: Delay discounting—the tendency to choose immediate rewards over delayed but more valuable ones—is a sign of impulsivity associated with multiple substance-use disorders. Impulsivity is correlated with greater activity of catechol-O-methyltransferase (COMT), the genetically encoded dopamine-degrading enzyme. COMT may preferentially degrade cortical but not striatal dopamine, and delay discounting may depend on the balance between cortical and striatal dopamine tone. Tolcapone is a COMT inhibitor that preferentially increases dopamine tone in the frontal cortex.
**Methods:** Twenty-three subjects, aged 19–41 years, with no neurologic or psychiatric illnesses participated in a placebo-controlled randomized crossover study of tolcapone. After some introductory training and ingesting the study medication, participants performed a series of delay discounting tasks under functional magnetic resonance imaging. They were presented with hypothetical options to receive increasing sums of money (from $1 to $100) after increasing spans of time (1 week to 6 months). In the 4 different types of discounting trials, subjects were instructed to choose 1 of 3 options: the option they wanted; did not want; or to choose the largest or soonest reward. A control test involved no choice motivated by a reward. The primary behavioral outcome was the Impulsive Choice Ratio (ICR), the ratio of sooner to total choices in the “wanted” tests.

**Results:** Participants displayed the entire range of sooner choices, with ICRs ranging from 0 to 100%. During tolcapone administration, the ICR was significantly reduced compared to placebo (p=0.025). ICR decreases were variable across subjects, and those with the highest baseline impulsivity demonstrated the largest decreases in the ICR, while those with low impulsivity had smaller declines or increases. Responses to the other types of tests indicate that the tolcapone-related changes were not due to nonspecific dopaminergic effects on motor response.

Imaging studies indicated that tolcapone administration was associated with increases of activity in specific task-active regions of the frontal cortex: the dorsolateral and medial frontal cortices and visual association areas. Decreased activity was seen in areas associated with the default mode network. Regardless of tolcapone administration, later discounting choices were associated with greater activity in the left anterior insula and the dorsal anterior cingulate, compared to sooner discounting choices.

**Discussion:** These observations are consistent with the hypothesis that lower cortical dopamine tone and may promote impulsive behaviors. COMT inhibition with tolcapone may be a relatively specific way to decrease impulsivity by increasing dopamine but not other catecholamines in the frontal cortex.


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**Escitalopram to Prevent Interferon-Associated Depression**

In a randomized trial, escitalopram prevented the development of depression in patients with no psychiatric risk factors who were undergoing interferon-α treatment for chronic hepatitis C virus (HCV) infection.

**Background:** Mild-to-moderate depression develops in up to 70% of HCV-infected patients treated with interferon-α, and 20–40% experience major depression. This adverse effect negatively impacts treatment adherence and response to antiviral therapy.

**Methods:** Prophylactic escitalopram was compared with placebo in 181 patients with HCV who were undergoing treatment with peginterferon-α-2a and ribavirin. Patients with a history of an axis I disorder, those who had received antidepressant treatment in the previous 3 years, and those in whom depression developed during the 12 weeks before receiving HCV therapy were excluded. Participants were randomly assigned to double-blind treatment with either 10 mg/day escitalopram or placebo for 2 weeks before beginning antiviral therapy. Both antiviral treatment and randomized study medication were continued for 24 or 48 weeks, depending on the HCV viral genotype. Psychiatric assessments were carried out using the DSM-IV Structured Clinical Interview at 14, 8, and 2 weeks before the start of antiviral therapy, on multiple occa-
sions during therapy, at the end of antiviral treatment, and after 24 weeks of follow-up. The primary efficacy outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS), with a cutoff score of 13 for major depression and 25 for severe depression.

**Results:** During treatment, MADRS scores reached ≥13 points, indicating depression, in 25 escitalopram-treated patients, compared with 49 placebo-treated patients (32% vs 59%; p<0.001; number needed to treat,* 3.7). One patient (1%) treated with escitalopram met MADRS criteria (≥25) for severe depression, compared with 11 (12%) in the placebo group. Using more stringent DSM-IV criteria, major depression was diagnosed by a psychiatrist in 8% of escitalopram-treated patients, compared with 19% of the placebo group (p=0.03).

