Dear Healthcare Professional,

Thank you for your interest in Hardy Nutritionals® Daily Essential Nutrients (DEN) – a unique technology-enhanced vitamin-mineral formulation for the treatment of mood, anxiety, and behavioral symptoms.

This summary lists the independent research backing DEN by indication, and also provides detailed information about select studies.

For Treatment Guidelines and other information relevant to clinical applications, please refer to the Clinical Reference Guide for Healthcare Professionals and the Frequently Asked Questions Guide on our website. Both resources bring together a wealth of knowledge accumulated through extensive research and valuable feedback from healthcare professionals, and are designed to facilitate the clinical use of DEN.

We welcome any feedback, questions or concerns you may have. Please feel free to call us and speak with a Product Specialist.

We appreciate working with you for your patients’ health!

Sincerely,

The Hardy Nutritionals® team
www.GetHardy.com

Toll free: 1-855-955-1114
Fax: 1-587-271-1117
Email: info@GetHardy.com

Office Hours: Monday - Friday 9:00 AM - 5:00 PM (MST)
Daily Essential Nutrients is the result of a long history of independent medical research and extensive clinical experience. This broad-spectrum micronutrient therapy has been used successfully to alleviate the symptoms of almost everything neurologically—from brain injury and autism to attention, anxiety, mood, and other psychiatric disorders. The following are summaries of 2 of the nearly 30 medical journal publications.

**Traumatic Brain Injury**

A rat model study performed at the Canadian Centre for Behavioural Neuroscience provides exciting evidence that micronutrient treatment could revolutionize recovery from traumatic brain injuries and neurodegenerative disorders.1,2

At 4 days old, researchers administered either medial frontal or posterior parietal lesions to the treatment rats. From surgery to adulthood, half of the control animals and half of the injured animals received vitamin & mineral supplementation.

After 100 days, both parietal and frontal lesion animals fed the micronutrient formula exhibited significantly less anxiety in open field tests as measured by mean distance and horizontal activity (treatment effects for both groups p<0.001).

Amazingly, brains of frontal lesion rats were completely regrown with micronutrient supplementation, and cognitive function was restored to a level statistically not different from normal as measured by Morris water maze tests (p<0.05).

The brains of both lesioned and unlesioned animals fed micronutrients had greater mean cortical thickness than unsupplemented animals in post-mortem examinations (p<0.05), and the neurons of the supplemented rats also had longer, more complexly-branched dendritic endings (p<0.05).

This breakthrough research has broad clinical application. The enhanced brain cell health in the micronutrient-fed rats may explain why micronutrients have produced dramatic results in people with brain injuries such as stroke or concussion.

The proven ability of micronutrient therapy to increase cortical thickness and connectivity also speaks to its potential to prevent and treat neurodegenerative disease, including Alzheimer’s, Autism, Parkinson’s and any other condition where brain cell deterioration and loss of cortical thickness are evident.

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ADHD in Adults

In 2014, the British Journal of Psychiatry published a double-blind randomized placebo-controlled trial conducted at the University of Canterbury in New Zealand, which provides evidence of efficacy for micronutrient therapy in the treatment of ADHD symptoms in adults, with a reassuring safety profile.³

Adults diagnosed with ADHD (DSM-IV criteria) who took the nutrient treatment showed “statistically robust improvements in a variety of areas of psychological functioning” in just 8 weeks.

