

8-17-2023

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### Recommended Citation

Guinan, Riley, "Safety and Efficacy of Adjunctive Esketamine vs. MAOIs in TRD in Adults" (2023). *Master of Science in Physician Assistant Studies Capstone Presentations (Center City)*. 15.

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# Safety and Efficacy of Adjunctive Esketamine vs. MAOIs in TRD in Adults

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## Introduction

- Background:**
  - Depression affects millions globally
  - Treatment-resistant depression (TRD) is defined as failure to respond to two antidepressant trials of adequate dose and duration
- Traditional Treatment for TRD:**
  - Switching or adding medications atypical antipsychotics
  - Limitations include delayed action, side effects, and limited efficacy
- Alternative Treatment Options:**
  - **Ketamine:**
    - A dissociative anesthetic with potential antidepressant effects
    - Targets the NMDA receptor and activates AMPA receptor.
    - Shows rapid and potent antidepressant effects; however, not FDA-approved for depression
  - **Monoamine Oxidase Inhibitors (MAOIs):**
    - Antidepressants used since the 1950s
    - Inhibits the enzyme metabolizing neurotransmitters.
    - Limitations: Dietary restrictions and drug interactions and longstanding safety concerns
- Importance of Comparison:**
  - Given limitations of traditional treatments and promising results from Ketamine and MAOIs, there's a need to compare their safety and efficacy. This will provide clinicians with informed choices for their patients.
- Objective:**
  - To compare the safety and efficacy of ketamine and MAOIs for TRD to guide clinical decisions and future research.

## Methods

- Database & Date:** PubMed search on January 29th, 2023.
- Inclusion Criteria:**
  - Meta-analyses, randomized-control trials, systematic reviews, and reviews
  - Published within the past 10 years, preferably within the last 5
  - Articles in English
- Search Strategy:**
  - **MAOI Efficacy:**
    - MeSH terms combined to target TRD and specific MAOIs.
    - 19 results found; 2 relevant after exclusions
  - **MAOI Safety:**
    - MeSH term focused on MAOI adverse effects
    - 1364 results found; 4 relevant after exclusions
  - **Intranasal Ketamine Efficacy & Safety:**
    - MeSH terms combined to target intranasal ketamine in TRD.
    - 44 results found; 5 relevant after exclusions.
- Additional Research:**
  - Two studies added from manual PubMed search.

## Results

### Key Studies on Reviews on MAOIs' Safety and Efficacy:

- STAR\*D Trial:**
  - Examined tranylcypromine vs. combination of extended-release venlafaxine and mirtazapine
  - Remission rates: Tranylcypromine - 6.9%; Venlafaxine + mirtazapine - 13.7% (not statistically significant)
  - Dose of tranylcypromine may have been suboptimal
  - Drop-out rate due to side effects: 41% for MAOI
  - Study limitations: Non-randomized design, open-label treatment
- Stewart, Deliyannides & McGrath:**
  - Evaluated tranylcypromine doses of up to 60mg/d and 120mg/d
  - Remission rates: 26% at 60mg/d; 30% at 120mg/d (total 48%)
  - Significant side effects: Insomnia, orthostatic hypotension, hypertensive effects
  - Emphasized dose-related benefits and side effects of tranylcypromine
- **"MAOIs – Does the Evidence Warrant Their Resurrection?":**
  - Median response rate for tranylcypromine in TRD: 50%.
  - Limitations: Open-label trials and non-randomized studies included
- "Current place of MAOIs in the treatment of depression":**
  - Efficacy rate for MAOIs: ~50% in TCA-resistant patients
  - Limitation: Focus on patients resistant to TCAs, not modern first-line treatments
- "A reassessment of the safety profile of monoamine oxidase inhibitors":**
  - **Concerns:** Hypertensive crises from dietary tyramine and serotonin syndrome
    - Reviewed >150 recent papers on tyramine content in modern foods
    - Modern diets greatly reduce risk of hypertension from high-tyramine foods
    - Advocated for a more nuanced understanding and individualized dietary advice
- Observational cohort study (Ontario, Canada):**
  - Decade-long study on irreversible MOAIs in older adults with recurrent depression
  - No recorded cases of serotonin syndrome or hypertensive crises, despite concomitant use of serotonergic medications
  - Limitation: Observational design without control group

### Key Studies on Esketamine Safety and Efficacy:

- TRANSFORM-1:**
  - Evaluated esketamine 84 mg and 56 mg doses (given twice weekly) as an adjunct to a new open-label antidepressant
  - Clinically meaningful treatment effect for both doses, but the 84 mg dose didn't achieve statistical significance (2-sided p=0.088)
  - Adverse events included nausea, dissociation, dizziness, vertigo, and headache
- TRANSFORM-2:**
  - Compared the efficacy and safety of esketamine nasal spray plus a new antidepressant to a new antidepressant plus placebo nasal spray
  - Significant improvement in MADRS score with esketamine combination by day 28
  - Adverse events similar to TRANSFORM-1, but resolved about 1.5 hours post-dosing
  - 7% in the treatment group and 0.9% in the control group discontinued due to adverse events
- SUSTAIN-1:**
  - Assessed the efficacy of esketamine nasal spray plus an oral antidepressant in delaying relapse post stability
  - Significant delay in relapse among stable remitters and responders with esketamine treatment
  - Adverse events similar to TRANSFORM studies, with additional symptoms like transient dysgeusia, somnolence, and dizziness
- SUSTAIN-2:**
  - Examined the long-term safety and efficacy of esketamine nasal spray in TRD patients
  - Esketamine showed a manageable long-term safety profile
  - Most adverse events were mild to moderate and resolved on the same day
  - Improvements in depression sustained for up to a year in TRD patients
- 2014-2015 Double-Blind RCT:**
  - Investigated the efficacy, safety, and dose-response of intranasal esketamine
  - Significant improvement across all doses (28 mg, 56 mg, 84 mg), with 84 mg showing the most improvement (p<0.001)
  - 5% in the double-blind phase and 2% in the open-label phase discontinued due to adverse events like syncope, headache, and dissociation
  - Major limitation: The short double-blind phase, lasting only from days 1-15

## Conclusion

- Depression & Treatment:**
  - Significant number suffer from treatment-resistant depression (TRD)
  - MAOIs and intranasal ketamine are potential treatments for TRD
- Efficacy of MAOIs and Esketamine:**
  - Both have shown positive effects for TRD, with nuances in study outcomes
  - Safety concerns exist for for esketamine and MAOIs (e.g., dissociation).
- Re-evaluation of MAOIs:**
  - Risks associated with dietary interactions are minimal
  - Positive safety profile in older adults, even with serotonergic drugs.
- Role of Physician Assistants:**
  - Knowledge of both treatments crucial for effective patient care in psychiatry
  - Critical as PAs grow in importance and number in psychiatry
- Future Research Direction:**
  - Despite recent focus on ketamine, there's a need to balance MAOI research given similar study outcomes and safety reassessment
  - Direct comparison studies between MAOIs and esketamine are required

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