Psychological Medicine (2017), **47**, 363–375. © Cambridge University Press 2016
doi:10.1017/S0033291716002476

ORIGINAL ARTICLE

Adjunctive memantine in clozapine-treated refractory schizophrenia: an open-label 1-year extension study

S. R. T. Veerman[1]*, P. F. J. Schulte[2], J. B. Deijen[3] and L. de Haan[4]

[1] *Mental Health Service Noord-Holland Noord, Community Mental Health Division, Flexible Assertive Community Treatment, Alkmaar, The Netherlands*
[2] *Mental Health Service Noord-Holland Noord, Division for Specialized Treatment, Treatment Centre for Bipolar Disorders, Alkmaar, The Netherlands*
[3] *Vrije Universiteit, Faculty of Behavioural and Movement Sciences, Section Clinical Neuropsychology, Amsterdam, The Netherlands*
[4] *Early Psychosis Department, Academic Medical Centre, University of Amsterdam, Academic Psychiatric Centre, Arkin, Amsterdam, The Netherlands*

Background. In a recent placebo-controlled, double-blind crossover trial ($n = 52$), significant beneficial effects on memory ($d = 0.30$) and negative symptoms ($d = 0.29$) were found after 12 weeks of memantine augmentation in patients with clozapine-refractory schizophrenia. In this open-label 1-year extension study we report the long-term effects and tolerability of memantine add-on therapy to clozapine.

Method. Completers of the first trial who experienced beneficial effects during 12 weeks of memantine treatment received memantine for 1 year. Primary endpoints were memory and executive function using the Cambridge Neuropsychological Test Automated Battery, the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression Severity Scale (CGI-S).

Results. Of 31 randomized controlled trial completers who experienced beneficial effects from memantine, 24 received memantine for 1 year. The small improvement in memory found in the memantine condition in the placebo-controlled trial remained stable in the extension study. Executive function did not improve. After 26 weeks of memantine add-on therapy to clozapine, PANSS negative symptoms ($r = 0.53$), PANSS positive symptoms ($r = 0.50$) and PANSS total symptoms ($r = 0.54$) significantly improved. Even further significant improvement in all these measures was observed between 26 weeks and 52 weeks of memantine, with effect sizes varying from 0.39 to 0.51. CGI-S showed a non-significant moderate improvement at 26 weeks ($r = 0.36$) and 52 weeks ($r = 0.34$). Memantine was well tolerated without serious adverse effects.

Conclusions. In the 1-year extension phase the favourable effect of adjunctive memantine on memory was sustained and we observed further improvement of negative, positive and overall symptoms in patients with clozapine-treated refractory schizophrenia.

Received 23 May 2016; Revised 19 August 2016; Accepted 24 August 2016; First published online 25 October 2016

Key words: Clozapine, cognitive functioning, glutamate antagonists, memantine, therapy-resistant schizophrenia.

Introduction

Treatment-resistant schizophrenia (TRS) is a major clinical problem, since in approximately a third of schizophrenia patients psychotic symptoms persist despite appropriate antipsychotic treatment (Elkis, 2007). In TRS negative symptoms are prominent (de Bartolomeis *et al.* 2013) and associated with impaired working memory (Zierhut *et al.* 2013), impaired verbal memory (de Bartolomeis *et al.* 2013; Anderson *et al.* 2015) and deficits in cognitive flexibility, processing speed, executive functions and verbal fluency (Frydecka *et al.* 2016).

Patients with TRS may be suffering from a normodopaminergic subtype of schizophrenia (Howes & Kapur, 2014; Kahn & Sommer, 2015; Lawrie *et al.* 2016), since in patients with TRS the striatal dopamine synthesis capacity is not increased (Demjaha *et al.* 2012). Moreover, anterior cingulate cortex glutamate levels are elevated in TRS compared with patients with treatment-responsive schizophrenia (Demjaha *et al.* 2014; Mouchlianitis *et al.* 2015). Therefore glutamatergic alterations may be a plausible explanation for the lack of response to dopamine-blocking antipsychotic medication in TRS patients. Glutamate receptors (*N*-methyl-D-aspartate; NMDA) are therefore

* Address for correspondence: S. R. T. Veerman, M.D., Mental Health Service Noord-Holland Noord, Community Mental Health Division, Flexible Assertive Community Treatment, Oude Hoeverweg 10, 1816 BT Alkmaar, The Netherlands.
(Email: s.veerman@ggz-nhn.nl)

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

a candidate target for intervention in TRS (Veerman *et al.* 2014*b*). Clozapine acts as a glutamate agonist and has proven superior efficacy for positive symptoms relative to other antipsychotic medication (Leucht *et al.* 2013). However, up to 70% of patients treated with clozapine show insufficient response (Buckley *et al.* 2001; Agid *et al.* 2010) and clozapine is not consistently associated with improvement of cognitive impairments (Bourque *et al.* 2013).

Memantine targets the NMDA receptor and has been shown to improve cognition in patients with Alzheimer's disease (McShane *et al.* 2006). Findings of two proton magnetic resonance spectroscopy (^{1}H-MRS) studies showed elevated γ-amino butyric acid (GABA) and glutamate levels in the medial prefrontal cortex (Kegeles *et al.* 2012; de la Fuente-Sandoval *et al.* 2015) and in the dorsal caudate (de la Fuente-Sandoval *et al.* 2015) in antipsychotic-naive patients with schizophrenia and subjects at ultra-high risk. In a ^{1}H-MRS study memantine decreased hippocampal glutamate levels, which supports the hypothesis that memantine protects against excitotoxicity (Glodzik *et al.* 2008). In a functional magnetic resonance imaging (fMRI) study memantine augmentation of atypical antipsychotics normalized brain activity in the inferior frontal gyrus (Cerullo *et al.* 2007), which is altered in patients with schizophrenia (Fletcher *et al.* 1998; Thermenos *et al.* 2005) and is involved in working memory (Lawrence *et al.* 2003; Tomasi *et al.* 2006).

de Lucena *et al.* (2009) found substantial effects of adjunctive memantine to clozapine in TRS on global cognitive functioning, negative symptoms, positive symptoms and overall symptoms with exceptionally large effect sizes (ESs) varying from 1.32 to 3.33. In a larger and more elaborate crossover study ($n = 52$) we found more modest favourable effects of memantine augmentation in TRS on memory (ES = 0.30) and negative symptoms (ES = 0.29). Executive function (ES = 0.12), positive symptoms (ES = 0.15), overall symptoms (ES = 0.19) and global severity of disease (ES = 0.11) did not significantly improve (Veerman *et al.* 2016).

Given the paucity of effective interventions to ameliorate cognitive dysfunction, negative and positive symptoms in TRS these results are clinically relevant. There are several indications that longer treatment than the mean trial duration of 8–12 weeks may be needed for an optimal treatment effect (Keefe *et al.* 2013). In order to show an enduring effect on cognition the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) guidelines recommend a trial duration of at least 26 weeks (Buchanan *et al.* 2005). And, for instance, Zoccali *et al.* (2007) showed a robust improvement of negative and positive symptoms (ESs 1.21 and 0.97, respectively) after 24 weeks of lamotrigine treatment, while in four trials with a treatment duration varying from 12 to 14 weeks those symptoms did not significantly improve (Veerman *et al.* 2014*a*).

