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Why is Memantine Not Recommended in Vascular and Frontotemporal Dementia?

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Introduction

According to the NICE guidelines on Pharmacological treatment of Dementia, Memantine is recommended in moderate to severe Dementia in Alzheimer's disease, mixed dementia, dementia in Parkinson's disease (PDD) and Lewy body dementia (LBD). It is not recommended in Vascular and Frontotemporal dementia (FTD). Cholinesterase inhibitors (ChEIs) and Memantine are indicated to slow the progression of dementia. In clinical practice, Memantine has an additional benefit where it is used in the management of behavioral and psychological symptoms of dementia (BPSD). However, it is only used if it is of Alzheimer's, mixed, Parkinson's or Lewy body type of dementia. Since Memantine requires limited monitoring and has fewer side effects, it is used as a first line in managing aggressive behavior before initiating antipsychotic medication. According to the NICE guidelines [1], Risperidone which is an atypical antipsychotic is recommended in BPSD. Antipsychotics are generally used as a last resort because of established adverse effects (e.g. prolonged QTc, weight gain, hyperprolactinaemia, impaired glucose tolerance/diabetes and hyperlipidaemia [2] and regular monitoring. However, when it comes to BPSD in Vascular and Frontotemporal dementia, antipsychotics are preferred over Memantine.

It is difficult to understand the rationale behind this approach so I decided to read the relevant reports and systematic reviews contributing to the recommendation. I observed the following:

•According to TA217 report [3], maximum data comprised of Memantine monotherapy or combination therapy in Alzheimer's disease. There was very limited data on the use of Memantine in other types of dementia. "The Assessment Group considered the quality of new placebo-controlled studies published since 2004 to be 'disappointing'. Issues include the inappropriate use of last observation carried forward and observed cases analysis instead of intention-to-treat analysis, inadequate reporting of randomization and allocation and the small size of the studies. According to the Assessment Group, the robustness of the new evidence provided by the head to head studies was limited by the poor quality of all but one of the studies. Important gaps in the evidence remain".

• According to a recent Cochrane systematic review of Memantine for Dementia, the authors identified 44 randomized controlled trials including almost 10,000 participants, the majority of which (n=29) were in people with Alzheimer's disease (n=7885) [4].

• The Cochrane review identified small clinical benefits in cognitive function and in behaviour and mood in people with vascular dementia and post-hoc analysis showed there may be greater benefits in people with more severe disease. Secondly, for people with frontotemporal dementia, the NICE guidelines [1] recommend that ChEIs and Memantine should not be offered stating that there is not usually a cholinergic deficit in people with FTD. According to Cochrane review [4], it may be that the guideline has conflated the findings for ChEIs with those for Memantine. However, Memantine has a non-cholinergic mechanism of action which may have potential for benefit.

• (Table 1) illustrates the findings of Cochrane review [4] on the effectiveness of Memantine in different types of Dementia.

Table 1: Cochrane Systematic Review (2019).

	Alzheimer's Disease	Vascular Dementia	PDD & LBD	FTD
Findings	Beneficial	Negative outcome	Positive outcome	Negative outcome
Sample Size	7885	500-900	60-240	100-115
GRADE	High	Low	Low	Very Low

•I was surprised to discover that despite limited evidence on the use of Memantine in Dementia in Parkinson's disease and Lewy Body dementia, it is still recommended. However, with a similar poor evidence profile in Vascular and Frontotemporal dementia it is not recommended.

•In addition, there are studies that have shown Memantine to be effective in reducing agitation, e.g an open-label, self-controlled study [5] with 42 participants diagnosed with FTD showed a statistically significant reduction in agitation when treated with 10 mg of Memantine, twice daily over 6 months (P value-0.033).

It can be difficult to do trails on vascular dementia and Frontotemporal dementia In Vascular Dementia; it can be difficult to differentiate from Alzheimer's as both have similar risk factors. FTD is a complex disease with different pathophysiologies. However, if Memantine is harmless and not contraindicated, then it is difficult to understand why it cannot be used in addressing behavioral symptoms associated with Vascular and Frontotemporal dementia. Based on the above rationale I suggest that Memantine should be considered before an antipsychotic even in Vascular and Frontotemporal dementia. If the generic effect of Memantine can reduce the behavioral symptoms or even delay the requirement for an antipsychotic, it would definitely be a safer option.

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