Memantine as treatment for compulsivity in child and adolescent psychiatry: Descriptive findings from an incompleted randomized, double-blind, placebo-controlled trial

Larissa Niemeyer [a],[1], Konstantin Mechler [a],[*],[1], Ralf W. Dittmann [a], Tobias Banaschewski [a], Jan Buitelaar [b], Sarah Durston [c], Alexander Häge [a]

[a] Pediatric Psychopharmacology, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
[b] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands
[c] Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht, the Netherlands

ABSTRACT

Background: Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are mental disorders with a considerable overlap in terms of their defining symptoms. The glutamatergic agent memantine appears to be a promising candidate for the treatment of ASD and OCD in children and adolescents. The aim of this study was to investigate the clinical efficacy and tolerability/safety of memantine in this population.
Methods: This randomized, double-blind, placebo-controlled multicenter add-on trial comprised patients aged 6 to 17; 9 years with a confirmed diagnosis of ASD and/or OCD. Participants were randomized to either memantine or placebo for 10 consecutive weeks, including an up-titration phase.
Results: A total of 7 patients were included in the study. N = 4 (57.1%) participants were treated with verum (memantine) and n = 3 (42.9%) received placebo. Patients receiving memantine showed a more pronounced reduction in their CY-BOCS score, as well as greater CGI-Improvement, compared to patients receiving placebo. No serious adverse events (SAEs) were reported.
Conclusions: Our findings, although based on a very small number of patients and therefore insufficient to draw clear conclusions, appear to be in line with the hypothesis that memantine is an effective, tolerable and safe agent for children and adolescents.
Trial registration: EudraCT Number: 2014-003080-38, Registered 14 July 2014, https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-003080-38.

1. Background

Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are mental disorders with a considerable overlap in terms of their defining symptoms [1–3]. Moreover, a longitudinal study by Meier et al. (2015) reported that compared to healthy controls, individuals diagnosed with ASD had a twofold higher risk of developing OCD later in life, and that OCD patients had a fourfold higher risk of ASD [4].

ASD is a lifelong condition with a highly variable clinical course throughout childhood and adolescence [5]. While a wide variety of intervention programs for children with autism exists (i.e. [6,7]), there

is currently no approved pharmacological treatment for the core symptoms of ASD [8,9]. Antipsychotics, psychostimulants or atomoxetine are often prescribed to control co-morbidities or specific symptoms like irritability, impulsivity and hyperactivity [10–12]. Risperidone and aripiprazole have been found to show a limited beneficial effect on core ASD symptoms, while often being accompanied by significant adverse events, e.g. weight gain and risk for metabolic syndrome, sedation or extrapyramidal syndromes [10,13,14].

OCD is characterized by repetitive thoughts or impulses (obsessions) and/or repetitive behaviors or mental acts (compulsions) and is mostly treated with cognitive behavioral therapy and/or selective serotonin

---

reuptake inhibitors (SSRIs) [15–17]. SSRI treatment of OCD in children and adolescents appears to be well tolerated and is associated with a 29–44% reduction of symptoms. However, since most patients are only partial responders, persistent low-grade symptoms and impairment are the norm [16,18,19].

Compulsivity is considered as a cross-disorder trait that is one of the core symptoms of several pediatric psychiatric disorders such as substance use disorder, ASD and OCD. It is defined as the repetitive and irresistible urge to perform a behavior, the experience of loss of control over this urge, the diminished ability to delay or inhibit certain thoughts or behaviors, and the tendency to perform repetitive acts in a habitual or stereotyped manner [20,21]. While the psychological mechanisms underlying the compulsive behavior in ASD and OCD differ (self-soothing vs. stress-reducing), the contributory biological mechanisms appear to be related [22,23]. Indeed, multiple neuroimaging studies have found an increased glutamatergic activity in the striatum and the anterior cingulate cortex in subjects with compulsivity (including ASD and OCD) compared with controls [23,24].

A proton magnetic resonance spectroscopy study in children and adolescents with ASD or OCD found that both groups had increased glutamate concentrations in the midline anterior cingulate cortex (ACC) compared to healthy controls [25]. There appeared to be no differences in glutamate levels between the two disorders, but a positive correlation between compulsive behavior and ACC glutamate concentration was reported [25]. Modulating glutamate release or its action at receptors in this brain region may therefore represent a possible treatment strategy for compulsivity.