We therefore performed a 1-year extension study of our former 26-week randomized, double-blind placebo-controlled crossover study evaluating memantine augmentation in clozapine-refractory schizophrenia. Since there is some preliminary evidence that memantine has beneficial effects on depressive and obsessive–compulsive symptoms (Zdanys & Tampi, 2008; Sani *et al.* 2012; Gameiro & Esteves, 2015), we explored the effects of memantine on these co-morbid symptoms as well. We also evaluated the long-term effects on severity of impairments of psychosocial functioning, quality of life and tolerability of memantine add-on therapy to clozapine.

Method

Study design

A 1-year open follow-up study was carried out in which all patients who had completed a previous double-blind, placebo-controlled randomized trial (RCT) were asked to participate (see Fig. 1). Participants who experienced beneficial effects during 12 weeks of memantine in the trial were allowed to be treated with memantine for 1 year. Those without beneficial effect on 12 weeks of memantine could participate without memantine augmentation.

Study population, and inclusion and exclusion criteria

The study was conducted from August 2014 to September 2015 at 11 Flexible Assertive Community Treatment (FACT) facilities of the Mental Health Service Organization Noord-Holland Noord (the Netherlands) (van Veldhuizen, 2007).

In the original single-centre, double-blind, placebo-controlled crossover study 52 severely ill patients were included [mean Clinical Global Impression Severity Scale (CGI-S) score 6.15, mean age 42.35 years and mean duration of illness 22.88 years], both male ($n = 39$) and female ($n = 13$), who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for schizophrenia on the Mini International Neuropsychiatric Interview Plus (MINI-Plus) (Overbeek *et al.* 1999). At inclusion participants suffered from persistent residual psychopathology (Andreasen *et al.* 2005) after treatment with clozapine for at least 6 months (mean clozapine plasma level 421 ng/ml, range 50–878 ng/ml) (Veerman *et al.* 2016). All participants received care from an out-patient

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

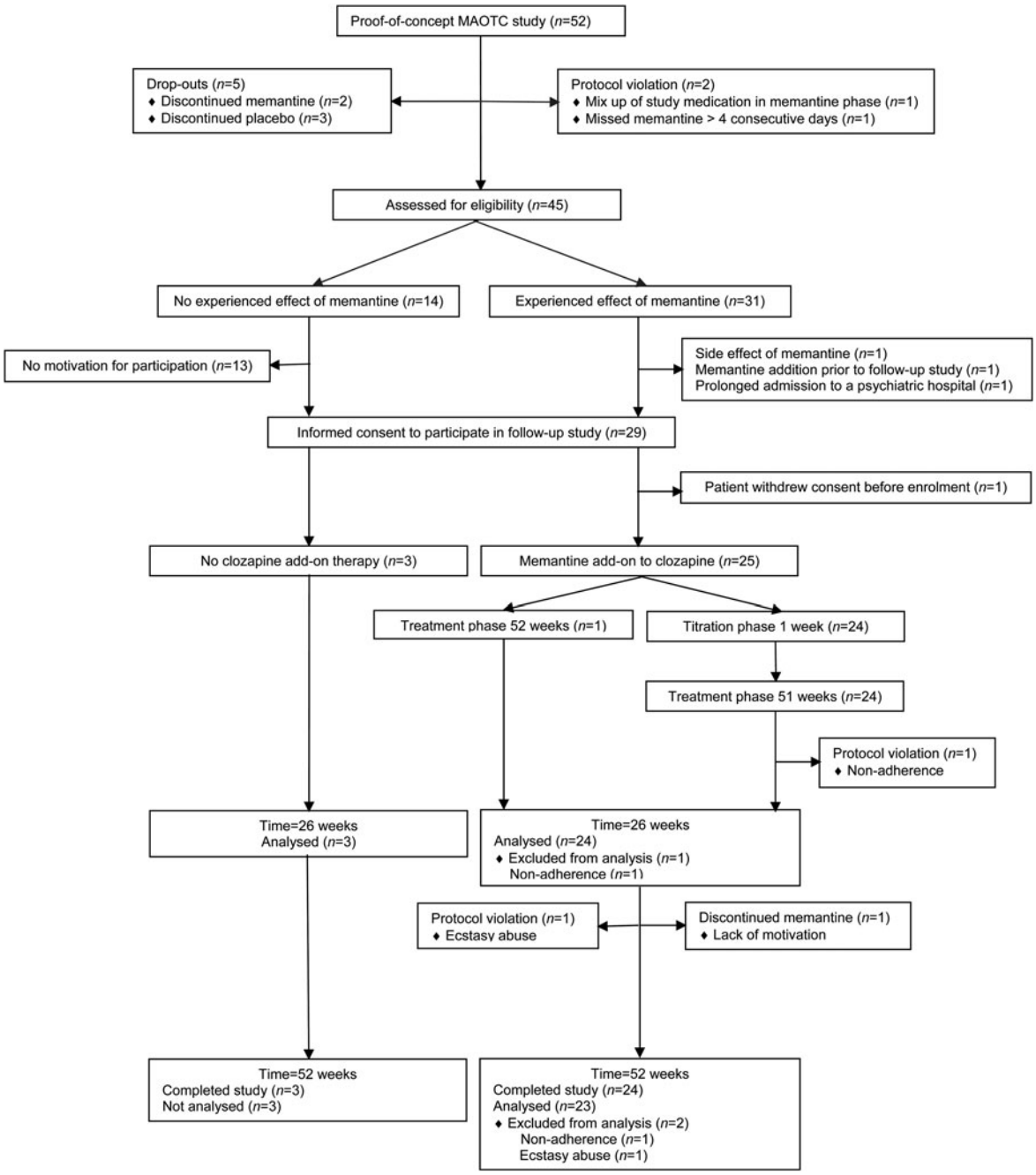


Fig. 1. Patient disposition in an open-label extension study of adjunctive memantine for clozapine-resistant schizophrenia. MAOTC, Memantine add-on therapy to clozapine.

facility, while living independently ($n = 30$), in a sheltered home ($n = 16$) or in an open long-stay ward ($n = 6$).

Adjunctive memantine treatment was allowed provided that more beneficial effects were established in the memantine phase compared with the placebo phase on primary outcomes after 12 weeks memantine add-on therapy in the placebo-controlled trial. Exclusion criteria included admission to an acute treatment ward, pregnancy, lactating women and female subjects without adequate contraception, known hypersensitivity to memantine, co-medication with glutamate modulators, lactose intolerance, uncontrolled epilepsy, myocardial infarction, uncontrolled hypertension, renal insufficiency, liver failure or Alzheimer's disease (Wesemann *et al.* 1983). Substance use was not an exclusion criterion, but needed to remain as stable as possible, while changes were monitored throughout the study as a possible confounder.

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

All subjects gave informed consent after receiving a complete description of the extension study from the principal investigator. Compliance was monitored on a daily basis in patients in sheltered homes and open long-stay wards and was at the discretion of the care providers in patients who lived independently.

