Efficacy of methylphenidate and mirtazapine combination therapy in terminally ill cancer patients with major depressive disorder

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Clinical Question
- In a 66-year-old male diagnosed with major depressive disorder and terminal cancer, would adding methylphenidate to mirtazapine therapy provide adequate relief of depressive symptoms?

Case Scenario
- A 66-year-old male patient with pancreatic cancer presents with ongoing depression. He was evaluated and started on a standard antidepressant, mirtazapine (Remeron®) 2 months ago after being diagnosed with cancer.
- He complains of a continued depressed mood for nearly every day with anhedonia.
- His current Montgomery-Asberg Depression Rating Scale (MADRS) is 36, indicating severe depression.

Background
- When diagnosed with terminal cancer, patients commonly develop major depression. The high prevalence can be attributed to many factors, particularly, poor prognosis.
- These patients experience physical and cognitive symptoms including depressed mood, loss of interest, hopelessness, fatigue, weight loss, sleep disturbances, and decreased concentration.
- MADRS is a validated diagnostic questionnaire used to measure severity of depressive symptoms.
- Conventional antidepressant treatments are aimed at increasing the brain’s levels of monoamine neurotransmitters—serotonin, norepinephrine, and dopamine. Mirtazapine increases both norepinephrine and serotonin.
- Methylphenidate, a piperidine derivative, is a central nervous system stimulant traditionally used to treat attention deficit disorder. The mechanism of action is not fully understood, but it primarily works to increase dopamine levels in the brain.
- There is an increased interest in prescribing this medication due to its rapid rate of onset. This can serve to alleviate depression in conjunction with current antidepressants, which are hampered by a longer lag time before symptoms improve.

Search Strategy
- A search of PubMed Clinical Queries using the terms methylphenidate AND depression AND cancer as a primary database retrieved 53 results.
- Clinical study categories were kept at therapy and the scope broad without any other limitations.
- Only one article addressed the effects of methylphenidate and mirtazapine combination therapy.
- Searches through the PsycInfo and Cochrane databases offered no other relevant articles.

Table 1: Mean change of MADRS score from Day 1 (baseline) to Day 3 between groups (MTZ+MPH vs MTZ+PLB).

<table>
<thead>
<tr>
<th>Reference LOE</th>
<th>Citation Population and Setting</th>
<th>Treatment</th>
<th>MADRS score Day 1 Mean (SD)</th>
<th>MADRS score Day 3 Mean (SD)</th>
<th>Net Change (95% CI)</th>
<th>Application P value of difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al. (2013) 1</td>
<td>Adult cancer patients diagnosed with major depression, Malaysia (2011-2012) MTZ + MPH (N=44)</td>
<td>31.9 ± 6.2</td>
<td>26.1 ± 7.6</td>
<td>5.8 (2.8 to 8.7)</td>
<td>0.0247</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MTZ + PLB (N=44)</td>
<td>32.3 ± 6.1</td>
<td>31.2 ± 7.2</td>
<td>1.1 (1.8 to 3.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 2: Mean change of MADRS score from Day 1 (baseline) to Day 28 between groups (MTZ+MPH vs MTZ+PLB).

<table>
<thead>
<tr>
<th>Reference LOE</th>
<th>Citation Population and Setting</th>
<th>Treatment</th>
<th>MADRS score Day 1 Mean (SD)</th>
<th>MADRS score Day 28 Mean (SD)</th>
<th>Net Change (95% CI)</th>
<th>Application P value of difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al. (2013) 1</td>
<td>Adult cancer patients diagnosed with major depression, Malaysia (2011-2012) MTZ + MPH (N=44)</td>
<td>31.9 ± 6.2</td>
<td>15.9 ± 6.7</td>
<td>16.0 (13.3 to 18.8)</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td></td>
<td>MTZ + PLB (N=44)</td>
<td>32.3 ± 6.1</td>
<td>26.7 ± 8.5</td>
<td>5.5 (2.4 to 8.7)</td>
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</tbody>
</table>


Conclusions
- In this four-week randomized, double-blind, placebo-controlled study, a significant reduction of depressive symptoms was noted as early as Day 3 with combination methylphenidate and mirtazapine therapy.
- A greater reduction was noted on Day 28 compared to Day 3.

Application to Patient
- The Asian study population included patients with a heterogeneous group of cancers, which made certain adverse events hard to correlate with treatment, and not the cancer process itself.
- However, a significant relief of depressive symptoms as measured by the MADRS was achieved with this population including those with pancreatic cancer.
- Therefore, the treatment could be recommended for the patient in this case scenario.

Future Directions
- Repeat of this study with larger and more diverse populations may help establish a higher level of evidence and enhance the ability to identify life-threatening side effects before recommending this treatment to those with terminal illnesses.

References