Magnesium in integrative psychiatry:

Dosage, bioavailability and evidence-based formulations*

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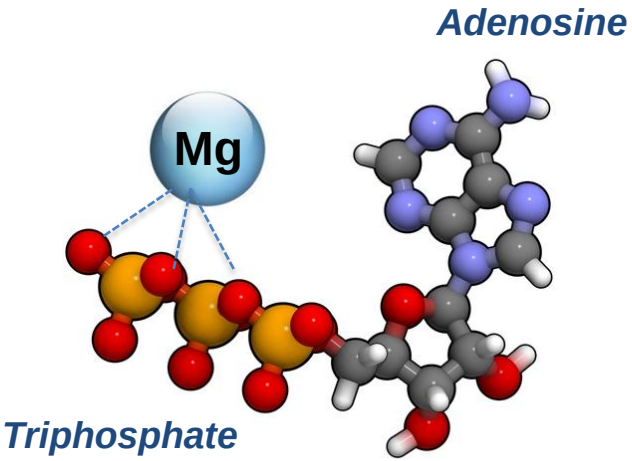
Biochemical individuality

Magnesium

- 4th most abundant mineral in the body
- 2nd most prevalent mineral inside of cells (next to potassium)
- Highest levels are found in the brain and heart
- 1% is in the blood, and this is maintained fairly consistently, even if intake is poor
- 40% is in tissues (inside of cells)
- Because it is so sequestered, identifying deficiency is challenging

An essential mineral

- Every year, new research provides more support for its necessity for life and health
- Required for more than 325 enzymatic reactions. Many of these reactions are essential for
  - Production, transfer and utilization of energy
  - DNA and protein synthesis
  - Control of nerve action and neurotransmission
  - Relaxation of muscles



Magnesium is part of the structure of ATP, the cellular energy currency

Declining levels in the food supply

- Levels in soil, water and food supply have gradually declined over the last 100 years. Why?
  - Soil erosion
  - Acid rain
  - Use of fertilizers that decrease magnesium assimilation by crops
- Food processing depletes many nutrients, but magnesium is most susceptible
  - Flour refining → up to 80% lost
  - Polishing of rice → 83%
  - Production of starch from corn → 97%

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Magnesium intake in the U.S. fall below requirements

- Gradual decline in average daily magnesium intakes from 500 mg/day in 1900 to 175-220 mg today
- 1999-2000 National Health and Nutrition Examination Survey: Two thirds of American adults fail to consume the recommended dietary intakes
  - Men: 420 mg/day
  - Women: 320 mg/day
- National Academy of Sciences determined that most men and women in the U.S. consume 80% and 70% of the requirements, respectively
- Many magnesium researchers consider the recommended intakes to be inadequate, raising greater concerns

Magnesium: Roles in the brain

- Magnesium deficiency influences many aspects of brain function*
- Studies demonstrate critical roles in mental and emotional health:*
  - Mood*
  - Relaxation*
  - Cognition*
  - Memory*
  - Sleep*

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Research on psychiatric relevance of magnesium

- Studies dating back to the 1920s have established that magnesium status is an important consideration in psychiatry*
- 1921: Study documented significant mood benefits in 220 out of 250 patients receiving a supplement*
- Studies over the last 50 years: repletion is associated with positive changes in mood, healthy eating behavior, balanced stress responses and sleep quality*
- Research also suggests magnesium may support the efficacy of other modalities*

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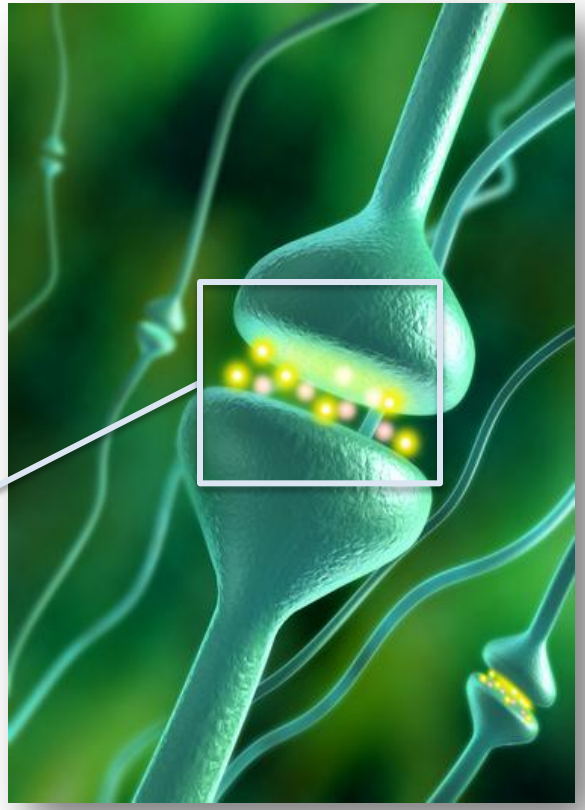
How does the "mind mineral" work?