Clinical assessments

Outcome measures and assessments were identical to those in the double-blind trial. Key primary outcomes were memory and executive function. We used the MATRICS Consensus Cognitive Battery (MCCB) to assess six cognitive domains using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Levaux *et al.* 2007): reaction time and psychomotor speed, sustained visual attention, verbal memory, visuospatial memory, learning and association ability, working visuospatial memory and strategy use, spatial planning and motor control and emotion recognition (Nuechterlein *et al.* 2008; Barnett *et al.* 2010). A composite memory score was assessed by computing the sum of the CANTAB scores of four tasks: verbal recognition memory (VRM) free recall and VRM recognition, and paired associates learning (PAL) total errors and PAL first trial memory score. A parallel form of the VRM task, equivalent in difficulty, was used for the second measurement in order to reduce practice effects. Executive function was assessed by computing a composite score of the sum of three CANTAB task scores: spatial working memory (SWM) strategy, SWM between errors and One Touch Stockings of Cambridge problems solved on first choice.

Other primary outcomes included effects on the severity of negative, positive and total symptoms of schizophrenia, using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987), and on global severity of psychopathology, using the CGI-S (Guy, 1976).

Secondary outcome measures related to social cognition (facial emotion recognition and theory of mind, as assessed with the Emotion Recognition Task of the CANTAB and the Reading the Mind in the Eyes test; Baron-Cohen *et al.* 1997), severity of depressive symptoms (Calgary Depression Scale for Schizophrenia; Addington *et al.* 1990), severity of obsessive–compulsive symptoms (Yale–Brown Obsessive–Compulsive Scale; Goodman *et al.* 1989), severity of impairments of psychosocial functioning [Health of the Nation Outcome Scales (HoNOS); Wing *et al.* 1999] and quality of life (Manchester Short Assessment of Quality of Life; Priebe *et al.* 1999).

Analyses of the safety and tolerability of memantine augmentation to clozapine included measurements of blood pressure and waist circumference, laboratory tests of white blood cell count and differentiation, liver and renal function, blood glucose, lipids, and clozapine plasma level (12 ± 0.5 h after ingestion). Subjects used the self-rating Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) to determine the occurrence and severity of side effects (Day *et al.* 1995). Three possible side effects of memantine (thrombosis, dyspnoea and mycosis) were assessed with separate Likert scales.

All primary and secondary outcomes were rated at baseline (t0), after 26 weeks (t26) and after 52 weeks (t52). In one patient the baseline measurement was conducted directly after the 12-week memantine treatment phase of the double-blind study and the second and third assessments were conducted after a treatment period of 38 weeks and 64 weeks of continuous treatment with memantine. The trainers in the instruments to assess severity of psychopathology in the first study also trained the three raters of the extension study. Inter-rater agreement between the first two raters was moderate, as indicated by the Spearman correlation coefficient ($\rho = 0.42$, $p = 0.001$) based on four live patient interviews under supervision (Mukaka, 2012). Inter-rater agreement between the second and third rater was high, ($\rho = 0.81$, $p < 0.0005$), based on seven assessments of joint interviews with subjects. Inter-rater agreement between the first and third rater was high ($\rho = 0.78$, $p < 0.0005$) based on three interviews under supervision.

Any undesirable experience occurring to a subject during the study, whether or not considered to be related to memantine, was defined as an adverse event (AE). AEs were reported by either the subject or his or her case manager, community mental health nurse or psychiatrist. Alternative causes of AEs were explored through physical examination by a general practitioner and additional laboratory measurements. Criteria for premature termination of the study were withdrawal of consent, lack of motivation of the participant to complete the study, or a medical emergency.

Statistical analysis

We conducted the analyses of the effects of memantine using a per-protocol analytic approach including protocol completers. To analyse the three repeated measurements we used the Skillings–Mack test (Chatfield & Mander, 2009). We chose this within-subject non-parametric statistical test because it can be used to analyse longitudinal data when some data are missing completely at random.

Post-hoc analyses for t26 *v.* t0 and t52 *v.* t26 were conducted by means of Wilcoxon signed-rank tests. The ES *r*'s of significant differences were calculated as *Z*/sqrt *N* (Tomczak & Tomczak, 2014).

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

We applied the highly conservative Holm–Bonferroni method (Holm, 1979) to control for the family-wise error rate inherent in multiple comparisons with the following criteria:

Primary cognitive parameters (CANTAB memory composite score, CANTAB executive function composite score): Skillings–Mack test [Holm–Bonferroni correction for two parameters ($\alpha = 0.05/2 = 0.025$)] and Wilcoxon [Holm–Bonferroni correction for two parameters and two *post-hoc* tests ($\alpha = 0.05/4 = 0.0125$)].

Primary rating scale parameters (PANSS negative symptoms, PANSS positive symptoms, PANSS total symptoms and CGI-S): Skillings–Mack test [Holm–Bonferroni correction for four primary parameters ($\alpha = 0.05/4 = 0.0125$)] and Wilcoxon [Holm–Bonferroni correction for four parameters and two *post-hoc* tests ($\alpha = 0.05/8 = 0.0062$)].

Secondary parameter (HoNOS total): Skillings–Mack test [no Holm–Bonferroni correction ($\alpha = 0.05$)] and Wilcoxon [Holm–Bonferroni correction for two *post-hoc* tests ($\alpha = 0.05/2 = 0.025$)].

Memantine-related side effects and all subscales of the LUNSERS of the entire group were analysed. Changes in laboratory measurements, waist circumference and blood pressure were analysed in individual subjects.

In accordance with the first study we conducted a *post-hoc* analysis on the effect of memantine on two subdomains of primary negative symptoms. We used a two-factor model of the PANSS constructed by Liemburg *et al.* (2013): (1) expressive deficits [flat affect (N1), poor rapport (N3), lack of spontaneity and flow of conversation (N6), mannerisms and posturing (G5), motor retardation (G7) and avolition (G13)]; and (2) social amotivation [emotional withdrawal (N2), passive/apathetic social withdrawal (N4) and active social avoidance (G16)].

We conducted a second *post-hoc* analysis using the five-factor model of the PANSS constructed by van der Gaag *et al.* (2006) to explore effects of memantine on specific PANSS subscales.

Patients who did not receive memantine add-on therapy to clozapine ($n = 3$) were not analysed due to the small sample size of this control group.

Reliability of analyses

Change in clozapine dosage, concomitant medication, substance use, and psychotherapy during the study were analysed in individual subjects as possible confounders.

The element of expectation was analysed by examining a correlation between pre-trial expectations of positive effects of memantine and difference scores (t26 – t0 and t52 – t26) of the PANSS and the HoNOS.

The original RCT was approved by the Central Committee on Research Involving Human Subjects and the Medical Research Ethics Committee (MREC) of Alkmaar Medical Centre. The MREC was informed about the 1-year open-label extension study, which did not require official approval, because the study was conducted in accordance with the post-trial provisions of the Declaration of Helsinki (World Medical Association, 2013), enabling all participants in an RCT to be treated with memantine augmentation (see Fig. 1).