Memantine is currently used for the treatment of Alzheimer's disease as an EMA (European Medicines Agency) and FDA (Food and Drug Administration) approved medication [26]. It antagonizes the action of glutamate at N-methyl-D-aspartate (NMDA) receptors, a glutamate receptor subfamily broadly involved in brain function [27]. Clinically, it is used as a 'cognitive enhancer', significantly improving not only cognitive function but also behavior, activities of daily living, and agitation [28].

In children and adolescents diagnosed with ASD, memantine has been used in both open-label and controlled trials [29,30]. It has further been used as an augmenting agent in adolescents and adults with OCD [31]. Hardan et al. (2019) conducted three phase 2 open-label trials (OLTs) assessing the efficacy and long-term tolerability/safety of memantine treatment in children with ASD. The authors concluded that no new safety concerns were evident. Moreover, although the a priori defined efficacy results (in primary outcome/s) were not achieved, the considerable improvements in mean Social Responsiveness Scale scores from baseline were presumed to be clinically important [32]. According to a systematic review on glutamatergic agents in the treatment of compulsivity and impulsivity in child and adolescent psychiatry performed as part of the TACTICS project (see below), three OLTs in patients with ASD suggested significant improvements in irritability, stereotypic behavior, hyperactivity, attention and memory. Furthermore, a very beneficial tolerability and safety record was reported and most adverse events (i.e. headache, dizziness, vomiting) resembled those seen in adult dementia populations [29].

With respect to OCD in children and adolescents, a single-case report of a 15-year old girl with chronic, severe and SSRI treatment-resistant OCD showed significant improvement when memantine was added to a previously ineffective citalopram treatment [33]. A review by Lu et al. (2018) regarding memantine treatment in adults found that memantine improved OCD symptoms (as stand-alone therapy or augmentation to SSRIs) in most published studies [34]. Similar results were reported by Modaressi et al. (2018), who conducted a randomized placebo-controlled trial in adults with SSRI-refractory OCD and concluded that memantine is an effective and well-tolerated augmentation in patients with severe OCD [35].

Based on the aforementioned findings, memantine appears to be a promising candidate for the treatment of ASD and OCD in children and adolescents, especially as, to date it has shown a good risk-benefit profile.

The present study is the first to investigate memantine treatment of compulsivity in children and adolescents with autism spectrum disorder (ASD) or obsessive-compulsive disorder (OCD), in an add-on, randomized, double-blind, placebo-controlled design. Clinical efficacy (improving symptoms of compulsivity) and tolerability/safety of the glutamatergic agent memantine were investigated in this population at four university-based clinical study sites: (1) Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany; (2) Departments of Neuroimaging and Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom; (3) Department of Child and Adolescent Psychiatry, Brain Center Rudolf, University Medical Center Utrecht, The Netherlands, and (4) Karakter Child and Adolescent Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands. This placebo-controlled clinical trial (GOAT trial (Glutamatergic medication in the treatment of Obsessive Compulsive Disorder and Autism Spectrum Disorder)) was part of the large, translational project TACTICS (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes; http://www.tactics-project. eu/) funded by the European Union (EudraCT Number: 2014-003080-38) [36].

2. Methods

The findings reported here are part of the exploratory GOAT trial within the TACTICS project. The study was approved by the Ethics Committee II of the Medical Faculty Mannheim, University of Heidelberg (January 2015). Further applications for ethical approvals in the UK (National Research Ethics Service Committee London – Camberwell St Giles) and in the Netherlands (Commissie Mensgebonden Onderzoek, Regio Arnhem-Nijmegen) were granted in June 2016 (Nijmegen), March 2017 (Utrecht) and June 2018 (London), respectively. Due to a small sample size, only descriptive statistical analyses of the data were performed (see Niemeyer et al. [50] for details on recruitment difficulties). This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline.

2.1. Trial design

Subjects and their parents/legal guardians received informed assent/ consent documents explaining the study and its potential risks and benefits. Informed assent and consent forms were signed before inclusion. The study was divided into three periods. Study period I was a 2-week screening and wash-out period (visits 1–2), during which patients were screened for eligibility, undergoing psychiatric screening tests and safety screening procedures. Furthermore, during this period, the intake of excluded medication as per study protocol was discontinued. Further details regarding concomitant medication may be obtained by accessing the published study protocol [36]. In study period II (visits 3–9; 8 weeks), patients were randomized into an active drug or placebo group in a 1:1 ratio. The dosage of the active agent/placebo depended on the patient's weight and was up-titrated over 2–3 weeks (depending on a dosing schedule by body weight). During study period III (visits 9–10; 2 weeks), study medication was down-titrated in a blinded fashion. For full details on the study procedures, see Hage et al. (2016) [36].