<p>| Table 2 Baseline and post 8-week data on primary and secondary outcome measures⁴ |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Micronutrient formula group (n = 42) | Placebo group (n = 38) |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (s.e.)</th>
<th>Post Mean (s.e.)</th>
<th>Change from baseline⁵</th>
<th>Baseline Mean (s.e.)</th>
<th>Post Mean (s.e.)</th>
<th>Change from baseline⁵</th>
<th>Difference (95% CI)</th>
<th>P</th>
<th>Effect size⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAARS DSM-IV ADHD symptoms total</td>
<td>79.4 (1.5)</td>
<td>67.3 (2.2)</td>
<td>-11.81</td>
<td>75.3 (1.9)</td>
<td>70.5 (2.3)</td>
<td>-5.10</td>
<td>-6.71 (-11.72 to -1.70)</td>
<td>0.009</td>
<td>0.61</td>
</tr>
<tr>
<td>Observer</td>
<td>69.5 (2.0)</td>
<td>61.4 (2.3)</td>
<td>-8.44</td>
<td>70.5 (2.0)</td>
<td>66.2 (2.1)</td>
<td>-4.30</td>
<td>-5.14 (-9.65 to -0.63)</td>
<td>0.026</td>
<td>0.59</td>
</tr>
<tr>
<td>Clinician</td>
<td>73.4 (1.4)</td>
<td>65.0 (1.7)</td>
<td>-8.69</td>
<td>69.0 (1.4)</td>
<td>61.1 (1.7)</td>
<td>-7.60</td>
<td>-5.02 (-2.61 to 0.21)</td>
<td>0.331</td>
<td>0.23</td>
</tr>
<tr>
<td>CGI-I ADHD⁵</td>
<td>2.8 (0.2)</td>
<td>2.8 (0.2)</td>
<td>0.00</td>
<td>3.4 (0.2)</td>
<td>3.4 (0.2)</td>
<td>0.00</td>
<td>-0.56 (-1.03 to -0.09)</td>
<td>0.020</td>
<td>0.53</td>
</tr>
<tr>
<td>CGI-I – Overall Impression⁸</td>
<td>2.8 (0.2)</td>
<td>2.8 (0.2)</td>
<td>0.00</td>
<td>3.5 (0.2)</td>
<td>3.5 (0.2)</td>
<td>0.00</td>
<td>-0.71 (-1.16 to -0.27)</td>
<td>0.012</td>
<td>0.57</td>
</tr>
<tr>
<td>MADRS, total</td>
<td>17.2 (1.1)</td>
<td>11.5 (1.3)</td>
<td>-5.32</td>
<td>14.2 (1.1)</td>
<td>12.0 (1.3)</td>
<td>-2.75</td>
<td>-2.66 (-5.64 to 0.31)</td>
<td>0.078</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Compared with placebo, those taking the micronutrient treatment reported more than double the improvement in attention, hyperactivity, and impulsivity symptoms.

Post-hoc analysis also revealed nearly double the improvement in moderate or severe depression, as rated by clinical psychologists, and more than twice as many people were ‘very much improved’ or ‘much improved’ overall, compared with the placebo group as rated by the Clinical Global Impressions – Improvement in attention-deficit hyperactivity disorder symptoms scores (CGI-I-ADHD).

A one year follow-up to this trial showed that those remaining on the micronutrient treatment continued to experience improved mood whereas those who discontinued it or reverted to medications worsened.

“I have many patients who previously required close medication management on conventional drugs, but who now check in every 3 to 12 months with little symptomatology to report.”⁵⁵

- Charles W. Popper, M.D.

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ADHD in Children

Double-blind research conducted at five universities has investigated the safety and efficacy of micronutrient therapy in the treatment of ADHD and related symptoms in children.

A 2018 double-blind, placebo-controlled study† randomized unmedicated children diagnosed with ADHD, together with significant mood, aggression and emotional dysregulation symptoms, to take Hardy Nutritionals® Daily Essential Nutrients or matching placebo for 10-weeks. Clinician ratings revealed "significant between-group differences favoring micronutrient treatment on the Clinical Global Impression-Improvement (ES = 0.46), with 47% of those on micronutrients identified as ‘much’ to ‘very much’ improved versus 28% on placebo.” An additional 22% in the micronutrient group showed less dramatic clinical improvement.

A 2021 multi-center, randomized, placebo-controlled trial‡ replicated these results, with a higher response rate: “For the Clinical Global Impression-Improvement, 54% of the micronutrient and 18% of the placebo group were responders (Risk Ratio=2.97, 97.5% CI: 1.50, 5.90, p<0.001).” ‘Responders’ were rated ‘much improved’ or ‘very much improved’ by clinicians and does not include those who showed less dramatic clinical improvement. As with the first study, “No serious adverse events nor clinically significant changes from baseline in blood and urine tests occurred.” Researchers also reported that during the 8-week trial, “The micronutrient group grew six millimeters more than the placebo group (p=0.002).”