Results

Baseline characteristics

Fig. 1 presents participant screening and enrolment flow data. Of 31 patients who had experienced beneficial effects of memantine, three patients did not participate in the extension study for various reasons and two patients chose to participate without adjunctive memantine, one patient withdrew consent, leaving 25 patients to be included in the extension study. Table 1 presents demographic and clinical characteristics of the study population of these 25 patients (mean age 42 years and mean duration of illness 19.6 years). Online Supplementary Table S1 shows demographic and clinical characteristics of the three patients who participated without adjunctive memantine, but were not included in the analysis. Subjects received care from an out-patient facility while living independently ($n = 14$) or in a sheltered home ($n = 9$), or had been admitted to an open long-stay ward ($n = 2$).

After the crossover RCT, the interval without memantine treatment varied (range = 4–35 weeks). Memantine augmentation was restarted with a dose of 10 mg memantine taken orally once daily and titrated to the full dose of 20 mg after 1 week. In one patient memantine treatment was not interrupted between the RCT and the current extension study: the memantine phase of the crossover study was followed directly by the extension study. As much as possible, all medication remained unaltered throughout the study. Treating psychiatrists notified the principal investigator of any changes in medication.

Clinical efficacy results

Table 2 summarizes results and statistics on all primary and secondary outcomes. Analysis of effects using the Skillings–Mack test indicated no significant differences between the three repeated measurements for the CANTAB composite scores for executive function and memory. Significant differences were found between the three repeated measurements for the remaining primary outcome variables: PANSS

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

Table 1. *Patient demographics and baseline characteristics*

Variable	Memantine add-on therapy ($n = 25$)
Sex, *n* (%)	
Female	6 (24)
Male	19 (76)
Education level, *n* (%)	
Low	16 (64)
Middle	6 (24)
High	3 (12)
Living conditions, *n* (%)	
Independently	14 (56)
Sheltered home	9 (36)
Long-stay ward	2 (8)
Alcohol use, *n* (%)	5 (20)
Nicotine use, *n* (%)	14 (56)
Cannabis use, *n* (%)	3 (12)
Cocaine use, *n* (%)	0
Clozapine use, *n* (%)	
Clozapine: single antipsychotic	18 (72)
Combination clozapine + second/third antipsychotic[a]	7 (28)
Combination clozapine + antidepressant[b]	16 (64)
Combination clozapine + mood stabilizer[c]	4 (16)
Combination clozapine + benzodiazepine	10 (40)
Combination clozapine + E-EPA	1 (4)
Combination clozapine + fish oil	2 (8)
Psychotherapy during past 6 months, *n* (%)	2 (8)
Mean age, years (S.D.)	42 (10.4)
Mean duration of education, years (S.D.)	12.3 (1.9)
Mean age of onset, years (S.D.)	19.6 (5.1)
Mean duration of untreated psychosis, months (S.D.)	32.2 (42.8)
Mean duration of illness, years (S.D.)	19.6 (5.1)
Mean clozapine daily dose, mg (S.D.)	333 (159.7)
Mean interval between extension study and memantine treatment in placebo-controlled trial, weeks (S.D.)	23.58 (10.14)

E-EPA, Ethyl eicosapentaenoic acid; S.D., standard deviation.

[a] Six aripiprazole, one aripiprazole and pimozide.

[b] Seven fluvoxamine, one fluvoxamine and sertraline, one sertraline, one paroxetine, one fluoxetine, three citalopram, one nortriptyline and one amitriptyline.

[c] Three valproate, one lithium.

negative symptoms ($Q = 32.23$, $p < 0.0001$), PANSS positive symptoms ($Q = 20.89$, $p < 0.0001$), PANSS total symptoms ($Q = 31.33$, $p < 0.0001$) and CGI-S ($Q = 9.16$, $p = 0.01$). *Post-hoc* Wilcoxon signed-rank tests revealed a significant improvement between t0 and t26 in PANSS negative symptoms ($r = 0.53$), PANSS positive symptoms ($r = 0.50$) and PANSS total symptoms ($r = 0.54$). Improvement of CGI-S did not survive the Holm–Bonferroni correction and showed a positive trend with a moderate ES ($r = 0.36$). After Wilcoxon signed-rank *post-hoc* tests the same primary outcome variables showed significant improvement between t26 and t52: PANSS negative symptoms ($r = 0.51$), PANSS positive symptoms ($r = 0.39$) and PANSS total symptoms ($r = 0.51$). Once again, improvement of CGI-S did not survive the Holm–Bonferroni correction ($r = 0.34$). However, between t0 and t52 a *post-hoc* Wilcoxon signed-rank test revealed a large significant improvement of CGI-S ($r = 0.67$, $p = 0.001$).

A *post-hoc* analysis of the two dimensions of negative symptoms (Liemburg *et al.* 2013) showed a substantial significant effect of memantine add-on therapy on expressive deficits between t0 and t26 ($r = 0.40$, $p = 0.006$) and between t26 and t52 ($r = 0.34$, $p = 0.022$). Similar results were found for social amotivation at t26 ($r = 0.35$, $p = 0.016$) and t52 ($r = 0.48$, $p = 0.001$).

A *post-hoc* analysis of PANSS subscales (van der Gaag *et al.* 2006) showed moderate significant

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

Table 2. *Results and analysis of primary and secondary treatment effects of memantine addition to clozapine*

Variable	Time = 0 – 26 – 52 weeks (n = 24)		Time = 0 weeks (n = 24)	Time = 26 weeks (n = 24)			Time = 52 weeks (n = 23)		
	Q	p	Mean (S.D.)	Mean (S.D.)	ES r	p	Mean (S.D.)	ES r	p
Primary outcome parameters									
Cognitive domains and CANTAB tasks									
Verbal memory									
VRM free recall – total correct (phase 1)	3.39	0.18	4.7 (1.87)	3.96 (1.43)	N.A.	N.A.	4.96 (1.70)	N.A.	N.A.
VRM recognition – total correct	1.22	0.54	21.30 (1.92)	21.83 (1.86)	N.A.	N.A.	21.09 (1.81)	N.A.	N.A.
Associative learning and short-term visuospatial memory									
PAL total errors (adjusted)	0.31	0.86	60.41 (40.92)	62.92 (46.43)	N.A.	N.A.	61.13 (40.16)	N.A.	N.A.
PAL first trial memory score	0.16	0.92	10.64 (6.64)	10.13 (6.33)	N.A.	N.A.	10.87 (6.82)	N.A.	N.A.
Memory composite	2.47	0.29	−0.39 (2.32)	−0.29 (2.52)			−0.44 (2.93)	N.A.	N.A.
Working visuospatial memory/strategy use									
SWM strategy	0.07	0.97	17.64 (4.19)	17.33 (4.35)	N.A.	N.A.	16.82 (4.98)	N.A.	N.A.
SWM between errors	0.74	0.69	21.36 (10.51)	19.67 (11.30)	N.A.	N.A.	18.45 (13.68)	N.A.	N.A.
Visual planning, reasoning and impulsivity									
OTS problems solved on first choice	0.33	0.85	6.70 (3.57)	7.42 (4.08)	N.A.	N.A.	7.55 (3.58)	N.A.	N.A.
Executive function composite			−0.21 (2.48)	−0.27 (2.52)	N.A.	N.A.	−0.24 (3.17)	N.A.	N.A.
CGI-S	9.16	0.01[a]	5.54 (0.78)	5.21 (0.78)	0.36	0.011	4.87 (0.69)	0.34	0.02
PANSS-N	32.23	<0.0001[a]	17.33 (6.23)	15.17 (6.12)	0.53	<0.001*	13.65 (5.93)	0.51	<0.001*
PANSS-P	20.89	<0.0001[a]	15.00 (3.65)	12.96 (2.93)	0.50	0.001*	11.96 (2.55)	0.39	0.006*
PANSS total	31.33	<0.0001[a]	60.25 (14.16)	53.42 (14.07)	0.54	<0.001*	50.52 (13.80)	0.51	<0.001*
Secondary outcome parameters									
Reading the Mind in the Eyes test	1.17	0.56	18.55 (3.43)	19.14 (4.78)	N.A.	N.A.	18.86 (4.27)	N.A.	N.A.
CANTAB ERT % correct	0.30	0.86	48.54 (11.14)	43.64 (17.11)	N.A.	N.A.	49.58 (12.69)	N.A.	N.A.
CDSS	4.55	0.10	2.88 (3.55)	2.17 (3.23)	N.A.	N.A.	1.22 (2.19)	N.A.	N.A.
Y-BOCS total	1.41	0.49	3.46 (6.44)	2.71 (5.53)	N.A.	N.A.	1.35 (3.61)	N.A.	N.A.
HoNOS total	18.99	<0.0001[a]	13.58 (8.04)	11.00 (6.46)	0.33	0.018†	5.92 (3.25)	0.49	<0.001†
MANSA	1.25	0.53	63.79 (10.9)	64.75 (8.68)	N.A.	N.A.	66.78 (7.13)	N.A.	N.A.