1. Neurotransmission*
2. Endocrine mechanisms*
3. Cytokine signaling*



Synapse

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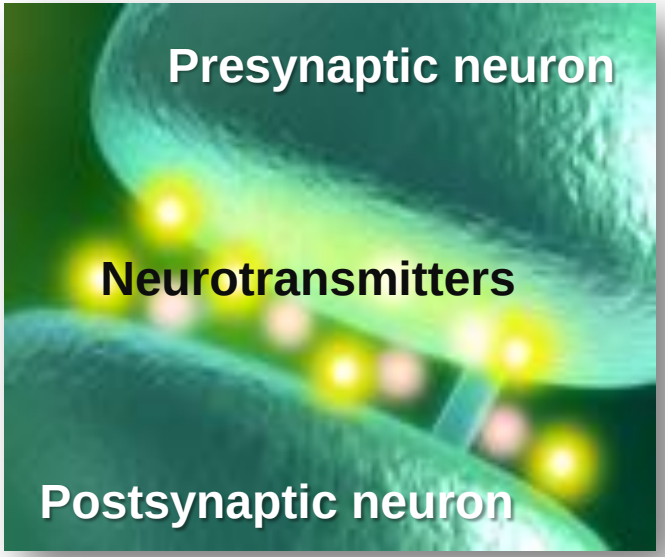
Neurotransmitters and their receptors

- Neurotransmission mediates all aspects of brain and nervous system function
- Neurotransmitters are synthesized by one neuron (presynaptic) and released into the synapse, the space between two neurons
- They are recognized by another neuron (postsynaptic) via a receptor
- Magnesium influences the levels of the neurotransmitters and the responses via receptors*



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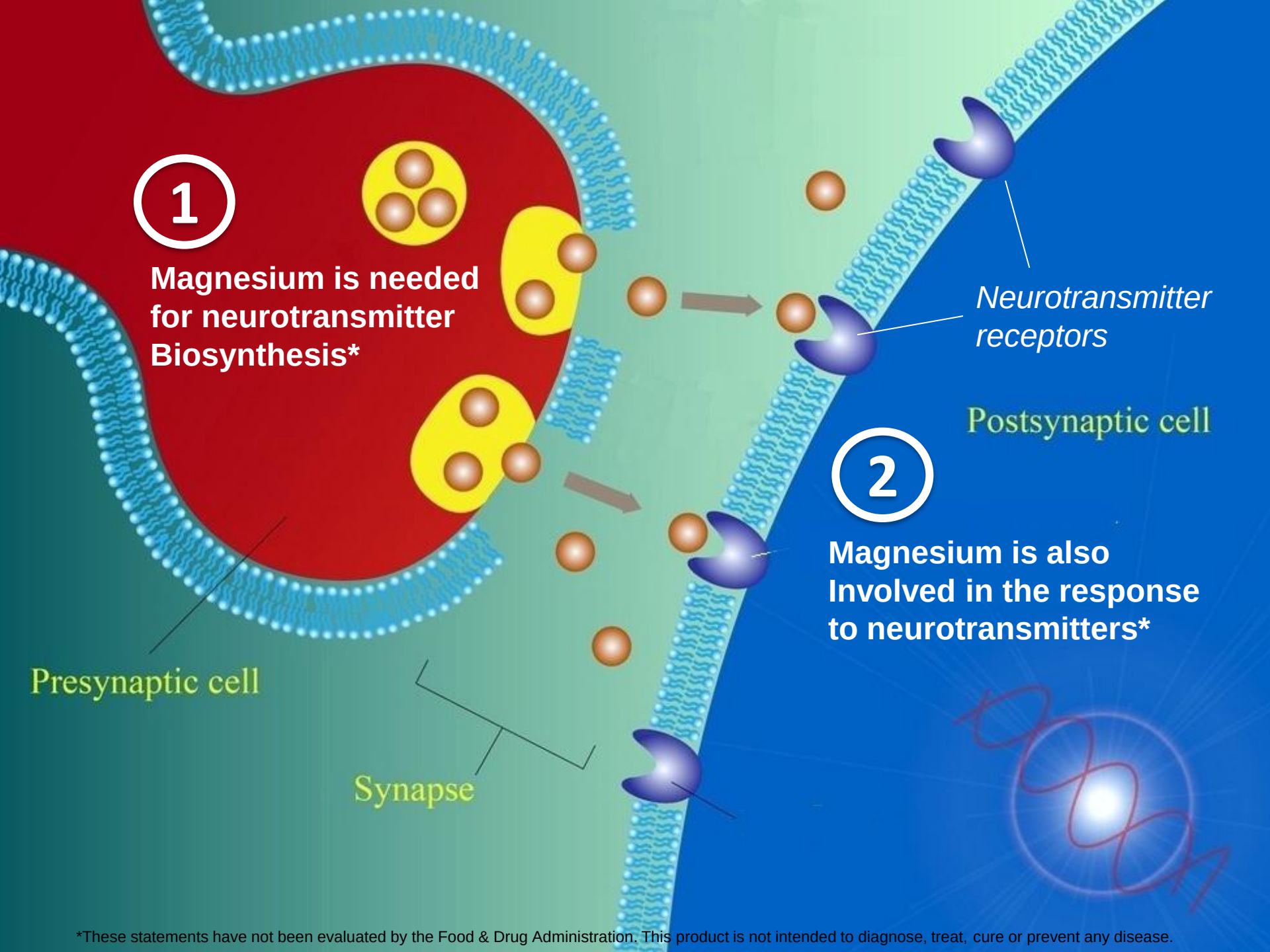

