Memantine Augmentation in Clozapine Refractory Schizophrenia: a Randomized, Double-blind, Placebo-controlled Crossover Study and an Open-label Extension Study

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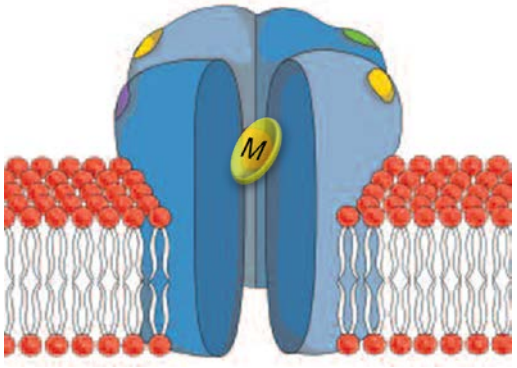
Phrenos

Memantine



- **Memantine – Ebixa®**
- Adequate dose 20 mg/day

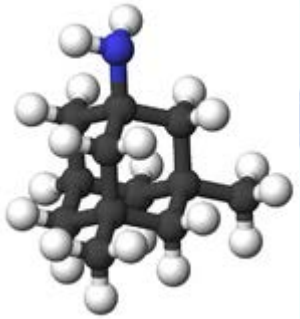
- Voltage-dependent
- Non-competitive antagonist of NMDA (N-methyl-D-aspartate)-R
- Stronger binding than Mg^{2+}

→ **Signal transduction at a strong stimulus**

- Neuroprotective properties
- Pharmacodynamic interactions with clozapine: upregulation NMDA-R

Veerman SR, Schulte PF, de Haan L (2014). The glutamate hypothesis: a pathogenic pathway from which pharmacological interventions have emerged. *Pharmacopsychiatry* 47, 121-130.

Memantine



- Experimental use of a product which is not licenced for treatment of schizophrenia
- Memantine is licenced for treatment of moderate-to-severe Alzheimer's disease
- Memantine is prescribed off-label in therapy-resistant schizophrenia

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Memantine Add-on Therapy to Clozapine

Study	Adjunctive agent	N	Trial duration (weeks)	Outcome of measure	ES	P
Lucena et al., 2009	Memantine (20 mg)	10	12	Overall clinical symptoms (BPRS total)	2.75	0.001
	Placebo	11				
No drop outs				Negative symptoms (BPRS-N)	3.33	0.001
				Positive symptoms (BPRS-P)	1.38	0.007
				Global severity of symptoms (CGI)	1.56	0.001
				Cognitive functioning (MMSE)	1.32	0.005

de Lucena D, Fernandes BS, Berk M et al. Improvement of negative and positive symptoms in treatment-refractory schizophrenia: a double-blind, randomized, placebo-controlled trial with memantine add-on therapy to clozapine. J Clin Psychiatry 2009; 70: 1416-23

Proof-of-concept studie MAOTC

12 FACT facilities

Mental Health Service Organisation

North Holland North

- Flexible Assertive Community Treatment (FACT)
- 26-week double-blind, placebo-controlled crossover trial (N=52)
- Inclusion: August 5, 2013 – December 17, 2013
- End: August 5, 2014 jul

Veerman SR, Schulte PF, Smith JD, de Haan L. Memantine augmentation in clozapine refractory schizophrenia: a randomised, double-blind, placebo-controlled crossover study. Psychological Medicine 2016; 46: 1909-1921

Primary Outcome

- Memory: **ES=.30**, *p*=.032
- Negative symptoms: **ES=.29**, *p*=.043

Veerman SR, Schulte PF, Smith JD, de Haan L. Memantine augmentation in clozapine refractory schizophrenia: a randomised, double-blind, placebo-controlled crossover study. Psychological Medicine 2016; 46: 1909-1921

Side effects

- Higher score on the Allergic Reactions subscale of the LUNSERS (**ES=.44**)
- 1 patient discontinued memantine due to dizziness