Table 2 Baseline and post 10-week data on primary and secondary outcome measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Micronutrients (n = 47)</th>
<th>Placebo (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I-Overall†</td>
<td>2.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Clinician ADHD-RS-IV Symptoms Total</td>
<td>44.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Parent CPRS-R-L DSM-IV ADHD Symptoms Total</td>
<td>42.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Additional measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I-ADHD†</td>
<td>2.9</td>
<td>0.2</td>
</tr>
<tr>
<td>CGI-I-Mood†</td>
<td>2.9</td>
<td>0.2</td>
</tr>
<tr>
<td>C-GAS</td>
<td>48.1</td>
<td>0.9</td>
</tr>
<tr>
<td>CMRS-P</td>
<td>25.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Clinician ADHD-RS-IV DSM-IV Inattention</td>
<td>24.1</td>
<td>0.5</td>
</tr>
<tr>
<td>DSM-IV H/I</td>
<td>20.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Teacher CTRS-R-L DSM-IV Total†</td>
<td>34.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Parent SDQ – total problem score</td>
<td>23.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Parent SDQ – conduct problems score</td>
<td>5.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Teacher SDQ – total problem score</td>
<td>18.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Teacher SDQ – conduct problems score</td>
<td>4.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Teacher BRIEF – Behavioural Regulation Index</td>
<td>62.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Teacher BRIEF – Emotional Control Subscale</td>
<td>18.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

†Adjusted for baseline.
‡Cohen’s d (effect size) measured as the mean difference in the change divided by the within-group SD of the difference in the change.
§Assesses change not measured at baseline.
*p < .05 based on per-protocol.
Based on completed questions (n = 72).
Results in bold are significant.
H/I, hyperactivity/impulsivity; C-GAS, Child Global Assessment Scale; CGI-I, Clinical Global Impression-Improvement; SDQ, Strengths and Difficulties Questionnaire; CMRS-P, Child Mania Rating Scale – Parent; CPRS-R, Conners Parent Rating Scale-Revised:Long version; CTRS, Conners Teacher Rating Scale-Revised:Long version; BRIEF, Behaviour Rating Inventory of Executive Function.

**Percent of participants who experienced a 30% or greater reduction in clinician-rated ADHD Inattention Subscale scores (DSM-IV), p=0.005, n=99.

***Percent of participants rated by clinicians as “much improved” or “very much improved” on the Overall Clinical Global Impression-Improvement assessment in per-protocol analysis, p<0.001, n=126.


Improvement in Attention†

<table>
<thead>
<tr>
<th>Percent</th>
<th>Placebo</th>
<th>Daily Essential Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
<td>20%</td>
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<tr>
<td>15%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>20%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Percent of participants who experienced a 30% or greater reduction in clinician-rated ADHD Inattention Subscale scores (DSM-IV), p=0.005, n=99.

Improvement in Global Functioning‡

<table>
<thead>
<tr>
<th>Percent</th>
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<th>Daily Essential Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>5%</td>
<td>10%</td>
<td>15%</td>
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<tr>
<td>10%</td>
<td>15%</td>
<td>20%</td>
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<tr>
<td>25%</td>
<td>30%</td>
<td>35%</td>
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<tr>
<td>30%</td>
<td>35%</td>
<td>40%</td>
</tr>
</tbody>
</table>

***Percent of participants rated by clinicians as “much improved” or “very much improved” on the Overall Clinical Global Impression-Improvement assessment in per-protocol analysis, p<0.001, n=126.
Product-specific Research by Indication

**Anxiety & Stress**

A randomised trial of nutrient supplements to minimise psychological stress after a natural disaster.


Psychological functioning 1 year after a brief intervention using micronutrients to treat stress and anxiety related to the 2011 Christchurch earthquakes: a naturalistic follow-up.


Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses.


Post-earthquake psychological functioning in adults with attention-deficit/hyperactivity disorder: positive effects of micronutrients on resilience.


**Attention & Hyperactivity**

Micronutrients for Attention-Deficit/Hyperactivity Disorder in Youth: A Placebo-Controlled Randomized Clinical Trial.