Q, Test statistic Skillings–Mack; S.D., standard deviation; ES, effect size (r) = Z/sqrt(N); CANTAB, Cambridge Neuropsychological Test Automated Battery; VRM, verbal recognition memory-immediate (free recall) and verbal recognition memory-delayed (recognition); N.A., not applicable, since the Skillings–Mack test indicated no significant differences between the three repeated measurements; PAL, paired associates learning; SWM, spatial working memory; OTS, One Touch Stockings of Cambridge; CGI-S, Clinical Global Impression Severity Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-N, PANSS negative subscale; PANSS-P, PANSS positive subscale; PANSS total, PANSS total symptom score; ERT, emotion recognition task; CDSS, Calgary Depression Scale for Schizophrenia; Y-BOCS total, Y-BOCS total symptom score; HoNOS total, Health of the Nation Outcome Scales total symptom score; MANSA, Manchester Short Assessment of Quality of Life.

[a] Skillings–Mack test indicated significant differences between the three repeated measurements at baseline, t = 26 weeks and t = 52 weeks.

* Significant beneficial effect after Holm–Bonferroni correction for two *post-hoc* tests and four primary observation scales (α = 0.0062).

† Significant beneficial effect after Holm–Bonferroni correction for two *post-hoc* tests (α = 0.025).

improvement of excitement ($r = 0.37$, $p = 0.009$) and emotional distress ($r = 0.47$, $p = 0.001$) after *post-hoc* Wilcoxon signed-rank tests between t0 and t26. *Post-hoc* Wilcoxon signed-rank tests revealed substantial improvement of disorganization between t0 and t26 ($r = 0.54$, $p < 0.001$) and between t26 and t52 ($r = 0.38$, $p = 0.011$).

The Skillings–Mack test indicated significant differences between the three repeated measurements for a single secondary outcome variable: the HoNOS. After Wilcoxon signed-rank *post-hoc* tests the HoNOS showed significant improvement between t0 and t26 ($r = 0.33$) and again between t26 and t52 ($r = 0.49$). Social cognition, depressive symptoms, obsessive–compulsive symptoms and subjective quality of life did not significantly change during the study.

One patient discontinued memantine at t26 after a period of non-compliance. Discontinuation was not related to memantine treatment.

Possible confounders

Clozapine dosage (mean 333 mg, range = 75–700 mg) remained unaltered in all but four subjects and alterations in concomitant medications were limited to seven subjects (see online Supplementary Table S2). During the extension study psychotherapy and use of substances did not change significantly. One patient started using ecstasy on a weekly basis after 26 weeks, whereas he had not used this psychoactive substance during the first 6 months of the extension study. External factors which were deemed to be not related to memantine treatment triggered ecstasy abuse.

Safety and tolerability

Memantine did not affect liver and renal function or metabolic parameters, such as waist circumference, blood pressure, blood glucose, or lipids. There was no significant increase in reported side effects assessed by LUNSERS (see Table 3).

Table 4 represents AEs. Only two AEs were possibly related to memantine: both regurgitation and mycosis are rare side effects of memantine ($\geqslant$1/1000 and $\leqslant$1/100). An alternative cause for regurgitation was a high plasma clozapine level in this patient. A hazard for the development of transient mycosis in the other patient was labour in an animal shelter. No serious AEs were observed.

Discussion and conclusions

In our former placebo-controlled crossover study (n = 52) we found a small improvement of memory and negative symptoms after 12 weeks of memantine treatment (Veerman *et al.* 2016). The current 1-year extension study provided an opportunity to find an indication whether further improvement can be expected from long-term memantine treatment of clozapine-refractory schizophrenia.

In the former placebo-controlled trial memantine showed a small significant improvement of memory after 12 weeks of treatment. This effect was sustained in the extension study without further improvement. Both the placebo-controlled trial and the extension study failed to show any effect of memantine on executive function.

While in the placebo-controlled trial negative symptoms significantly improved with a small ES, in the extension study negative symptoms ameliorated further, with a large ES between t0 and t26 and between t26 and t52. In the placebo-controlled trial a non-significant small effect was found for one subdomain: diminished expression ($d = 0.17$). An equal and moderate effect of memantine on expressive deficits and social amotivation was found after t26 and t52.

Although positive and overall symptoms of schizophrenia did not significantly improve in the placebo-controlled trial, these symptoms showed substantial significant improvement after 26 weeks of memantine adjunctive treatment, followed by even further improvement at t52. The ESs ranged from moderate to large.

Whereas in the primary placebo-controlled study only memory and negative symptoms significantly improved, in the 1-year extension study most outcomes (negative symptoms, positive symptoms, overall symptoms and impairments in psychosocial functioning) showed improvement, with moderate to large ESs. Long-term beneficial effects of memantine were also reflected in a moderate positive trend of the CGI-S at t26 and t52.

Memantine was well tolerated without significant change in side effects or metabolic parameters. No serious AEs were reported.

In summary, positive long-term effects of memantine add-on therapy to clozapine were found on nearly all aspects of interest, except executive function, social cognition, depressive symptoms, obsessive–compulsive symptoms and subjective quality of life.