The treatment effect did not vary by week of antiviral therapy. By 6 months after treatment, average MADRS scores returned to normal and did not differ between the 2 randomized groups. Sustained virologic response to treatment was observed in 46% of the escitalopram group and in 56% of the placebo group, a statistically nonsignificant difference. The proportion of patients completing antiviral therapy was similar in the 2 groups.

**Discussion:** Interferon-α-associated depression has been linked to a serotonergic deficit, which provides a rationale for SSRI therapy during HCV treatment. It is not known whether prophylactic treatment is preferable to a treat-as-needed approach. However, previous evidence suggests the treat-as-needed strategy may result in delayed or missed opportunities for antidepressant therapy.

**Study Rating*—17 (100%):** This study met all criteria for a randomized controlled trial.

Schafer M, Sarkar R, Knop V, Effenberger S, et al: Escitalopram for the prevention of peginterferon-α2a-associated depression in hepatitis C virus-infected patients without previous psychiatric disease. *Annals of Internal Medicine* 2012;157 (July 17):94–103. From Charite-Universitätsmedizin, Berlin, Germany; and other institutions. *Funded by Roche Pharma; Lundbeck; and other sources. The authors disclosed potential conflicts of interest.*

*Drug Trade Names: escitalopram—Lexapro; peginterferon-α2a—Pegasys; ribavirin—Copegus, Rebetol

*See Reference Guide.

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### High-Dose Rivastigmine Patch for Alzheimer's

In a randomized trial in patients who experienced cognitive decline with the rivastigmine (*Exelon*) patch at the currently recommended dosage, functional decline was slowed with a switch to a higher-dose patch.

**Methods:** The current recommended target maintenance dosage of rivastigmine is 9.5 mg/24 hours (10 cm²). The clinical trial enrolled community-dwelling patients, aged 50–85 years, who met DSM-IV criteria for Alzheimer’s dementia or criteria for “probable” Alzheimer’s dementia, according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association. A total of 1582 patients received open-label treatment with standard-dose rivastigmine for 24–48 weeks. Those who continued to experience functional and cognitive decline at week 24, 36, or 48 were switched to the double-blind randomized trial, in which they received either continued standard-dose therapy or a higher-dose patch, 13.3 mg/24 hours (15 cm²), for an additional 48 weeks. The primary outcomes were changes from baseline of the double-blind phase to week 48 in the Instrumental Activities of Daily Living domain of the Alzheimer’s Disease Cooperative Study–Activities of Daily Living (ADCS-IADL) scale and the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog).

**Results:** Of the 1582 patients treated with open-label standard-dose rivastigmine, 567 entered the randomized treatment phase. About 71% of patients completed the 48 weeks of double-blind treatment.
Both groups showed further declines in the ADCS-IADL total score during randomized treatment, but the declines were smaller in the group receiving higher-dose rivastigmine. The difference between groups was statistically significant at all time points (p=0.025, =0.005, <0.001, and =0.002 at weeks 16, 24, 32, and 48, respectively). ADAS-cog scores also declined, but to a lesser extent in the high-dose group, with a significant difference observed at week 24 (p=0.027) but not week 48. Secondary efficacy measures, such as executive function and time to functional decline, tended to favor the higher dose but were not statistically significant.

Adverse events were reported more frequently with the higher rivastigmine dose than with the standard dose, particularly GI complaints (29% vs 19%), but differences in the rate of most other adverse events were small. The proportion of patients with adverse events leading to treatment discontinuation was higher with standard-dose therapy (13%, compared with 10% in the higher-dose group).

**Discussion:** In the U.S., the highest approved dose of transdermal rivastigmine is 9.5 mg/24 hours (10 cm²). The study authors suggest that approval of the increased dose would offer physicians an additional option to improve functional outcomes in patients with Alzheimer's disease without compromising safety and tolerability.