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Serotonin

- Positive mood*
- Relaxation and calming*
- Moderate occasional stress*
- Healthy eating behavior*

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Dopamine

- Alertness*
- Cognitive function*
- Positive mood*
- Sense of reward*

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Healthy serotonin and dopamine levels require magnesium*

- Magnesium is a cofactor for the biosynthesis of these and other neurotransmitters that maintain healthy mood, behavior, appetite, sleep patterns and stress responses*
- Patients with adequate magnesium levels tend to exhibit healthy amounts of these chemical messengers in the cerebrospinal fluid*
- Supplementation has produced significant support for mood, sleep and cognition in clinical studies*

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Glutamate signaling

- Magnesium influences neurotransmission by interacting with certain receptors on the postsynaptic neuron*
- The most clearly defined example is the glutamate receptor subtype known as the NMDA receptor*
- NMDA receptors play central roles in the neurological mechanisms of emotionality and stress responses by mediating the effects of the excitatory neurotransmitter, glutamate. Glutamate must bind the NMDA receptor to exert its well-known excitatory effects
- Laboratory animals that lack the NMDA receptor cannot respond to glutamate, and therefore exhibit very calm behavior

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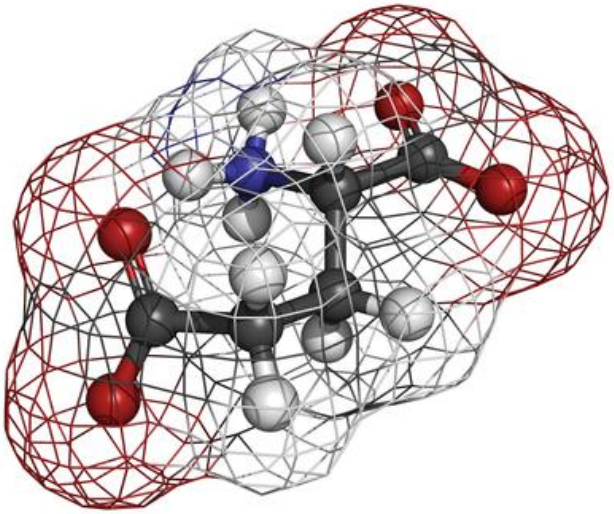
Keeping glutamate in check

- To exerts its stimulatory effects, glutamate must attach itself to this receptor
- Too much activation is undesirable
- Therefore, the brain has a device to keep the activity within healthy limits*
- This device is magnesium*



Glutamate, an excitatory neurotransmitter

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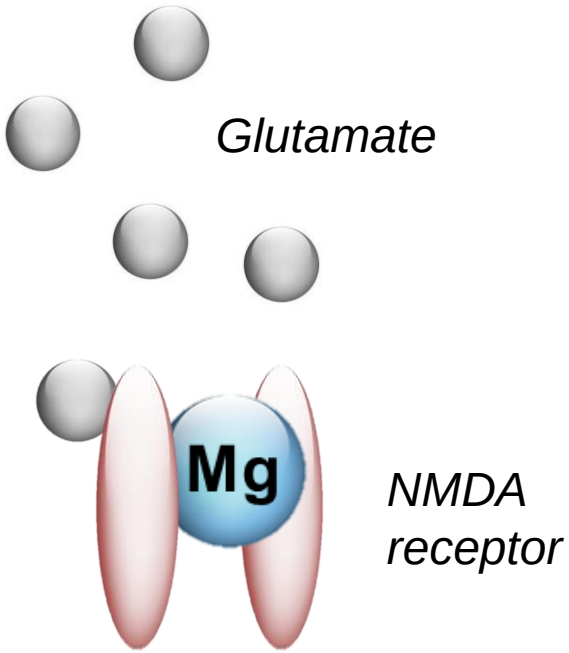
Magnesium is a “gatekeeper” in glutamate signaling*

Magnesium binds the glutamate (NMDA) receptor, but instead of activating it, it serves as a gatekeeper*

In doing so, magnesium keeps glutamate-mediated stimulation within a healthy range*



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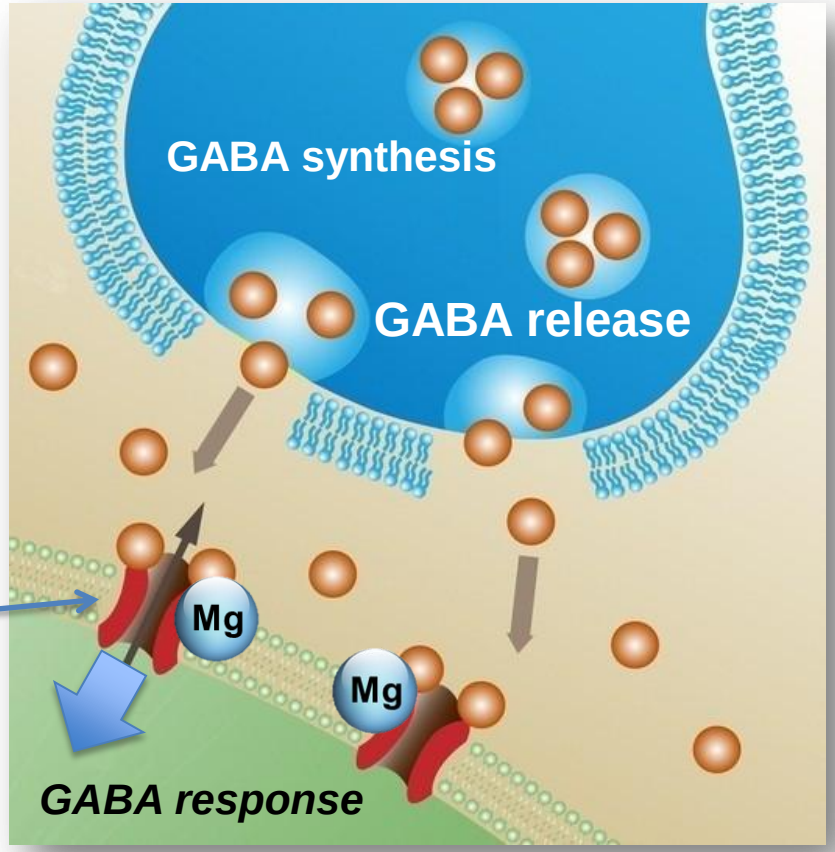
Magnesium supports GABA receptor function*