A possible explanation for the more substantial beneficial effects in the extension study compared with the placebo-controlled study is the longer treatment duration. It is conceivable that the 12-week treatment period with memantine in the placebo-controlled trial was too short and that clinical improvement would have occurred in more subjects in the placebo-controlled trial if memantine add-on therapy had been extended for a longer period. After 1 year of memantine addition to clozapine we found moderate to large beneficial effects for most outcomes. These effects were more substantial than in the double-blind trial, but still not

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

Table 3. *Side effects and safety measures*

Variable	Time = 0 weeks (n = 24)	Time = 26 weeks (n = 24)	Time = 52 weeks (n = 23)
Memantine-related AE mycosis, n (%)			
None	18 (75.0)	19 (79.2)	15 (65.2)
Very little	2 (8.3)	5 (20.8)	4 (17.4)
Little	3 (12.5)		2 (8.7)
Much	0		2 (8.7)
Very much	1 (4.2)		
Memantine-related AE dyspnoea, n (%)			
None	10 (41.7)	11 (45.8)	14 (60.9)
Very little	2 (8.3)	5 (20.8)	3 (13.0)
Little	8 (33.3)	4 (16.7)	4 (17.4)
Much	1 (4.2)	3 (12.5)	2 (8.7)
Very much	3 (12.5)	1 (4.2)	0
LUNSERS: mean (S.D.)			
Extrapyramidal symptoms	13.5 (5.1)	12.6 (4.1)	12.5 (4.8)
Anticholinergic side effects	8.6 (4.0)	8.7 (3.7)	9.0 (4.0)
Other autonomic side effects	9.3 (3.6)	9.1 (3.7)	9.4 (4.0)
Allergic reactions	5.1 (2.0)	5.3 (1.9)	5.5 (2.2)
Psychological side effects	24.5 (8.7)	22.8 (7.5)	21.4 (6.7)
Hormonal side effects	6.5 (2.4)	6.9 (2.9)	6.6 (2.7)
Miscellaneous side effects	6.8 (1.9)	6.7 (1.8)	6.8 (1.9)
Red herrings	14.9 (4.5)	15.2 (4.4)	15.0 (5.2)
Red herrings $\geqslant$20	0.80 (0.28)	0.17 (0.38)	0.22 (0.42)
Total	94.0 (24.7)	91.6 (23.9)	90.6 (26.2)
Total without red herring items	79.1 (20.9)	76.4 (20.1)	75.6 (21.4)
Laboratory measurement: mean (S.D.)			
Clozapine daily dose, mg	338.5 (160.7)	332.3 (166.4)	322.8 (163.4)
Clozapine plasma level, ng/ml	512.6 (247.8)	453.3 (196.3)	433.6 (216.0)
Range, ng/ml	90–1050	80–794	53–857
Physical examination: mean (S.D.)			
Waist circumference, cm	106.2 (16.4)	104.9 (15.3)	105.1 (15.0)
Systolic blood pressure, mmHg	127.3 (17.8)	126.5 (13.5)	120.5 (11.1)
Diastolic blood pressure, mmHg	81.4 (9.4)	82.9 (9.2)	80.9 (8.7)

AE, Adverse event; LUNSERS, Liverpool University Neuroleptic Side-Effect Rating Scale; S.D., standard deviation.

as large as the very large ESs of the short-term RCT by de Lucena *et al.* (2009). This discrepancy may be explained by the differences in patient population. Our participants were older (mean 7.7 years older), more severely ill (CGI-S scores 6.15 *v.* 5.34) due to severe cognitive impairments, and had been suffering from schizophrenia for a longer period of time (mean 5.04 years longer). Therefore, substantial improvement of symptoms may have been more difficult to reach in our patient population.

Our results must be interpreted within their limitations. Because only three patients chose to participate without adjunctive memantine treatment, we were unable to compare the intervention group with a control group. Moreover, the open-label design is susceptible to bias such as observer and participant expectancy effects, which may have resulted in overestimation of the beneficial effects of memantine (Sackett, 1979; Fisher & Greenberg, 1993; Crow *et al.* 1999). However, these biases are thought to have a more modest influence on CANTAB results (Barnett *et al.* 2010). Furthermore, subjective quality of life was not rated as significantly improved, at least showing that expectancy was not pervasive to all outcome domains. This is supported by measurements of expectations in participants before the extension phase. In our patient population the measured expectations of efficacy of memantine were very small to small in approximately 50%. Furthermore, no association was found between expectation scores and experienced effect of memantine (data not shown). Another potential bias is participation in a medication trial, which might possibly lead to better care and adherence which in turn might mediate better outcomes (Kinon *et al.* 2011). However, participating patients did not receive any extra attention or treatment apart from being given memantine

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

Table 4. *Adverse events*

Adverse event	Memantine add-on therapy	No add-on therapy	Time, weeks
No adverse event	15	1	
Increase in menopausal hot flashes	1		1
Mycosis (vagina/feet/hands)	1		4/24/34
Increase in paranoia	2		16/20
Nausea and vomiting		1	17
Reflux and dysphagia/urinary tract infection	1		25/36
Influenza-like symptoms/urinary tract infection	1		26/47
Collapse/hemifacial spasm/vitamin D deficiency		1	27/39/39
Dizziness	1		28
Disorientation and incoherent thought	1		30
Elevated triglycerides and cholesterol	1		37
Abdominal pain	1		42

and participating in three assessment sessions – at t0, at t26 and at t52. Substantial improvement due only to these three sessions seems unlikely. Practice effects for the CANTAB due to serial cognitive assessments are another possible limitation. In healthy subjects some CANTAB tests show low test–retest relability, in particular tests on executive function (Lowe & Rabbitt, 1998). Test–retest stability is lower in patients with schizophrenia (Beglinger *et al.* 2003). Practice effects in patients with severe cognitive impairments suffering from refractory schizophrenia are even more improbable. In our study comparisons of verbal memory were even less compromised than other cognitive domains, because the second VRM task differed from the first and third VRM tasks. Because the interval was 26 weeks between three cognitive assessments, significant practice effects in this patient population were highly unlikely.

Considering that robust evidence is limited for treatment options for residual symptoms in clozapine-refractory schizophrenia, future studies are imperative to find effective approaches. The presently available results on memantine in combination with clozapine in refractory schizophrenia should encourage a large, double-blind, placebo-controlled trial with a treatment duration of at least 26 weeks in order to ascertain any beneficial effects of memantine. In patients with less severe residual symptoms, memantine may have even stronger beneficial effects after a shorter treatment period, given the large ESs that de Lucena *et al.* (2009) found in this group. Because renal clearance of memantine is superior in adult patients compared with elderly, a higher dosage of 30–40 mg is thought to be safe (Wiech *et al.* 2001, 2004; Areosa & Sherriff, 2003; Beister *et al.* 2004; Schwenkreis *et al.* 2005; Ferguson & Shingleton, 2007; Schifitto *et al.* 2007) and may prove to be more efficacious. It is also conceivable that memantine has more efficacy in patients in the early stages of schizophrenia when neurodegenerative changes are more limited. At present no dose-ranging study has been conducted in schizophrenia patients. It would be interesting to investigate dose-dependent effects of memantine, because a higher dosage than 20 mg may yield more improvement. Future study could also include younger clozapine-treated patients with TRS. In our study as well as previous clinical trials in patients with TRS the effect of memantine on parameters of central glutamatergic transmission and brain activity was not assessed. In future studies it would be interesting to use ^{1}H-MRS and fMRI to investigate whether memantine normalizes glutamate levels and brain activity in TRS and whether this is related to treatment effects.