2.2. Study population

Overall, male or female patients with inpatient or outpatient status, aged 6 years (ASD patients)/8 years (OCD patients) to 17 years and 9 months at initial inclusion were enrolled.

We included patients with an IQ ≥ 70 (based on the Wechsler scales, four subtests) and a Clinical Global Impressions-Severity (CGI-S) score ≥4 at baseline (visit 3). Subjects with past or present clinically relevant somatic acute or chronic disorders, which in the opinion of the investigator might confound the results of tolerability/safety assessment, were excluded (for details, see Hage et al., 2016). Due to the described limited previous evidence regarding memantine in child and adolescent psychiatric populations, this study was intended to serve as a pilot study and designed accordingly. Therefore, in order to allow for descriptive analyses and further hypothesis generation and (ideally) more confirmatory statistical analyses, a total sample size of approx. N = 100 patients was planned for this study [36].

2.3. Assessments

Multiple different instruments were used for data acquisition, measuring rigid and compulsive patterns of behavior, severity of symptoms, and assessing tolerability/safety of the study drug:

- *Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)* [37]
- *Clinical Global Impression-Severity (CGI-S)* [38,39]
- *Clinical Global Impression-Improvement (CGI-I)* [38,39]
- *Children's Global Assessment (C-GAS)* [40]
- *Pediatric Adverse Event Rating Scale (PAERS)* [41]

Furthermore, blood and urine samples were collected at multiple study visits, vital signs, height and weight were measured, and electrocardiograms (ECGs) were performed. For full details and all instruments used, see Hage et al. (2016) [36].

2.4. Endpoints

Primary study endpoints were the baseline-to-endpoint change in compulsivity as measured by the CY-BOCS total score (clinical efficacy) and the rate of adverse events as reported in the PAERS (tolerability and safety). Additional endpoints were response rates measured with the CY-BOCS and CGI-I score; response was defined as an at least 30% reduction versus baseline (BL) in the CY-BOCS total score and a CGI-I score of 1 (very much improved) or 2 (much improved).