Magnesium can support the calming actions of GABA by binding to its receptor and facilitating GABA activity*



GABA receptor

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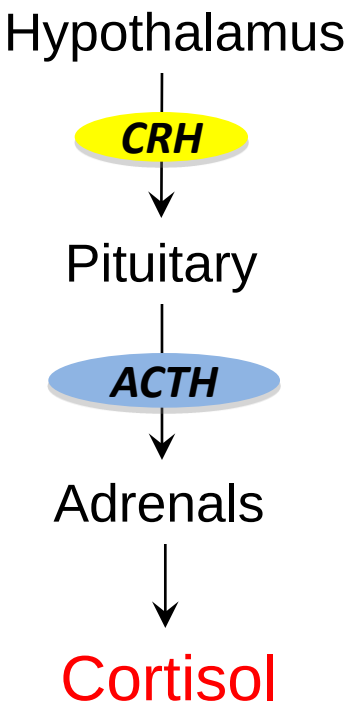
Magnesium supports healthy stress management*

- Stress evokes changes in both neurotransmitters and hormones
- Everyday stress can activate the hypothalamic-pituitary-adrenal (HPA) axis, stimulating the release of cortisol
- Inverse relationships between serum cortisol and magnesium levels are well-documented*
- The relationship between stress and magnesium is reciprocal*
  - Magnesium maintains healthy responses to stress*
  - Stress affects the body's retention of magnesium*



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The HPA axis

- By acting at both the pituitary and adrenal levels, magnesium helps to maintain homeostasis of the entire axis*
  - **Pituitary gland:** Magnesium modulates the release of ACTH, a hormone that travels to the adrenal glands to stimulating cortisol release*
  - **Adrenal gland:** Magnesium maintains a healthy response to the ACTH. In turn, cortisol release is kept within a normal range*

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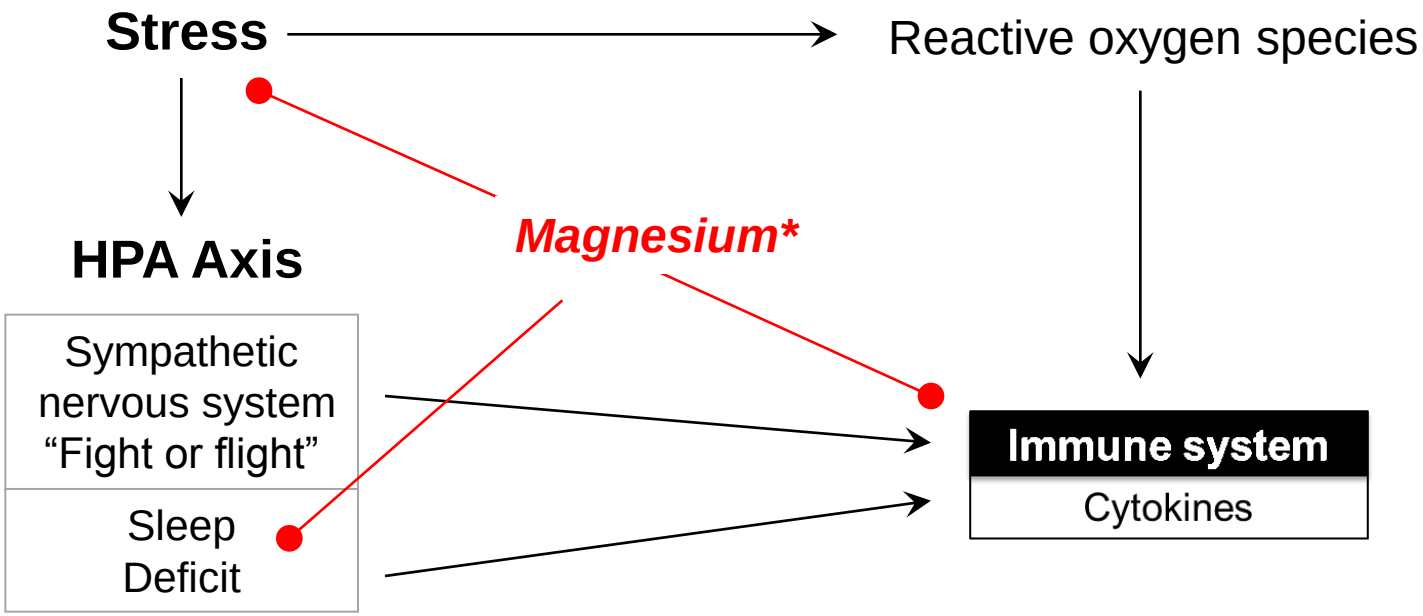
Stress, HPA activity and immune mediators (cytokines)