Cummings J, Froelich L, Black S, Bakchine S, et al: Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm²) in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders* 2012;33:341–353. From Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV; and other institutions. Funded by Novartis Pharma AG. All study authors disclosed relationships with commercial sources, including Novartis.

### Coping with Antidepressant Side Effects

A majority of patients who experience antidepressant side effects use self-devised strategies to cope with them, according to a survey. Unfortunately, these strategies are sometimes counterproductive; when the side effect is difficult to manage, such as tremor or sexual difficulties, patients may decide to reduce the antidepressant dose or stop taking the drug altogether.

**Methods:** Study subjects were recruited from a cohort of Japanese adults who had agreed to participate in health-related surveys. Patients (n=1305), aged ≥20 years, with major depressive disorder who were currently taking an antidepressant or had taken one in the past 2 years were invited to participate in an internet survey about antidepressant side effects. Participants were asked to endorse side effects they had experienced from a 16-item list and to freely report how they managed each side effect. Coping mechanisms were classified as either passive (i.e. sleeping or resting, waiting for the effect to end) or active. Active methods were further classified as adjustment of the prescription; additional medication; complementary therapy (e.g., yoga or supplements); consulting the physician; and daily relief, which included a broad range of strategies such as dietary and lifestyle changes, drinking alcohol, and massage.

**Results:** Of the 1305 screened adults, 856 completed the survey. Nearly 90% reported using an active coping strategy for at least 1 side effect. The percentage of patients using an active coping strategy ranged from 27% for sexual dysfunction to 90% for dry mouth. Adverse events with a low percentage of active coping were more likely to be managed by adjusting the prescription; about 33–43% of patients with sexual dysfunction, fatigue, tremor, or somnolence adjusted or stopped their medication to cope. Daily relief strategies were sometimes inappropriate; for example, patients drank alcohol to counter headaches or insomnia or they deliberately induced vomiting to cope with nausea or weight gain. For most adverse effects, few patients consulted their physician—28% of those with sexual problems, but about 12% or less for all of the other adverse effects. Many patients used additional medications to cope with side effects, such as constipation, diarrhea, insomnia, nausea, and headache. Complementary approaches were rarely used.
Discussion: While some antidepressant side effects are amenable to patient-initiated coping, others, such as sexual side effects, are best dealt with using physician-patient collaboration. Physicians should be aware that patients taking antidepressants may be managing their own side effects, sometimes inappropriately.

Kikuchi T, Suzuki T, Uchida H, Watanabe K, et al: Coping strategies for antidepressant side effects: an internet survey. Journal of Affective Disorders 2012; doi 10.1016/j.jad.2012.04.39. From Keio University School of Medicine, Tokyo, Japan; and other institutions. Funded by GlaxoSmithKline Japan; and other sources. All study authors disclosed financial relationships with commercial sources; 4 were with GlaxoSmithKline, the study sponsor.

### Ketamine Trial for Refractory OCD

In a pilot study, ketamine infusion had a modest, transient effect on OCD symptoms in patients with severe, highly refractory disease.

Methods: Ten patients participated in this open-label, single-dose trial. They were required to have OCD that had been nonresponsive to adequate trials of 2 different SSRIs and cognitive-behavioral therapy (CBT). Medication was continued at stable dosages for ≥2 months
before the ketamine trial. Patients were hospitalized from 1 week before to 1 week after the infusion in order to maintain a consistent environment to assess symptom responses. Ketamine was infused at 0.5 mg/kg over 40 minutes, in a protocol modeled after ketamine-infusion studies in patients with depression. The primary study outcome was OCD response, defined as a ≥35% reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score between 1 and 7 days after treatment.

**Results:** Patients in this study had severe OCD symptoms despite multiple drug trials (averaging 4.1 SRI trials and 2.7 trials of antipsychotic augmentation), and all had past participation in CBT. At the time of ketamine infusion, 7 patients were taking SRIs, 4 of whom were also taking antipsychotics, and 1 of whom was also taking glutamate-modulating agents (N-acetylcysteine and riluzole); 3 patients were drug-free.