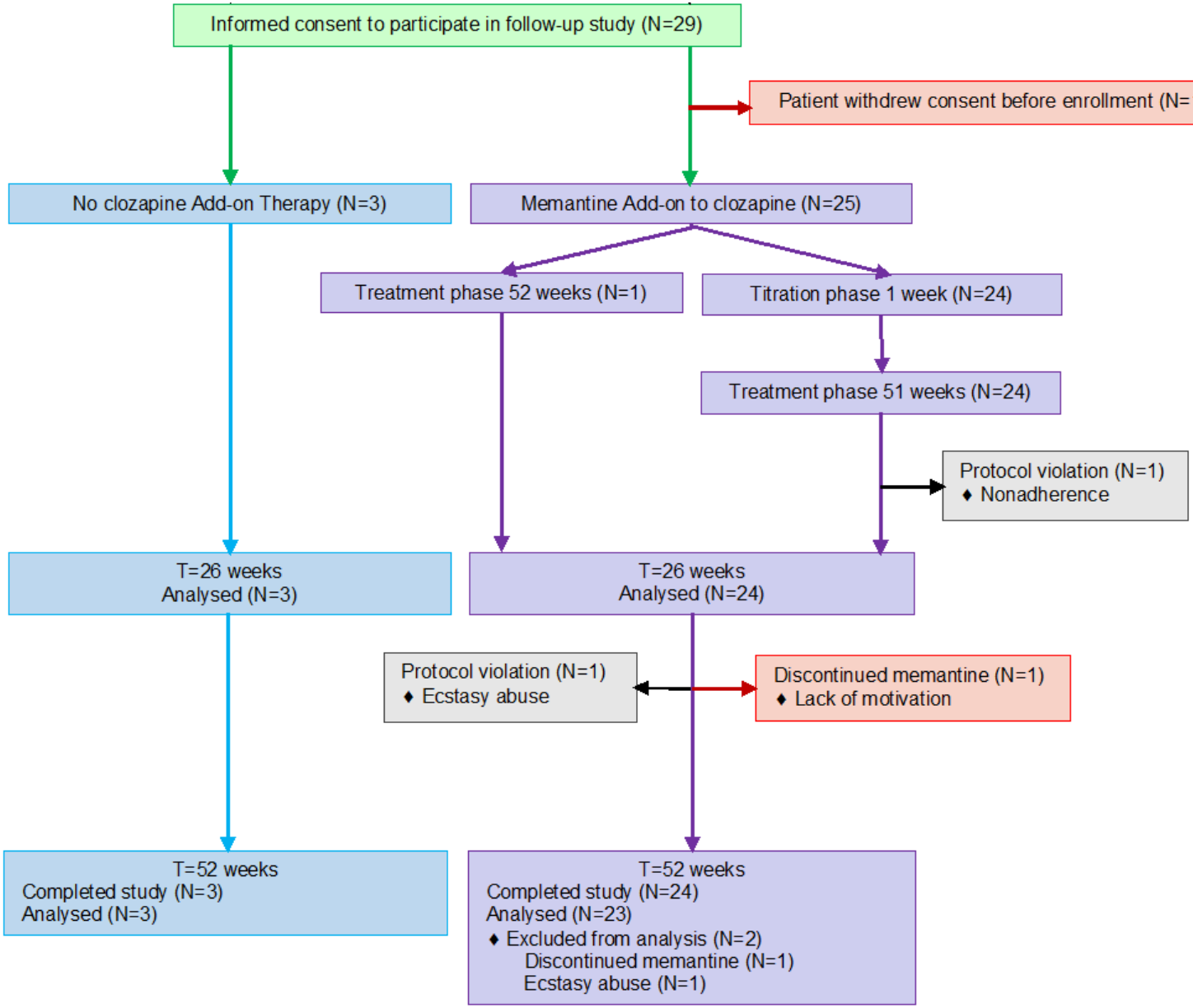
Veerman SR, Schulte PF, Smith JD, de Haan L. Memantine augmentation in clozapine refractory schizophrenia: a randomised, double-blind, placebo-controlled crossover study. Psychological Medicine 2016; 46: 1909-1921