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Supplementation: Clinical challenges

- Magnesium is difficult to detect in laboratory testing, as most magnesium is not in plasma, but is sequestered in the skeletal system and other cells throughout the body
- Plasma levels are not reliable
- Many different supplement forms exist, with varying bioavailability
- Bioavailability is influenced by dietary factors, stress levels and biochemical individuality
- The right dose for psychiatric applications depends on the patient*

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Positive effects of dietary factors on magnesium bioavailability*

Dietary factor	Effect on magnesium bioavailability
Existing magnesium deficiency	Increases absorption to expedite repletion
Supplementing with vitamin D_3	Increases cellular uptake by induction of active transport systems*
Taking in divided doses instead of a single daily dose	Improves absorption by circumventing down-regulation of transport systems associated with high doses*
Taking with carbohydrates	Improves absorption from the intestine*
Selecting an organic form (such as glycinate or citrate)	Improves absorption by protecting the mineral from antagonists in the digestive tract*

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Negative effects of dietary factors on magnesium bioavailability*

Dietary factor	Effect on magnesium bioavailability
Selecting an enteric-coated supplement	Decreases absorption from the intestine*
High phosphorus intake	Inhibits absorption by formation of magnesium phosphate complexes*
Protein deficiency or excess	May compromise magnesium retention through unknown mechanism*
Excessive fiber intake	Slightly inhibits absorption by forming insoluble complexes*

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Other interactions with other nutrients

- **Potassium:** Magnesium maintains potassium balance. Repletion of magnesium can support potassium retention when there is a deficiency*
- **Vitamin D:** Activation of vitamin D (hydroxylation in the liver) requires magnesium*
- **Vitamin B_6:** Supports the accumulation of magnesium in cells*

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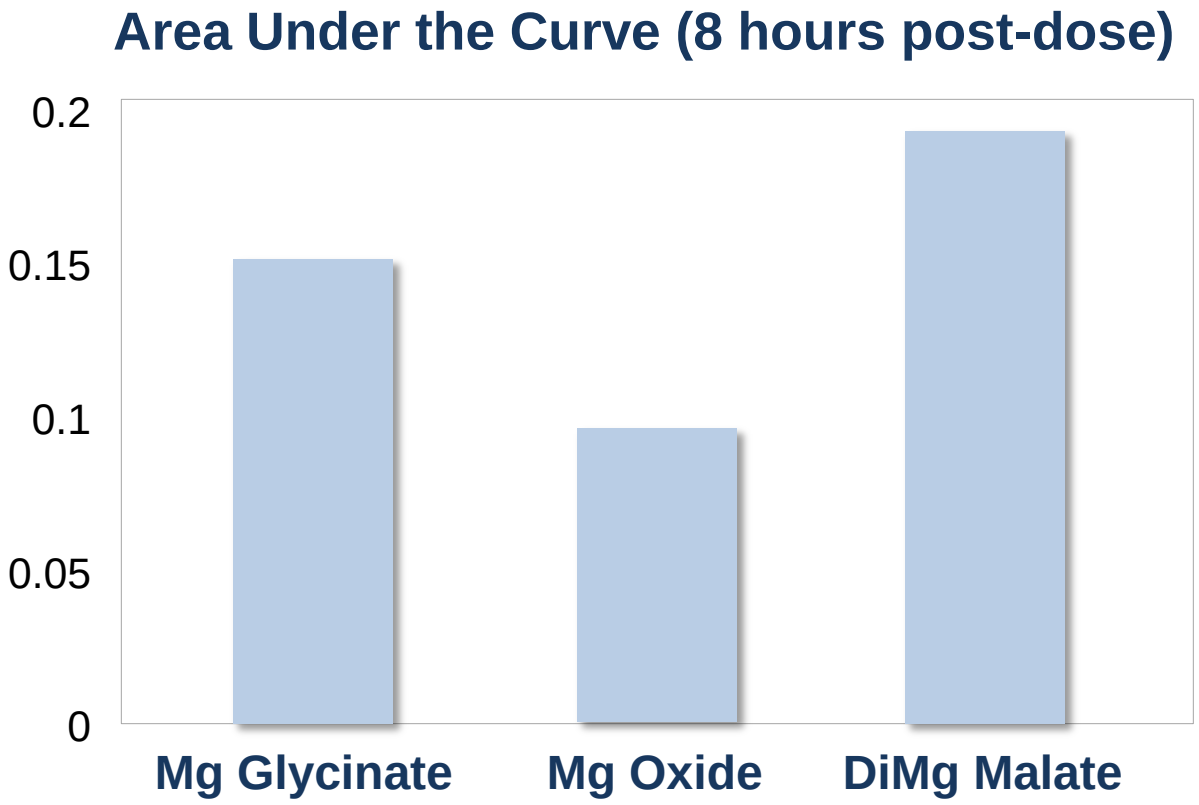
Serum levels of magnesium after a single 150 mg elemental dose



