UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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TODAY'S TOPIC:

Memantine for Analgesia?

Background:

N-methyl-D-aspartate (NMDA) receptors are glutamate receptors, which is the primary excitatory neurotransmitter in the brain. It is thought that overexcitation of these receptors by glutamate may contribute to the disease progression and symptomatic expression of dementia and Alzheimer's, as well as other neurodegenerative diseases. We know that these receptors are involved in neuroplasticity and the signaling of pain, and more research is being done to understand the physiological role that NMDA receptors may have in psychiatric disorders.

Memantine (Namenda) is an NMDA antagonist, FDA approved for the treatment of moderate to severe Alzheimer's disease. Memantine has low to moderate affinity for NMDA receptors and is an uncompetitive antagonist, which means that the effect of an agonist may be blocked but ultimately will not prevent an agonist from binding to the NMDA receptor. Memantine and glutamate can simultaneously bind to these receptors but memantine has the potential to dull the effect of glutamate, especially in the setting of overexcitation.

Ketamine, also an NMDA receptor antagonist, has shown predictable analgesic effect and is used in the perioperative setting. It has also been utilized in settings of refractory depression and psychiatric conditions, as well as in our field for opioid refractory pain and hyperalgesia.

Due to memantine's similar mechanism to ketamine hypotheses have been made regarding use in special populations for pain.

Importance:

Increasing interest in utilizing memantine for its mechanism as an NMDA antagonist, particularly as we explore alternative interventions for pain in our palliative population, may provide a future opportunity to maximize analgesic effect and target more specific pain modalities. It is important that palliative care clinicians review the current literature for other fields to see how we may apply it to our own.

The Literature:

Eur J Pain. 2019;23:1234–1250.

A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain

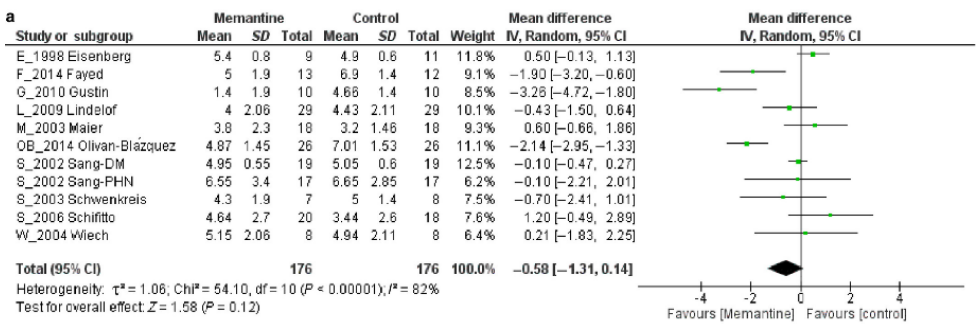
Objective: Assess the efficacy of memantine to prevent or reduce chronic pain.

Methods: 15 RCTs and cohort studies included; trials for a variety of pain syndromes in adults treated with memantine, compared to either active medications or placebo. Pain was the primary outcome. Secondary outcomes were analyzed if there were two or more studies that reported them.

- MEDLINE, EMBASE and CENTRAL databases reviewed
- Meta analyses conducted as mean differences (MD) or risk ratios (RR) with 95% confidence intervals (CI)

Results:

Figure 3. Analyses of pain treatment and prevention with memantine in chronic pain patients.
(a) Comparison of mean differences in end-of-treatment pain scores with memantine and control for chronic pain treatment; (b) comparison of mean differences with memantine and control for prevention of persistent pain after surgery; and (c) comparison of pain success with memantine and control for chronic pain treatment.



Pain Relief as Primary Outcome, Summary:

- No significant difference in the intensity of pain scores at end-of-treatment between memantine groups vs control
- Overall no significant difference in pain as characterized by "relief" as a meaningful intervention between memantine groups vs placebo
- In the prevention of persistent post-surgical pain, memantine group had significantly less pain versus control

Adverse Effects and other Secondary Outcomes, Summary:

- No reported deaths or hospitalizations in the studies relative to memantine
- Most common reported side effects: dizziness, drowsiness, headache, nausea
    - Dizziness was the only reported side effect that met significance
- Quality of Life: improvement from baseline in memantine group compared to placebo (EQ5D)
- Physical functioning: Mild improvement in one of three studies (SF−36 physical health)
- Emotional functioning: Some improvement in studies, although not for diabetic neuropathy population (SF−36 mental health and emotional wellbeing)
- Depression: improvement in depression with memantine alone in 2/3 studies (HADS, ADS)
- Pain threshold: two studies were able to report a raise in pain threshold using a pain sphygmomanometer, although most studies were lost to follow up

Conclusion:

- There is inconsistent and low-quality evidence to support memantine for the treatment of pain
- Memantine may be able to provide some prevention of chronic pain after surgery, as well as have potential efficacy in complex regional pain syndrome (CRPS) and fibromyalgia

Bottom Line:

- No recommendation can be made about memantine for its routine clinical use for pain management given the data that we have
- We do not have data surrounding memantine use for analgesia in a palliative care population
- More studies need to be conducted to better evaluate memantine's analgesic potential

References:

1. Memantine (namenda) prescribing information. Madison, NJ: Allergan USA Inc; 2018 Feb.
2. Kurian R, Raza K, Shanthanna H. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. *Eur J Pain.* 2019;23:1234–1250.
3. Olivan-Blázquez B, Herrera-Mercadal P, Puebla-Guedea M, et al. Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. *Pain.2014;*155(12):2517-2525.

CLINICAL PEARL: We have limited data to support use of memantine for analgesia in a palliative care population.