Extension study MAOTC

11 FACT facilities

- Inclusion: completers of placebo-controlled cross-over study
  - Experienced beneficial effect of memantine after 12 weeks Add-on Therapy
  - No memantine Add-on Therapy
- Inclusion: August 7, 2014 – August 22, 2014
- Assessments: similar to the proof-of-concept study
- End: September 11, 2015

Veerman SR, Schulte PF, Deijen JB, de Haan L. Adjunctive memantine in clozapine-treated refractory schizophrenia: an open-label 1-year extension study. Psychological Medicine 2016; 1-13


Informed consent to participate in follow-up study (N=29)
Patient withdrew consent before enrollment (N=1)
No clozapine Add-on Therapy (N=3)
Memantine Add-on to clozapine (N=25)
Treatment phase 52 weeks (N=1)
Titration phase 1 week (N=24)
Treatment phase 51 weeks (N=24)
Protocol violation (N=1)
♦ Nonadherence
T=26 weeks
Analysed (N=3)
T=26 weeks
Analysed (N=24)
Protocol violation (N=1)
♦ Ecstasy abuse
Discontinued memantine (N=1)
♦ Lack of motivation
T=52 weeks
Completed study (N=3)
Analysed (N=3)
T=52 weeks
Completed study (N=24)
Analysed (N=23)
♦ Excluded from analysis (N=2)
Discontinued memantine (N=1)
Ecstasy abuse (N=1)

Primary outcomes

- Memory improvement after 12 weeks
  memantine add-on to clozapine (**ES=.30**)
  sustained at follow-up
  after 26 weeks and 52 weeks