Mineral-vitamin treatment associated with remission in attention-deficit/hyperactivity disorder symptoms and related problems: 1-year naturalistic outcomes of a 10-week randomized placebo-controlled trial.


Can we predict treatment response in children with ADHD to a vitamin-mineral supplement? An investigation into pre-treatment nutrient serum levels, MTHFR status, clinical correlates and demographic variables.


Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial.


Vitamin–mineral treatment of ADHD in adults: a 1-year naturalistic follow-up of a randomized controlled trial.


Clinically Significant Symptom Reduction in Children with Attention-Deficit/Hyperactivity Disorder Treated with Micronutrients: An Open-Label Reversal Design Study.


Vitamin–mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial.


Can micronutrients improve neurocognitive functioning in adults with ADHD and severe mood dysregulation? A pilot study.


Effect of micronutrients on behavior and mood in adults with ADHD: evidence from an 8-week open label trial with natural extension.


**Autism Spectrum**

Micronutrients versus standard medication management in autism: a naturalistic case-control study.


**Brain Injury**

Micronutrient treatment of emotional dyscontrol following traumatic brain injury.


Factors influencing frontal cortex development and recovery from early frontal injury.


Dietary choline and vitamin/mineral supplement for recovery from early cortical injury [master’s thesis].


**Insomnia**

Effect of Micronutrients on Insomnia in Adults: A Multiple-Baseline Study.

Joanna Lothian, Neville M. Blampied, Julia J. Rucklidge. Clinical Psychological Science. Published online before print May 23, 2016.

**Mood & Behavior**

Feasibility of a nutritional supplement as treatment for pediatric bipolar spectrum disorders.


Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula.

Database analysis of adults with bipolar disorder consuming a micronutrient formula.
Gately D, Kaplan BJ. Clinical Medicine Insights: Psychiatry. 2009 Apr;4:3-16.

Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: a case study.

Successful treatment of OCD with a micronutrient formula following partial response to Cognitive Behavioral Therapy (CBT): a case study.

Multinutrient supplement as treatment: literature review and case report of a 12-year-old boy with bipolar disorder.

Improved mood and behavior during treatment with a mineral-vitamin supplement: an open-label case series of children.

Nutritional approach to bipolar disorder.

Treatment of mood lability and explosive rage with minerals and vitamins: two case studies in children.

Effective mood stabilization with a chelated mineral supplement: an open-label trial in bipolar disorder.

Do vitamins or minerals (apart from lithium) have mood-stabilizing effects?

Psychosis
Hospitalization cost of conventional psychiatric care compared to broad-spectrum micronutrient treatment: literature review and case study of adult psychosis.

Efficacy and cost of micronutrient treatment of childhood psychosis.

Other
Addiction/Dependency
Novel Mineral–Vitamin Treatment for Reduction in Cigarette Smoking: A Fully Blinded Randomized Placebo-Controlled Trial.

Use of micronutrients attenuates cannabis and nicotine abuse as evidenced from a reversal design: a case study.

Limiting Factors of Micronutrient Therapy
Moderators of treatment response in adults with ADHD treated with a vitamin-mineral supplement.

Could yeast infections impair recovery from mental illness? A case study using micronutrients and olive leaf extract for the treatment of ADHD and depression.

Safety
An observational preliminary study on the safety of long-term consumption of micronutrients for the treatment of psychiatric symptoms.

Nutritional and Safety Outcomes from an Open-Label Micronutrient Intervention for Pediatric Bipolar Spectrum Disorders.

Systematic review of safety and tolerability of a complex micronutrient formula used in mental health.

Mechanism
Human gut microbiome changes during a 10 week Randomised Control Trial for micronutrient supplementation in children with attention deficit hyperactivity disorder.

Resting-state networks and neurometabolites in children with ADHD after 10 weeks of treatment with micronutrients: results of a randomised placebo-controlled trial.

Methyolic changes in response to micronutrient supplementation and MTHFR genotype.

The micronutrient formulation studied was a pre-2013 version of EMPowerplus which was co-formulated by Daily Essential Nutrients formulator, David Hardy.

The micronutrient formulation studied was Daily Self Defense-for Women which was formulated by David Hardy.