Tolerability of Switching Cholinesterase Inhibitors to Memantine Monotherapy Versus Adding Memantine as Combination Therapy for All-Cause Neurodegenerative Disorders

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Abstract

Background: Prior studies have focused on the clinical efficacy of combination therapy, Donepezil and Memantine, for patient's diagnosed with Alzheimer's disease. However, the potential adverse drug reactions while described as mild can have serious sequelae in older adults who are already managing the side effects of polypharmacy.

Objective: This study looks to explore the tolerability of switching cholinesterase inhibitors to memantine monotherapy versus adding memantine as combination therapy for all-cause neurodegenerative disorders.

Methods: The study is a retrospective chart review that includes 175 patients aged 50 and older diagnosed with neurocognitive disorders (ICD 10 F00-F03.91 and ICD10 G30-G31.84) managed on combination therapy, memantine monotherapy and CI monotherapy from 2016-2019.

Results: The odds of a patient reporting side effects on combination therapy in comparison with those patients on memantine monotherapy reporting side effects were significantly greater (OR = 4.33, CI 95% (1.62, 11.52), p=0.003). There was marginal significance in variables such as polypharmacy (p=0.057) and dosing of cholinesterase inhibitors (p = 0.087) in a binary logistic regression model (Table 1). Of the patient population who qualified as excessive polypharmacy (>10), more than half 60% reported side effects.

Discussion: The likelihood of reporting side effects is significantly increased for patients on combination therapy when compared to those on monotherapy(p=0.003). Sample size was a limiting factor in determining significant predictors for those reporting side effects on combination therapy; however, there was marginal significance for patients on > 4 other medications while on combination therapy (p=0.057) in predicting outcomes. In our patient sample, more than 80% of the patients reporting side effects qualified as polypharmacy or excessive polypharmacy.

Results

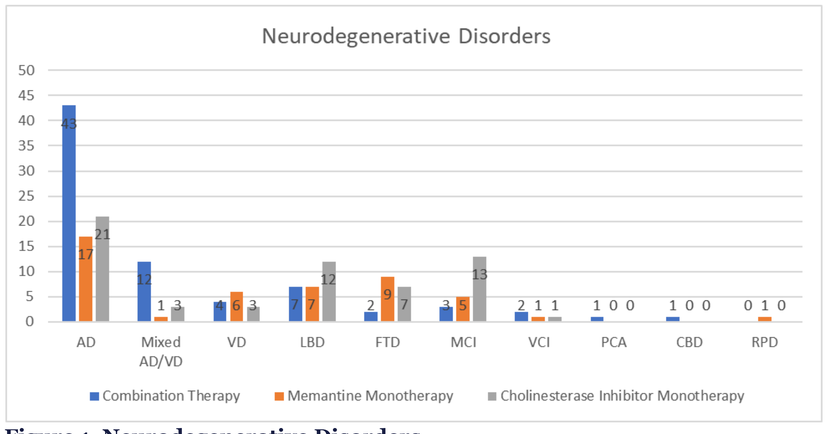

Figure 1. Neurodegenerative Disorders

All-cause neurodegenerative disorders were included in this study with a majority of patients diagnosed with AD in all 3 treatment groups (Figure 1). Followed by Mixed AD/VD in the combination therapy group, FTD in the memantine monotherapy group and MCI in the CI monotherapy group. The more frequently reported side effects in the combination therapy group were sleep impairment, dizziness, and diarrhea, respectively (Figure 2).