- No further improvement of memory

- No improvement of executive function

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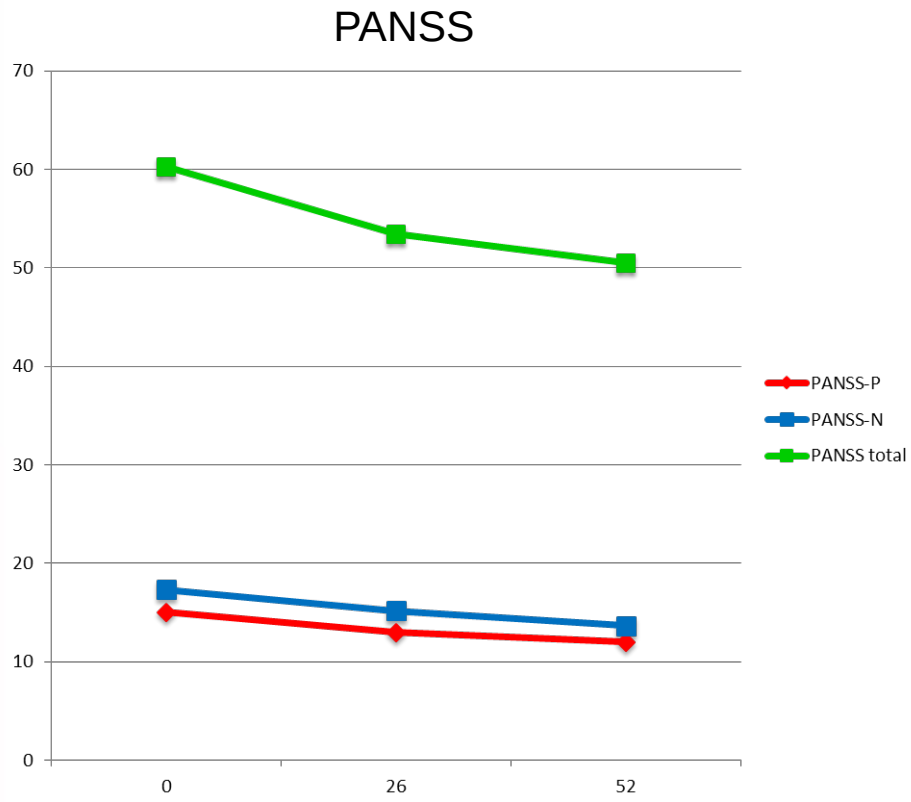
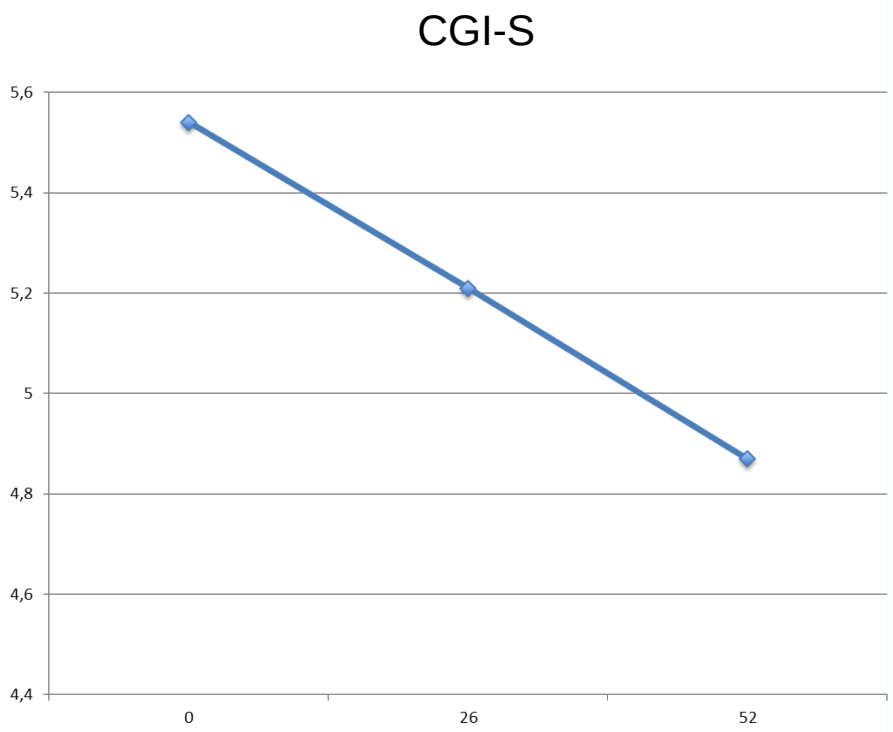
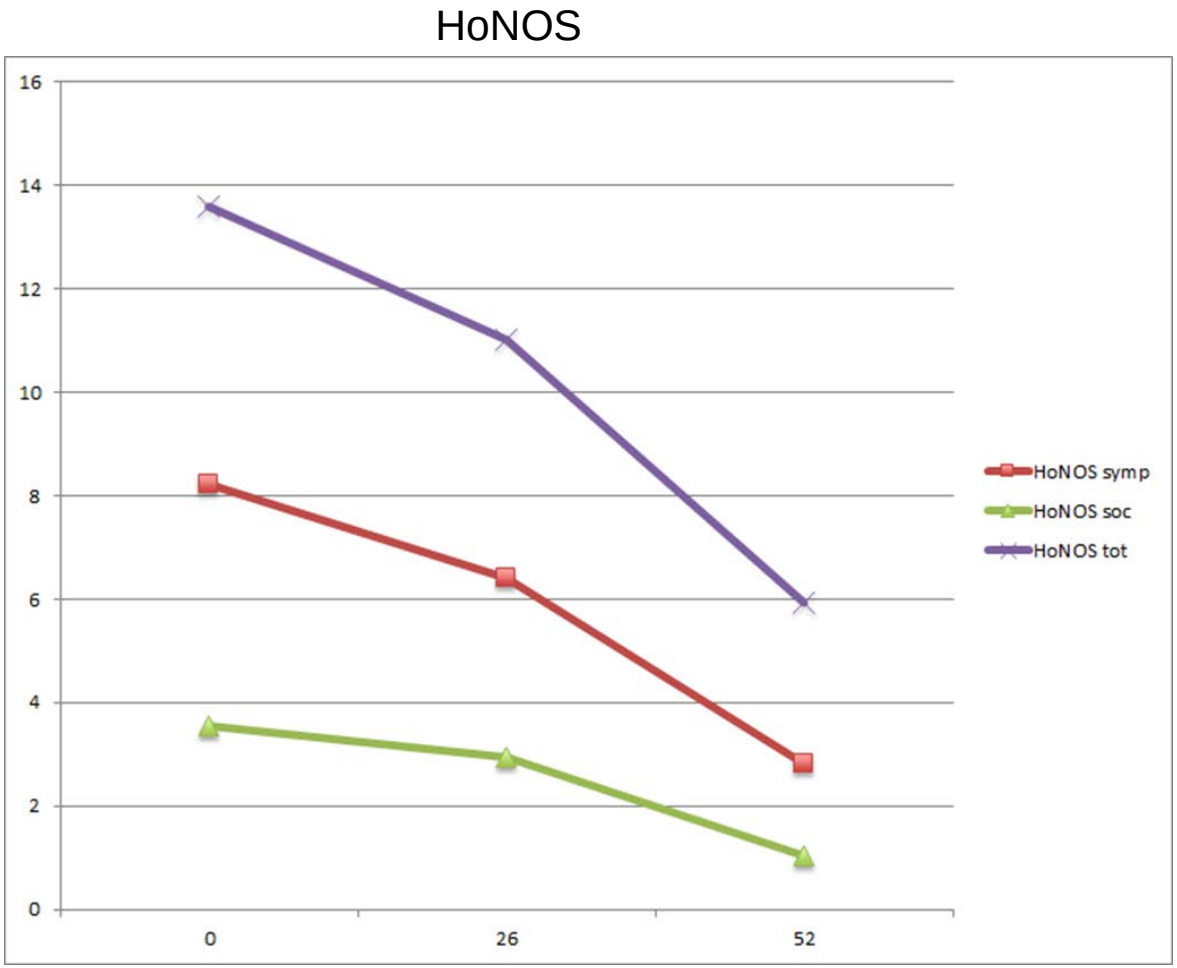
Primary outcomes