Given the paucity of efficacious pharmacological options for clozapine-refractory schizophrenia patients, adjunctive memantine is an interesting treatment option based on the glutamate hypothesis, two positive double-blind, placebo-controlled RCTs, and the current open-label extension study.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291716002476

Acknowledgements

This research received no specific grant from any funding agency, commercial or not-for-profit sectors. This work was funded by the Community Mental Health Division of Mental Health Service Noord-Holland Noord. We thank the participants of this study for their dedication and commitment and their care providers for their assistance and support. We also thank

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

M. Monden for his contribution to the excellent training of the raters.

Declaration of Interest

S.R.T.V. and J.B.D. report no financial relationships with commercial interests. P.F.J.S. reports personal fees from H. Lundbeck A/S, unrelated to the present work, and is a board member of the Dutch Clozapine Collaboration Group. L.d.H. has received investigator-led research grants or reimbursement for presenting his research from Eli Lilly, Bristol-Myers Squibb, Janssen-Cilag and AstraZeneca.

References

Addington D, Addington J, Schissel B (1990). A depression rating scale for schizophrenics. *Schizophrenia Research* **3**, 247–251.

Agid O, Foussias G, Singh S, Remington G (2010). Where to position clozapine: re-examining the evidence. *Canadian Journal of Psychiatry* **55**, 677–684.

Anderson VM, McIlwain ME, Kydd RR, Russell BR (2015). Does cognitive impairment in treatment-resistant and ultra-treatment-resistant schizophrenia differ from that in treatment responders? *Psychiatry Research* **230**, 811–818.

Andreasen NC, Carpenter Jr. WT, Kane JM, Lasser RA, Marder SR, Weinberger DR (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *American Journal of Psychiatry* **162**, 441–449.

Areosa SA, Sherriff F (2003). Memantine for dementia. *Cochrane Database of Systematic Reviews*, issue 3, CD003154.

Barnett JH, Robbins TW, Leeson VC, Sahakian BJ, Joyce EM, Blackwell AD (2010). Assessing cognitive function in clinical trials of schizophrenia. *Neuroscience and Biobehavioral Reviews* **34**, 1161–1177.

Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M (1997). Another advanced test of theory of mind: evidence from very high-functioning adults with autism or Asperger syndrome. *Journal of Child Psychology and Psychiatry* **38**, 813–822.

Beglinger LJ, Ahmed S, Derby MA, Siemers E, Fastenau PS, Crawford-Miller J, Shekhar A, Kareken DA (2003). Neuropsychological practice effects and change detection in people with schizophrenia. *Schizophrenia Research* **62**, 191–194.

Beister A, Kraus P, Kuhn W, Dose M, Weindl A, Gerlach M (2004). The *N*-methyl-D-aspartate antagonist memantine retards progression of Huntington's disease. *Journal of Neural Transmission* **68**, 117–122.

Bourque J, Lakis N, Champagne J, Stip E, Lalonde P, Lipp O, Mendrek A (2013). Clozapine and visuospatial processing in treatment-resistant schizophrenia. *Cognitive Neuropsychiatry* **18**, 615–630.

Buchanan RW, Davis M, Goff D, Green MF, Keefe RS, Leon AC, Nuechterlein KH, Laughren T, Levin R, Stover E, Fenton W, Marder SR (2005). A summary of the FDA–NIMH MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophrenia Bulletin* **31**, 5–19.

Buckley P, Miller A, Olsen J, Garver D, Miller DD, Csernansky J (2001). When symptoms persist: clozapine augmentation strategies. *Schizophrenia Bulletin* **27**, 615–628.

Cerullo MA, Adler CM, Strakowski SM, Eliassen JC, Nasrallah HA, Nasrallah AT (2007). Memantine normalizes brain activity in the inferior frontal gyrus: a controlled pilot fMRI study. *Schizophrenia Research* **97**, 294–296.

Chatfield M, Mander A (2009). The Skillings–Mack test (Friedman test when there are missing data). *Stata Journal* **9**, 299–305.

Crow R, Cage H, Hampson S, Hart J, Kimber A, Thomas H (1999). The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. *Health Technology Assessment* **3**, 1–96.

Day JC, Wood G, Dewey M, Bentall RP (1995). A self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. *British Journal of Psychiatry* **166**, 650–653.

de Bartolomeis A, Balletta R, Giordano S, Buonaguro EF, Latte G, Iasevoli F (2013). Differential cognitive performances between schizophrenic responders and non-responders to antipsychotics: correlation with course of the illness, psychopathology, attitude to the treatment and antipsychotics doses. *Psychiatry Research* **210**, 387–395.

de la Fuente-Sandoval C, Reyes-Madrigal F, Mao X, León-Ortiz P, Rodríguez-Mayoral O, Solís-Vivanco R, Favila R, Graff-Guerrero A, Shungu DC (2015). Cortico-striatal GABAergic and glutamatergic dysregulations in subjects at ultra-high risk for psychosis investigated with proton magnetic resonance spectroscopy. *International Journal of Neuropsychopharmacology* **19**, pyv105.

de Lucena D, Fernandes BS, Berk M, Dodd S, Medeiros DW, Pedrini M, Kunz M, Gomes FA, Giglio LF, Lobato MI, Belmonte-de-Abreu PS, Gama CS (2009). Improvement of negative and positive symptoms in treatment-refractory schizophrenia: a double-blind, randomized, placebo-controlled trial with memantine as add-on therapy to clozapine. *Journal of Clinical Psychiatry* **70**, 1416–1423.

Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, McGuire PK (2014). Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biological Psychiatry* **75**, e11–e13.

Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD (2012). Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *American Journal of Psychiatry* **169**, 1203–1210.

Elkis H (2007). Treatment-resistant schizophrenia. *Psychiatric Clinics of North America* **30**, 511–533.

Ferguson JM, Shingleton RN (2007). An open-label, flexible-dose study of memantine in major depressive disorder. *Clinical Neuropharmacology* **30**, 136–144.

Fisher S, Greenberg RP (1993). How sound is the double-blind design for evaluating psychotropic drugs? *Journal of Nervous and Mental Disease* **181**, 345–350.

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ (1998). Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Archives of General Psychiatry* **55**, 1001–1008.

Frydecka D, Beszlej JA, Gościmski P, Kiejna A, Misiak B (2016). Profiling cognitive impairment in treatment-resistant schizophrenia patients. *Psychiatry Research* **235**, 133–138.

Gameiro Z, Esteves H (2015). Should we use memantine in obsessive–compulsive disorder? *European Psychiatry* **30**, 1502.

Glodzik L, King KG, Gonen O, Liu S, De Santi S, de Leon MJ (2008). Memantine decreases hippocampal glutamate levels: a magnetic resonance spectroscopy study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **32**, 1005–1012.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, Charney DS (1989). The Yale–Brown Obsessive Compulsive Scale. *Archives of General Psychiatry* **46**, 1012–1016.

Guy W (1976). Clinical Global Impression Scale. In *ECDEU Assessment Manual for Psychopharmacology-Revised*, pp. 218–222. US Department of Health, Education and Welfare, ADAMHA, NIMH Psychopharmacology Research Branch: Rockville, MD.

Holm S (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* **6**, 65–70.

Howes OD, Kapur S (2014). A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *British Journal of Psychiatry* **205**, 1–3.