Dosage

- 125-300 mg magnesium glycinate per meal and at bedtime provides clinically significant mood benefits*
- 200-300 mg magnesium glycinate or citrate before bed supports sleep onset and duration through the night*
- Variability in dosage depending on the individual*
- Several weeks may be needed to take effect*

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Magnesium (glycinate)

- 120 mg elemental magnesium per capsule
- Gentle on the digestive tract*

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Magnesium liquid

- Magnesium citrate (215 mg elemental per teaspoon)
- 25 mg vitamin B_6 to support GABA biosynthesis and cellular assimilation of magnesium*
- Great-tasting liquid formula

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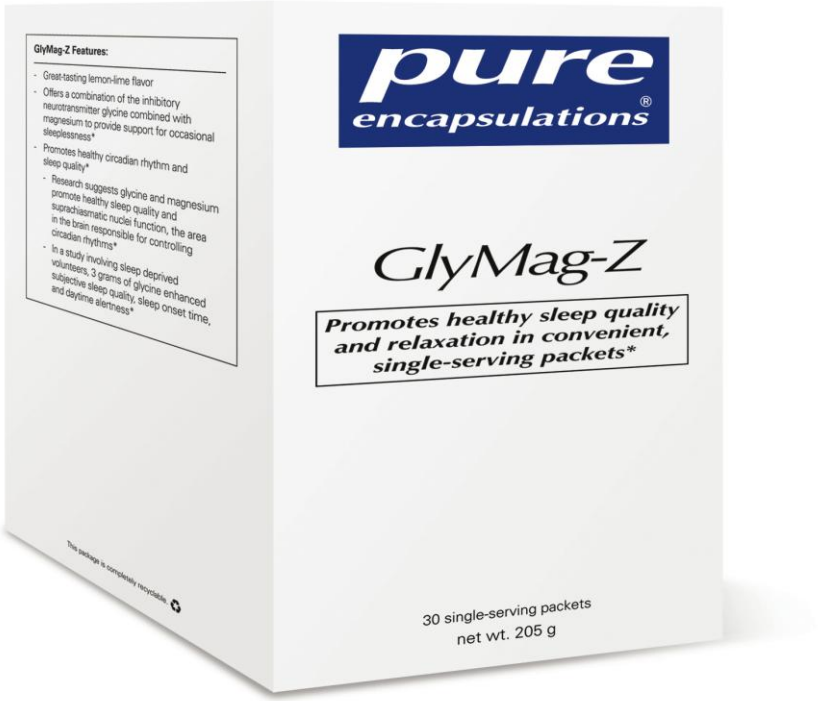
GlyMag-Z

Supports relaxation and restful sleep in portable, single-servin stick packets*

- Glycine (3 g)
- Magnesium citrate (150 mg elemental)



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GlyMag-Z

- Promotes healthy circadian rhythm and sleep quality*
- Glycine and magnesium promote healthy sleep quality and suprachiasmatic nuclei function, the area in the brain responsible for controlling circadian rhythms*
- Glycine has been associated with healthy sleep properties, including postsynaptic inhibition responsible for REM sleep atonia and a decreased core body temperature associated with sleep*
- In a small study involving sleep deprived volunteers, 3 g of glycine enhanced subjective sleep quality, sleep onset time and daytime alertness*

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GlyMag-Z

Delivers acute and long-term benefits*

- As-needed: By virtue of glycine, GlyMag-Z offers as-needed support for relaxation and restful sleep*
- Long-term: Repletes magnesium if taken over the longer term*

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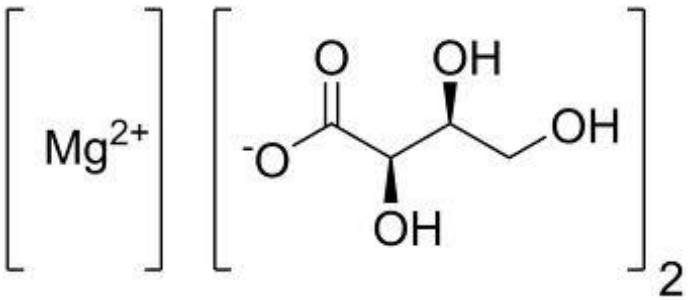
Magnesium-l-threonate (Magtein)

- Magnesium-l-threonate is a form of magnesium that most readily crosses the blood brain barrier*
- Ongoing research at MIT suggests magnesium-l-threonate supports learning ability, short and long-term memory and brain function*
- Promotes synaptic plasticity and density in the regions of the hippocampus correlated with learning and memory*



One magnesium is bound to two molecules of the amino acid l-threonine to create a highly bioavailable compound*