Veerman SR, Schulte PF, Deijen JB, de Haan L. Adjunctive memantine in clozapine-treated refractory schizophrenia: an open-label 1-year extension study. Psychological Medicine 2016; 1-13

Secondary outcomes



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Memantine + Clozapine

	Lucena et al. 2009	Veerman et al. 2016	Extension T=26 weeks	Extension T=52 weeks
	Cohen	Cohen	Wilcoxon	Wilcoxon
Primary parameters	d	d	r	r
Positive symptoms	**1.38**	0.15*	**0.50**	**0.39**
Negative symptoms	**3.33**	**0.29**	**0.53**	**0.51**
Overall symptoms	**2.75**	0.19*	**0.54**	**0.51**
Clinical global status	**1.56**	0.11*	0.36**	0.34**
Secondary parameter				
Psychosocial functioning		0.18*	**0.33**	**0.49**

* Non-significant improvement
** Non-significant improvement after Holm-Bonferroni correction

Results

- Memantine was well-tolerated
- Adverse events possibly related to memantine: reflux and mycosis
- No serious adverse events
- No admissions to a psychiatric hospital
- 1 patient discontinued memantine after a period of non-adherence

Veerman SR, Schulte PF, Deijen JB, de Haan L. Adjunctive memantine in clozapine-treated refractory schizophrenia: an open-label 1-year extension study. Psychological Medicine 2016; 1-13

Discussion

Overestimation of results (open-label design):

- Observer effect, better care and adherence
- Not controlled for element of expectation
- 3 patients without memantine as add-on therapy were not enough for further analysis

Future research

- Validation of favourable results:
  - Multicenter RCT with large sample size
  - Long term effects of memantine
  - Possibly dose-ranging (>20 mg memantine)
  - Younger TRS patients
  - ^{1}H-MRS and fMRI

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Questions?