Patients experienced a 60% average reduction in OCD symptoms at the 1-hour time point, but this effect dissipated rapidly. During follow-up, Y-BOCS improvement was small (peak symptom reduction was 11% on day 2) and transient.

Of the 7 patients with comorbid depression, 4 had an antidepressant response within the first 3 days after infusion. Reductions in OCD symptoms and depressive symptoms were correlated. Ketamine was generally well tolerated, producing mild infusion-related dissociative symptoms in about half of patients. Two initially non-depressed patients reported dysphoria, anxiety, and passive suicidal ideation within the first 2 days after infusion.

**Discussion:** Ketamine was investigated as a potential OCD treatment because it affects glutamatergic neurotransmission, possibly linked to OCD, and because of a prior positive case report. The negative results of this study do not rule out the possibility that prolonged or repeated infusions may be effective in patients with refractory OCD.

Bloch M, Wasylink S, Landeros-Weisenberger A, Panza K, et al: Effects of ketamine in treatment-refractory obsessive-compulsive disorder. *Biological Psychiatry* 2012; doi 10.1016/j.biopsych.2012.05.028. From Yale University School of Medicine, New Haven, CT; and other institutions, including Bristol Myers-Squibb. Funded by the National Alliance for Research on Schizophrenia and Depression; and other sources. Six of the 10 study authors disclosed relationships with commercial sources.

**Drug Trade Names:** ketamine—Ketalar; riluzole—Rilutek

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**Antipsychotics During Pregnancy: Metabolic Effects**

According to the results of a population-based cohort study, risks for gestational diabetes were not greater with clozapine and olanzapine, thought to be the most diabetogenic antipsychotics, than with other antipsychotic drugs. Metabolic effects on the fetus were few and were likely associated with confounding maternal factors such as smoking and body mass index (BMI).

**Methods:** The investigators analyzed data from all singleton births to Swedish women from July 2005 through December 2009, a total of more than 358,000 pregnancies. Of the mothers, 507 were dispensed antipsychotic drugs during the time between the last menstrual period and giving birth. Of these, 88% received a single antipsychotic agent throughout pregnancy. Drug exposure was divided into 2 classes: clozapine or olanzapine, alone or in any combination (group 1; 169 women), and all others (group 2; 338 women).

**Results:** Gestational diabetes developed in 7 women (4.1%) exposed to clozapine or olanzapine and in 15 (4.4%) exposed to other antipsychotics, twice the rate as in unexposed pregnant women (1.7%), nearly 10% of whom also had a psychiatric diagnosis. Unadjusted odds ratios* were similar for the drug groups: group 1 odds ratio, 2.44; group 2 odds ratio, 2.53. The odds ratios remained significant after adjustment for multiple other factors. When early-pregnancy BMI was included in the model, the odds ratios for gestational diabetes were
attenuated and no longer significant. Because quetiapine and risperidone may also have adverse metabolic effects, the authors repeated their analysis including these 2 drugs in group 1. Results were not substantially different.

Among the infants, 8% of those exposed to group-1 antipsychotics and 9.5% of those exposed to group-2 drugs were born preterm, compared with 5.1% of unexposed infants. The difference was not statistically significant for group 1 but was for group 2 (odds ratio, 1.94). Both groups of exposed infants had about a 2-fold higher risk of being small for gestational age, but this risk was not statistically significant after adjustment for multiple maternal factors such as smoking. Infants exposed to clozapine or olanzapine had increased risk of an abnormally large head circumference (odds ratio, 3.0), but no other apparent growth abnormalities. This difference was not explained by hydrocephalus, because none of the newborns had hydrocephalus.

**Discussion:** This appears to be the first population-based study to investigate maternal and fetal metabolic effects of different antipsychotics during pregnancy. Although clozapine and olanzapine are the agents with the most notorious effects on weight and insulin resistance, they appear to cause similar increases in risk as other antipsychotics


**Drug Trade Names:** clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

*See Reference Guide.

## Reference Guide

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

**Number Needed to Treat (NNT):** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value the less effective is the treatment.

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.