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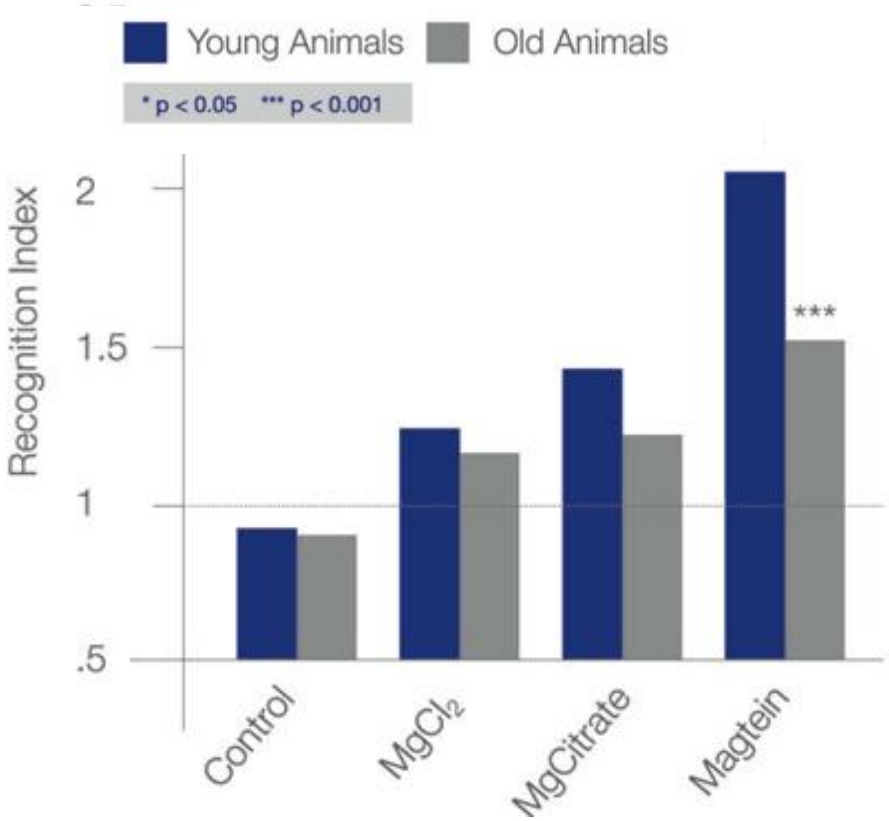
Magtein™ is a powerful tool for memory and cognitive support*

Magtein™ is highly effective in supporting spatial memory, according to a study in rats. Magtein™ provided a level of support in old animals that exceeded baseline memory of young animals.*



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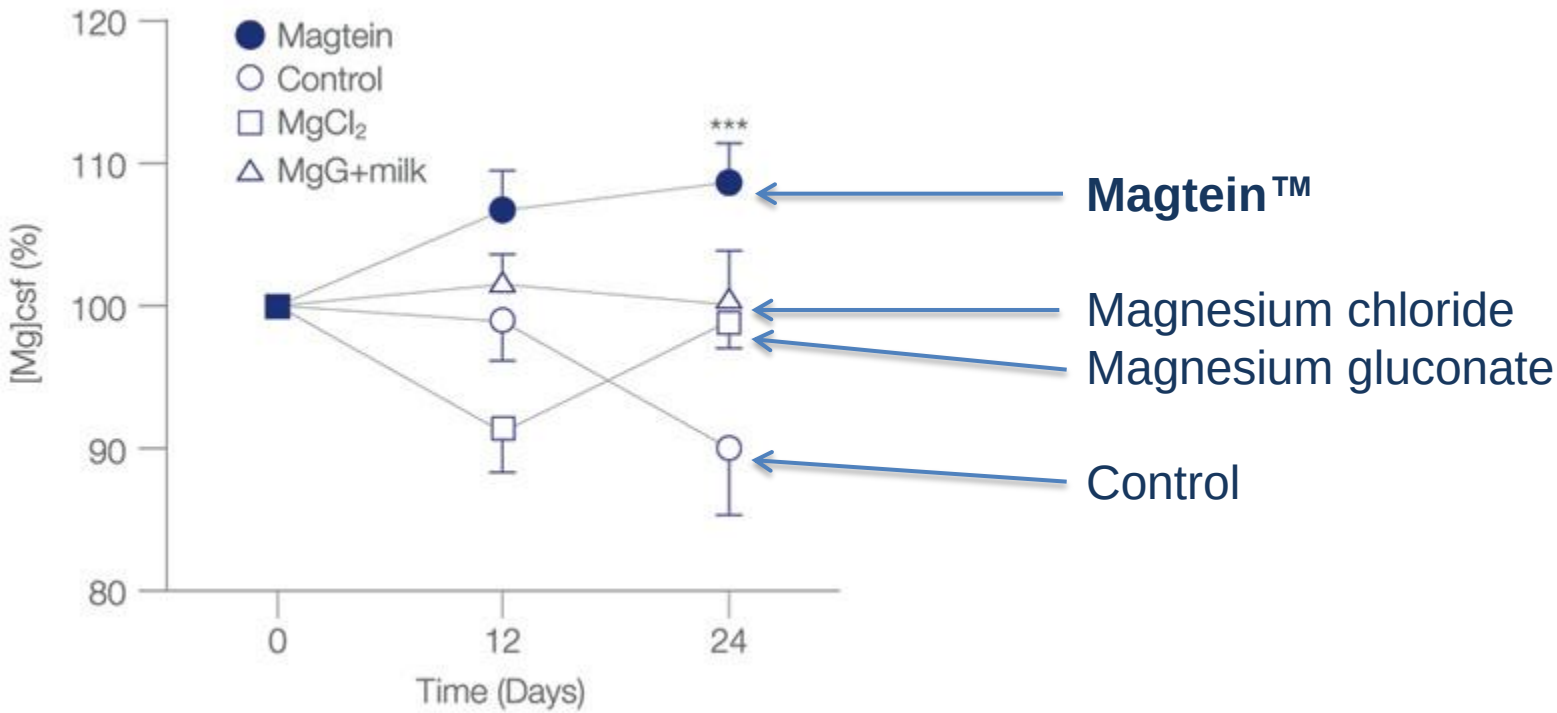
Bioavailability: Magtein™ produces significant CSF magnesium accumulation in rats*