Kahn RS, Sommer IE (2015). The neurobiology and treatment of first-episode schizophrenia. *Molecular Psychiatry* **20**, 84–97.

Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Keefe RS, Buchanan RW, Marder SR, Schooler NR, Dugar A, Zivkov M, Stewart M (2013). Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far? *Schizophrenia Bulletin* **39**, 417–435.

Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, Shungu DC (2012). Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured *in vivo* with proton magnetic resonance spectroscopy. *Archives of General Psychiatry* **69**, 449–459.

Kinon BJ, Potts AJ, Watson SB (2011). Placebo response in clinical trials with schizophrenia patients. *Current Opinion in Psychiatry* **24**, 107–113.

Lawrence NS, Ross TJ, Hoffmann R, Garavan H, Stein EA (2003). Multiple neuronal networks mediate sustained attention. *Journal of Cognitive Neuroscience* **15**, 1028–1038.

Lawrie SM, O'Donovan MC, Saks E, Burns T, Lieberman JA (2016). Towards diagnostic markers for the psychoses. *Lancet Psychiatry* **3**, 375–385.

Levaux MN, Potvin S, Sepehry AA, Sablier J, Mendrek A, Stip E (2007). Computerized assessment of cognition in schizophrenia: promises and pitfalls of CANTAB. *European Psychiatry* **22**, 104–115.

Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* **382**, 951–962.

Liemburg E, Catelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H; Genetic Risk and Outcome of Psychosis (GROUP) Investigators (2013). Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *Journal of Psychiatric Research* **47**, 718–725.

Lowe C, Rabbitt P (1998). Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Cambridge Neuropsychological Test Automated Battery. International Study of Post-Operative Cognitive Dysfunction. *Neuropsychologia* **36**, 915–923.

McShane R, Areosa SA, Minakaran N (2006). Memantine for dementia. *Cochrane Database of Systematic Reviews*, issue 2, CD003154.

Mouchlianitis E, Bloomfield MA, Law V, Beck K, Selvaraj S, Rasquinha N, Waldman A, Turkheimer FE, Egerton A, Stone J, Howes OD (2015). Treatment-resistant schizophrenia patients show elevated anterior cingulate cortex glutamate compared to treatment-responsive. *Schizophrenia Bulletin* **24**, 744–752.

Mukaka MM (2012). A guide to appropriate use of correlation coefficient in medical research. *Malawi Medical Journal* **24**, 69–71.

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese III FJ, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR (2008). The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability and validity. *American Journal of Psychiatry* **165**, 203–213.

Overbeek T, Schruers K, Griez E (1999). *MINI. Mini International Neuropsychiatric Interview. Dutch version* 5.0.0. *DSM-IV*. University of Maastricht: Maastricht, The Netherlands.

Priebe S, Huxley P, Knight S, Evans S (1999). Application and results of the Manchester Short Assessment of Quality of Life (MANSA). *International Journal of Social Psychiatry* **45**, 7–12.

Sackett DL (1979). Bias in analytic research. *Journal of Chronic Disease* **32**, 51–63.

Sani G, Serra G, Kotzalidis GD, Romano S, Tamorri SM, Manfredi G, Caloro M, Telesforo CL, Caltagirone SS, Panaccione I, Simonetti A, Demontis F, Serra G, Girardi P (2012). The role of memantine in the treatment of psychiatric disorders other than the dementias: a review of current preclinical and clinical evidence. *Central Nervous System Drugs* **26**, 663–690.

Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, Jarvik JG, Miller EN, Singer EJ, Ellis RJ, Kolson DL, Simpson D, Nath A, Berger J, Shriver SL, Millar LL, Colguhoun D, Lenkinski R, Gonzalez RG,

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press

Lipton SA; Adult AIDS Clinical Trial Group (ACTG) 301; 700 Teams; HIV MRS Consortium (2007). Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. *AIDS* **21**, 1877–1886.

Schwenkreis P, Witscher K, Pleger B, Malin JP, Tegenthoff M (2005). The NMDA antagonist memantine affects training induced motor cortex plasticity – a study using transcranial magnetic stimulation. *BMC Neuroscience* **6**, 35.

Thermenos HW, Goldstein JM, Buka SL, Poldrack RA, Koch JK, Tsuang MT, Seidman LJ (2005). The effect of working memory performance on functional MRI in schizophrenia. *Schizophrenia Research* **74**, 179–194.

Tomasi D, Ernst T, Caparelli EC, Chang L (2006). Common deactivation patterns during working memory and visual attention tasks: an intra-subject fMRI study at 4 Tesla. *Human Brain Mapping* **27**, 694–705.

Tomczak M, Tomczak E (2014). The need to report effect size estimates revisited. An overview of some recommended measures of effect size. *Trends in Sport Sciences* **21**, 19–25.

van der Gaag M, Hoffman T, Remijsen M, Hijman R, de Haan L, van Meijel B, van Harten PN, Valmaggia L, de Hert M, Cuijpers A, Wiersma D (2006). The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. *Schizophrenia Research* **85**, 280–287.

van Veldhuizen JR (2007). FACT: a Dutch version of ACT. *Community Mental Health Journal* **43**, 421–433.

Veerman SRT, Schulte PF, Begemann MJ, Engelsbel F, de Haan L (2014*a*). Clozapine augmented with glutamate modulators in refractory schizophrenia: a review and metaanalysis. *Pharmacopsychiatry* **47**, 185–194.

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

Veerman SRT, Schulte PF, Smith JD, de Haan L (2016). Memantine augmentation in clozapine-refractory schizophrenia: a randomized, double-blind, placebo-controlled crossover study. *Psychological Medicine* 46, 1909–1921.

Wesemann W, Sontag KH, Maj J (1983). Pharmacodynamics and pharmacokinetics of memantine. *Arzniemittelforschung* **33**, 1122–1134.

Wiech K, Kiefer RT, Töpfner S, Preiss H, Braun C, Unertl K, Flor H, Birbaumer N (2004). A placebo-controlled randomized crossover trial of the *N*-methyl-D-aspartic acid receptor antagonist, memantine, in patients with chronic phantom limb pain. *Anesthesia and Analgesia* **98**, 408–413.

Wiech K, Preissl H, Kiefer T, Töpfner S, Puali P, Grillon C, Birbaumer N (2001). Prevention of phantom limb pain and cortical reorganization in the early phase after amputation in humans. *Society for Neuroscience* **27**, 163–169.

Wing J, Lelliott P, Chaplin RH (1999). Reliability and validity of HoNOS (multiple letters). *Psychiatric Bulletin* **23**, 375.

World Medical Association (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Journal of the American Medical Association* **310**, 2191–2194.

Zdanys K, Tampi RR (2008). A systematic review of off-label uses of memantine for psychiatric disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **32**, 1362–1374.

Zierhut KC, Schulte-Kemna A, Kaufmann J, Steiner J, Bogerts B, Schiltz K (2013). Distinct structural alterations independently contributing to working memory deficits and symptomatology in paranoid schizophrenia. *Cortex* **49**, 1063–1072.

Zoccali R, Muscatello MR, Bruno A, Cambria R, Micò U, Spina E, Meduri M (2007). The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophrenia Research* **93**, 109–116.

https://doi.org/10.1017/S0033291716002476 Published online by Cambridge University Press