3. Results

3.1. Study population

In total, n = 7 patients (4 female, 3 male) with a mean age of 12.9 years (range 6–17 years) were included in the study (see Fig. 1):. N = 2 (28.6%) of the patients had a diagnosis of ASD, n = 4 (57.1%) had a diagnosis of OCD and n = 1 (14.3%) had a diagnosis of both disorders. N = 5 (71.4%) patients received concomitant psychotropic medication during the study period. N = 4 (57.1%) participants were treated with verum (memantine) and n = 3 (42.9%) received placebo. N = 2 patients (28.6%), one treated with memantine and one receiving placebo,
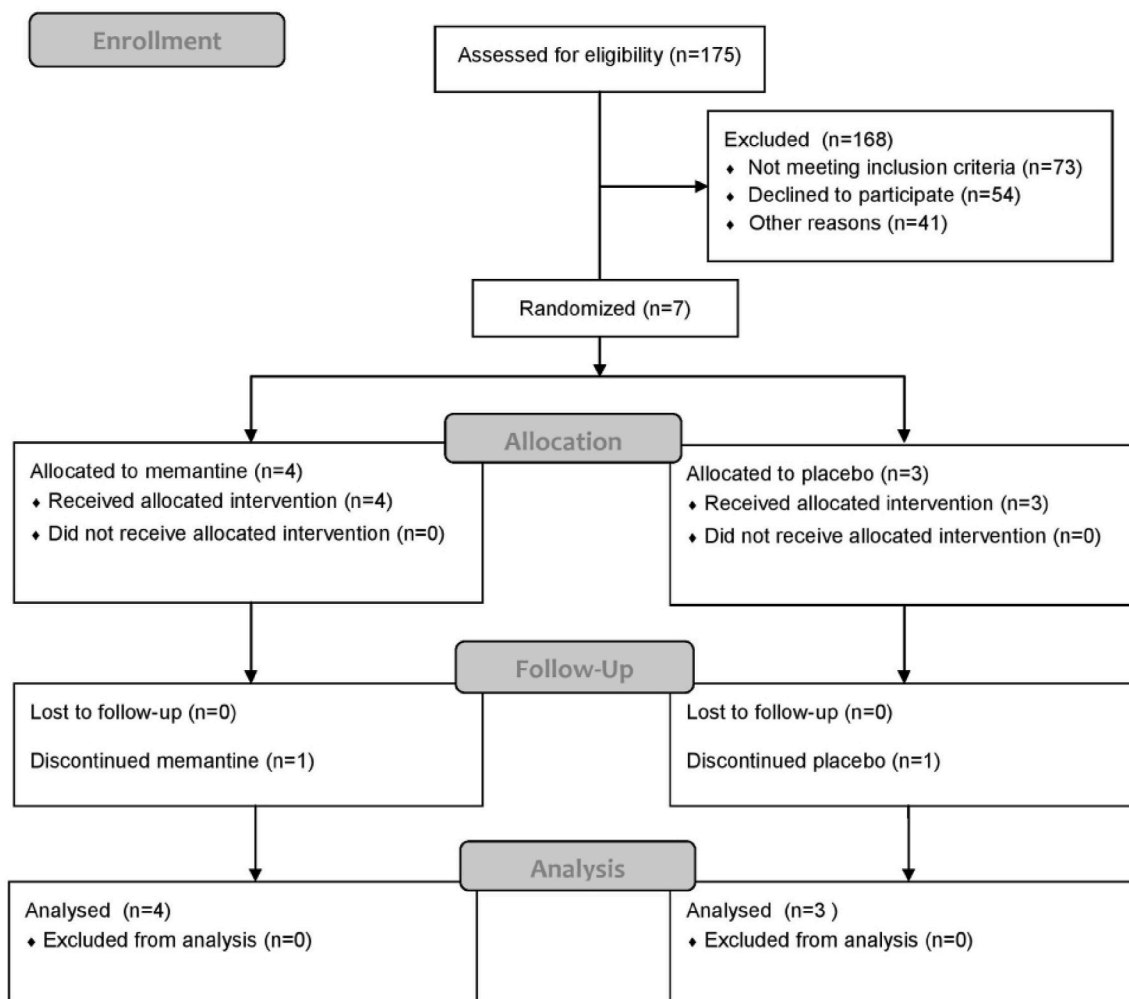

Fig. 1. CONSORT 2010 flow diagram.

discontinued the study early. Following an intention-to-treat approach these to participants were included in the presentation of the results here. Please see Table 1 for detailed information. Dosage was up-titrated depending on patients' weight, starting at 5 mg/d for all participants and ranging from 5 to 15 mg/d as the final dose.

3.2. Clinical effect

The CY-BOCS total score and subscores as well as the CGI-S and CGI-I were used to measure the severity of symptoms and their improvement (or deterioration) (for details on the study schedule, see Hage et al. (2016)). Additionally, the C-GAS was used at visits 3, 6 and 9 in order to rate participants' social and psychiatric functioning.

CY-BOCS total score reductions from baseline to end of treatment period were 5 points (26 → 21; 19.2%), 9 points (21 → 12; 42.9%), 7 points (30 → 23; 23.3%), and 5 points (22 → 17; 22.7%) in the memantine group and 0 points (0 → 0; 0%), 1 point (8 → 7; 12.5%), and 5 points (35 → 30; 14.3%) in the placebo group (see Fig. 2). The patient who showed 0% reduction in all CY-BOCS scores had a baseline score of 0, meaning that no improvement was possible in this case. Regarding CGI-I, at the end of the treatment period or at the early termination visit, in the memantine group two participants were rated as 'much improved', one as 'minimally improved' and one as 'minimally worse' while in the placebo group two participants were rated 'minimally improved' and one as 'no change' according to CGI-I. One participant in the memantine group (ID1) was rated as 'minimally worse' according to CGI-I despite a change in CGI-S from 'markedly ill' at baseline to 'moderately ill' at the end of treatment.

The mean change on the C-GAS lay at 9.5 points (range −3 to 24 points) for the memantine group and at 5.0 points (range 0–10 points) for the placebo group. The patient with a negative change discontinued the study early (shortly after visit 6).

3.3. Adverse events

Adverse events (AEs) were systematically recorded using the PAERS. Overall, n = 163 AEs were reported; out of these, n = 33 (20.2%) were classified as study drug-related, of which n = 22 (66.7%) were reported by participants treated with verum and n = 11 (33.3%) by participants receiving placebo. The most frequently reported AEs which were considered as study drug-related were sedation (n = 6; 18.2%) and stomach ache (n = 5; 15.2%), though both were reported by only one participant each. See Table 2 for detailed information. No serious adverse events (SAEs) were reported, and there were no early discontinuations due to adverse events.