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Magtein™ and relaxation

- Magtein™ influences brain synaptic architecture to support healthy adaptations to stress*
- Supporting plasticity in certain brain regions such as the prefrontal cortex (PFC) and/or hippocampus promote relaxation and healthy stress management, so researchers are investigating whether Magtein™ functions through this mechanism*
- Magtein™ can modulate "fear memories"*
- Magtein™ may also support sleep quality (ongoing research)*
- Overall brain benefits are significant despite the low elemental weight of Magtein™ (72 mg/1000 mg)*

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CogniMag

- 1,000 mg Magtein provides 72 mg of highly bioavailable elemental magnesium that readily crosses the blood brain barrier*
- PhytoMemory polyphenol blend supports healthy neurotransmission and neuronal signal transduction*

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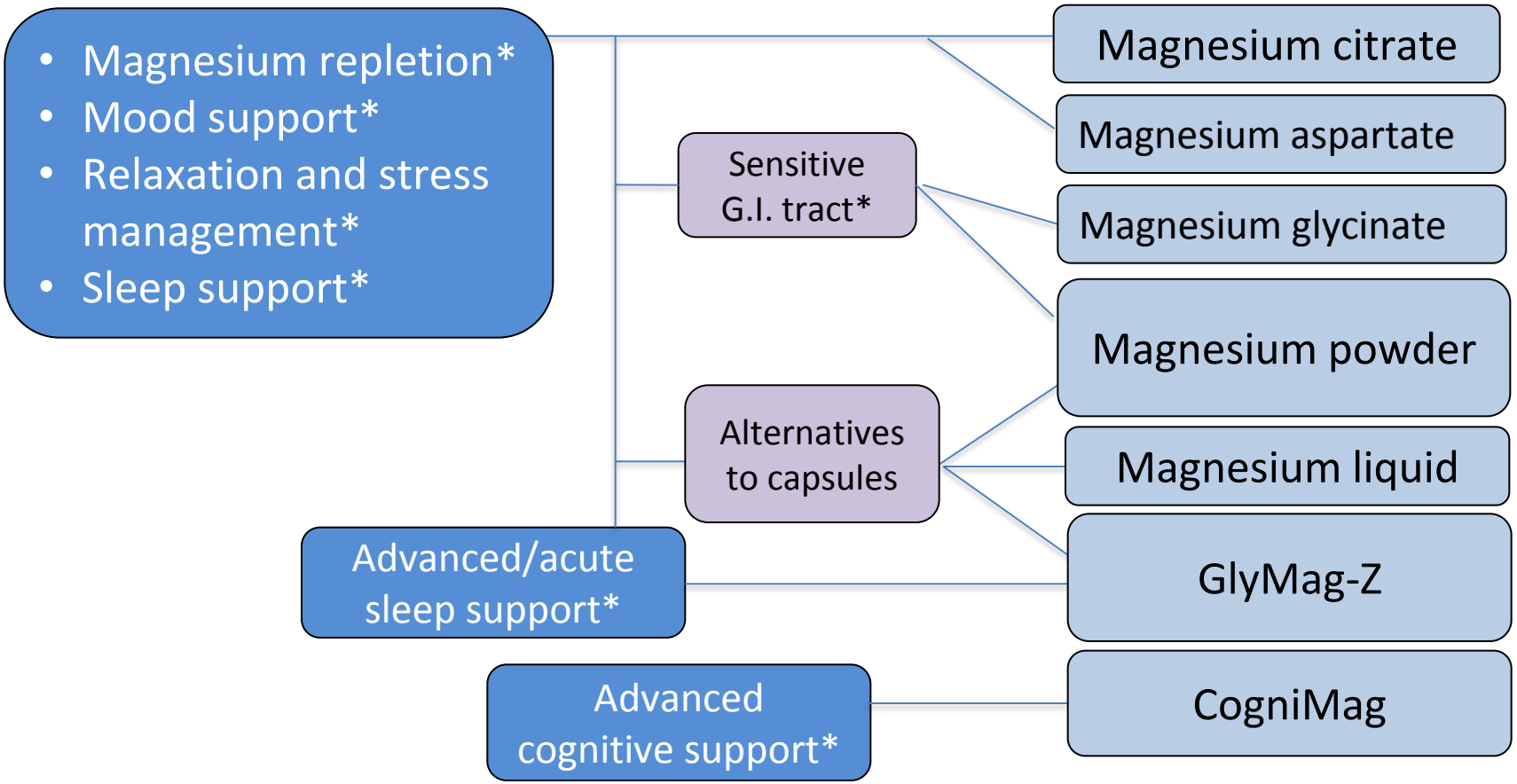
Selecting the ideal product



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