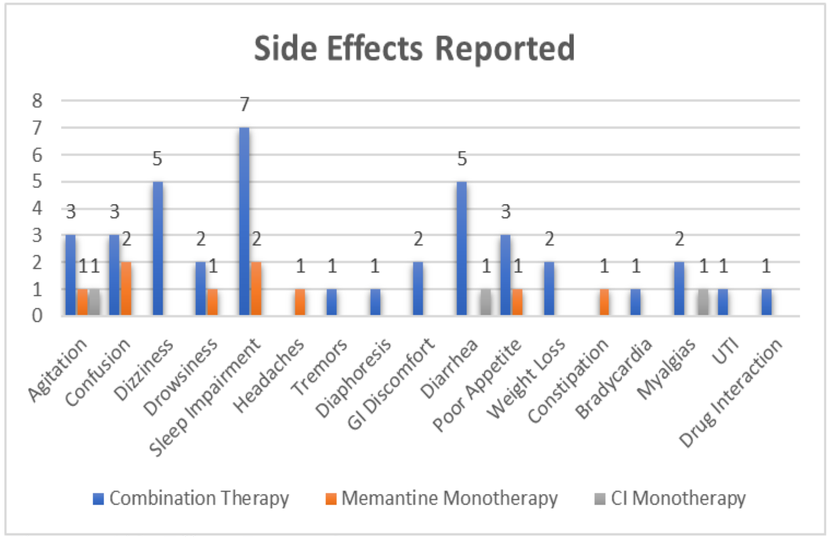

Figure 2. Side Effects Reported

The more frequently reported side effects in the combination therapy group were sleep impairment, dizziness, and diarrhea, respectively (Figure 2).

A majority of the patients 83.9% were on high dose memantine therapy and 12.9% were on high dose CI therapy.

Polypharmacy		Side Effects: No Side Effect	Side Effect
p=0.057	(< 4)	6	6
		50%	50%
	(4-10)	31	16
		66%	34%
	(>10)	6	9
		40%	60%
	Total	43	31
		58%	42%

CI Dose		Side Effects: No Side Effect	Side Effect
p = 0.087	Low	6	9
		40%	60%
	Medium	25	18
		58%	42%
	High	12	4
		75%	25%
	Total	43	31
		58%	42%

Severity		Side Effects: No Side Effect	Side Effect
p=0.148	Mild	12	15
		44%	56%
	Moderate	20	2
		91%	9%
	Severe	7	12
		37%	63%
	unknown	4	2
		67%	33%
	Total	43	31
		58%	42%

Memantine Dose		Side Effects: No Side Effect	Side Effect
p=0.868	Low	0	0
		0%	0%
	Medium	8	5
		62%	38%
	High	35	26
		57%	43%
	Total	43	31
		58%	42%

Table 1. Combination Therapy- Dosing Other Medications and Severity

Variables such as severity of disease (p=0.148) and memantine (p=0.868) were not significant predictors for those reporting side effects on combination therapy, however, there was marginal significance in variables such as polypharmacy (p=0.057) and dosing of cholinesterase inhibitors (p = 0.087) in a binary logistic regression model (Table 1). Of the patient population who qualified as excessive polypharmacy (>10), more than half 60% reported side effects (Table 1).

Combination Therapy*			Memantine Monotherapy		
	N	%		N	%
No Side Effect	43	32%	No Side Effect	35	26%
Side Effect	31	78%	Side Effect	6	14%

Table 2. Side Effects

The odds of a patient reporting side effects on combination therapy in comparison with those patients on memantine monotherapy reporting side effects were significantly greater (OR = 4.33, CI 95% (1.62, 11.52), p=0.003). (Table 2).

Discussion

- The odds of a patient reporting side effects on combination therapy in comparison with those patients on memantine monotherapy reporting side effects are significantly greater (p=0.003).
- Polypharmacy has previously been described as four or more medications and the potential for negative outcomes (adverse drug events, non-adherence or drug interactions) in older people.
- Sample size was a limiting factor in determining significant predictors for those reporting side effects on combination therapy; however, there was marginal significance for patients on > 4 other medications while on combination therapy (p=0.057) in predicting outcomes.
- In our patient sample, more than 80% of the patients reporting side effects qualified as polypharmacy or excessive polypharmacy.
- The rates of non-adherence around the world exceed 50% among the poly-medicated elderly with 50% of dropouts occurring in the first six months of treatment.
- Overall, this is a patient population that eventually succumbs to terminal-stage complications that relate to advanced debilitation, such as dehydration, malnutrition and infection.
- An objective for clinicians is to obtain a balance between aggressively treating diseases while avoiding medication related harm.
- Consider switching CI monotherapy to memantine monotherapy when managing patients with mild to moderate disease to increase the likelihood of tolerability. Consider the number of other medications the patient is taking and the severity of the patient's cognitive impairment to determine if the clinical benefit will outweigh the risk.
- Further research is needed to explore the efficacy in all-cause neurodegenerative disorders.
- Limitations: As a retrospective chart review causation cannot be determined, only association. Furthermore, the sample size was a limiting factor in determining more reliable predictors for those reporting side effects.

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