3.4. Vital signs, weight and height

Data on blood pressure, pulse, weight and height were systematically collected. There were no substantial changes in these parameters over the study period in both treatment groups. All patients treated with memantine lost weight during the study period (range 1.2 kg–5.5 kg) whereas all participants receiving placebo experienced weight gain (0.3 kg–2.9 kg).

4. Discussion

To our knowledge, this is the first randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of memantine in the treatment of compulsivity in children and adolescents diagnosed with ASD or OCD. Our results, although originating from a very small sample of patients, are consistent with the hypothesis that memantine is an effective, tolerable and safe agent in children and adolescents suffering from these disorders.
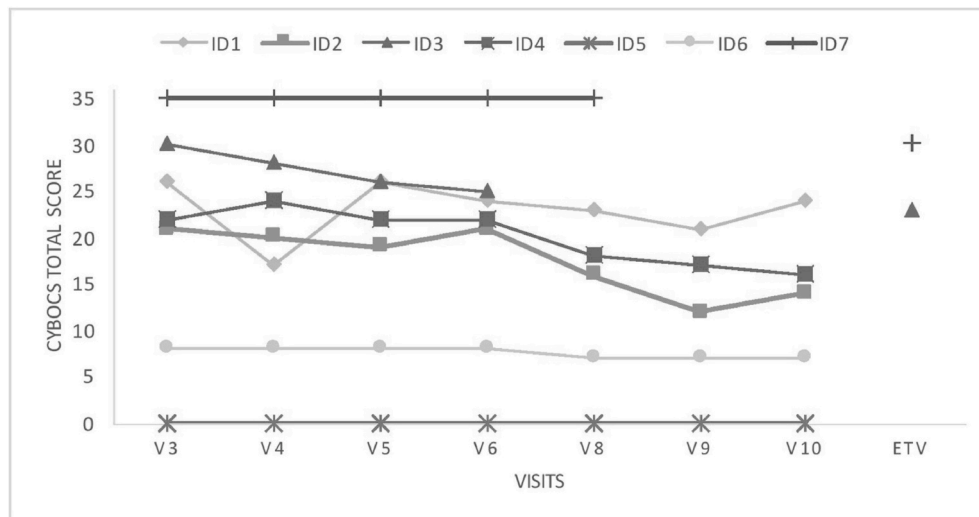
In this study, participants receiving verum, compared to those receiving placebo, numerically showed a greater reduction in the CY-BOCS total score and CY-BOCS compulsion subscore from baseline to end of treatment. In their study on SSRI-refractory OCD in an adult population, Modaressi et al. (2018) reported a significant reduction in the Y-BOCS total score in the memantine treatment group, while – in contrast to our results - no improvement was observed in the placebo group. The authors described a reduction of 40.9% in the mean Y-BOCS total score, resulting in 73.3% of patients achieving treatment response [35]. In line with these results, Marinova et al. (2017) reviewed multiple open-label and placebo-controlled trials on memantine treatment of OCD in adults, and summarized that patients receiving memantine showed a greater improvement in Y-BOCS scores compared to patients receiving placebo [42]. Stewart et al. (2010), e.g., found a mean Y-BOCS total score decrease of 27.0% (memantine group) compared to 16.5% (placebo group) in their single-blinded case-control study on adults with severe obsessive-compulsive disorder [43]. Similarly, in our small-sample pediatric study (N = 7), we found a mean reduction in the CY-BOCS total score of 27.03% (memantine group) and 13.4% (placebo group).

In accordance with these findings, in a randomized (memantine and risperidone group), open-label study in children and adolescents with ASD, Nikvarz et al. (2017) reported that after 8 weeks of treatment with memantine, 1 patient (6.7%) was very much improved, 7 patients (46.7%) much improved, 3 patients (20%) minimally improved and 4 patients (26.7%) showed no change as measured with the CGI-I [44]. Similar results were found in an open-label trial in which eleven of 18 (61%) adolescent ASD patients were considered responders to memantine based on a rating of "much improved" or "very much improved" on the CGI-I [45].

Interestingly, in our small sample, all four patients receiving memantine experienced weight loss over the study period, while patients receiving placebo experienced weight gain. Weight loss has so far not been mentioned as an adverse event of memantine, either in the treatment of elderly patients (with Alzheimer's disease) or in the treatment of children and adolescents. On the contrary, memantine has been considered as a favorable substance in the treatment of Alzheimer's disease, as a systematic literature review found that it did not cause weight loss, in contrast to cholinesterase inhibitors, which are often used for treatment in this population [46].

In accordance with previous findings, our study supports the perception that treatment with memantine in children and adolescents is well tolerated and safe [31]. Regarding study drug-related adverse events (AEs), cognitive impairment, sedation, sleep problems, stomach ache, constipation, vomiting and headache were reported in our verum

Table 1
Demographic data of participants.

Patient ID	Study site	Diagnosis	Gender	Age	Concomitant medication	Treatment
1	London	OCD	female	14	Sertraline	Verum
2	London	OCD + ASD	male	15	Sertraline, melatonin	Verum
3	Mannheim	OCD	female	17	Sertraline	Verum
4	Mannheim	OCD	female	15	Sertraline	Verum
5	Nijmegen	ASD	male	6	none	Placebo
6	Nijmegen	ASD	male	9	Risperidone, melatonin, methylphenidate	Placebo
7	Nijmegen	OCD	female	14	none	Placebo

No: Number; OCD: obsessive-compulsive disorder; ASD: autism spectrum disorder.

Fig. 2. CY-BOCS total scores for all included participants (receiving memantine or placebo) at all timepoints where CY-BOCS was assessed.
Light colors indicate memantine (ID1−ID4). Dark colors indicate placebo (ID5−ID7). ID 3: early termination visit (ETV) after visit 6; ID 7: early termination visit (ETV) after visit 8.

Table 2
Study drug-related adverse events.

	Memantine (N = 4) n N (%)		Placebo (N = 3) n N (%)	
Irritability	0	0	1	1 (33.3)
Cognition	2	1 (25)	0	0
Sedation	6	1 (25)	0	0
Sleep problems	1	1 (25)	2	1 (33.3)
Feeling hungry	0	0	4	1 (33.3)
Dizziness	0	0	2	1 (33.3)
Stomach ache	5	1 (25)	0	0
Constipation	3	1 (25)	0	0
Vomiting	3	1 (25)	0	0
Headache	2	2 (50)	2	1 (33.3)
Total	22	–	11	–

n: number of reported events; N: number of participants.

group, but – with the exception of headaches (described by two patients) – these AEs were only reported by one patient each. Similarly, in child and adolescent psychiatry, Erickson et al. (2007) described one patient (out of n = 18) with sedation and vomiting, and Nikvarz et al. (2017) reported somnolence in 2 patients (13.3%), insomnia in 2 patients (13.3%) and nausea in 1 patient (6.7%).

Furthermore, in their systematic review on memantine treatment in pediatric compulsivity and impulsivity, Mechler et al. (2018) [29] stressed that with the exception of headache (7.2%) and nasopharyngitis (5.3%), all of the AEs reported in the reviewed trials occurred in less than 5% of the reported patients. Interestingly, several trials found that (increased) irritability occurred (8–22%) under treatment with memantine [45,47,48]; in our study population, irritability was only reported by one patient, who was receiving placebo.

In contrast to a small number of study findings, but in line with multiple other study findings on memantine in children and adolescents, no serious adverse events (SAEs) or discontinuations due to AEs occurred in our study population [29,30,47].

Overall, our data do not contradict the hypothesis that memantine is an effective and well-tolerated agent for the treatment of compulsivity in children and adolescents with ASD and/or OCD.

Nevertheless, the findings of our study need to be interpreted in the context of several limitations. Even though recruitment took place in four international study centers, all with experience in performing pediatric psychopharmacology studies, and over the course of a total of 33 months, we were only able to include a total of N = 7 patients in the trial,

of whom only n = 5 (71.4%) completed the study. Due to this very small sample size, we were not able to perform statistical analyses and comparisons between the verum and placebo group. As is the case in many (pediatric) clinical psychopharmacology trials [49], low enrollment and high exclusion rates during the recruitment period raise the question of participants' representativeness of real-world patients and therefore the generalizability of the respective trial results [50]. Out of a total of N = 173 pre-screened patients, only n = 5 (2.9%) were eventually enrolled in the study. Out of the n = 168 not included patients, n = 73 (43.5%) failed to meet all of the trial inclusion criteria or met one or more of the exclusion criteria, n = 75 (44.6%) declined participation due to personal reasons, and n = 20 (11.9%) did not participate due to general or other reasons (e.g., not yet being stable on medication). Reasons for low enrollment in this study have been comprehensively analyzed and discussed separately [50].

Furthermore, due to randomization, only patients with OCD as their primary diagnosis were treated with memantine, whereas the two participants with ASD received placebo. No participants with a primary diagnosis of ASD received verum.

Despite these limitations, a specific strength of our study was the randomized, double-blind, placebo-controlled, multi-center study design, due to which, in principle, our results are more likely to accurately depict clinical response compared to open-label trials. All instruments used had been psychometrically validated and tested in various earlier clinical trials in this age group. By systematically and extensively recording adverse events and symptom severity, we could contribute and cautiously support the hypothesis that memantine is a well-tolerated, safe and effective agent in children and adolescents with OCD.

Additionally, to our knowledge, this is one of the very few studies in this patient population to be conducted without funding from the pharmaceutical industry. We were able to demonstrate that it is feasible to establish and implement a double-blind, placebo-controlled pediatric psychopharmacology clinical trial (formally registered in EudraCT, Number: 2014-003080-38) across several European centers and countries without support from the well-established clinical trial infrastructure and expertise of the pharmaceutical industry. More study centers, resources and funding as well as flexible timelines would most likely be helpful to increase the number of recruited patients and thus of completed clinical studies in pediatric psychopharmacology. Intensified private-public partnership programs ('PPP': cf. IMI = Innovative Medication Initiative; [51]) could offer an additional promising alternative in

this regard.

5. Conclusions

Our findings, although based on a very small number of patients and therefore insufficient to draw clear conclusions, appear to be in line with the hypothesis that memantine is an effective, tolerable and safe agent for children and adolescents with ASD and/or OCD. In this study, participants receiving verum, compared to those receiving placebo, showed a numerically greater reduction in the CY-BOCS total score and the CY-BOCS compulsion subscore from baseline to end of treatment. In accordance with previous findings, our study supports the perception that treatment with memantine in children and adolescents is well tolerated and safe; no serious adverse events (SAEs) or discontinuations due to AEs occurred in our study population.

Nevertheless, further research with more personnel and time resources as well as higher funding is needed to acquire larger study samples in order to complete a valid clinical development program for this patient population, and thus to provide a sound basis for drug registration and market authorization.

Our study findings appear to be consistent with the hypothesis that memantine is an effective, tolerable and safe agent in treating children and adolescents with ASD/OCD. As the currently existing therapeutic, including pharmaceutical, options to treat compulsivity are often insufficient, memantine still seems to be a promising treatment alternative. It is hoped that this incomplete study will contribute to stimulating further investigation in this field, as additional research on memantine in this population, possibly in larger study samples, is required.

Ethics approval and informed consent

This study was approved by the Ethics Committee II of the Medical Faculty Mannheim, University of Heidelberg (January 2015). Further applications for ethical approvals in the UK (National Research Ethics Service Committee London – Camberwell St Giles) and in the Netherlands (Commissie Mensgebonden Onderzoek, Regio Arnhem-Nijmegen) were granted in June 2016 (Nijmegen), March 2017 (Utrecht) and June 2018 (London). This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline.

Data sharing statement

The study protocol of this study has previously been published (Hage et al., 2016). All individual deidentified participant data leading to the presented results is included in this article. Additional data and other related documents can be made available by the authors upon request.

Funding

Author contributions

Larissa Niemeyer: Formal analysis, Writing – Original Draft, Writing – Review & Editing **Konstantin Mechler:** Methodology, Investigation, Formal analysis, Writing - Review & Editing.

Ralf W. Dittmann: Conceptualization, Funding acquisition, Project administration, Methodology, Investigation, Supervision, Writing – Review & Editing **Tobias Banaschewski** Conceptualization, Funding acquisition, Resources, Project administration, Methodology, Supervision, Writing – Review & Editing.

Jan Buitelaar: Conceptualization, Funding acquisition, Resources, Project administration, Methodology, Investigation, Supervision, Writing – Review & Editing.

Sarah Durston: Resources, Investigation, Supervision, Writing - Review & Editing.

Alexander Häge: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft, Writing – Review & Editing.

All authors provided critical feedback on the research. All authors critically revised the final manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2022.100982.

References

[1] S.E.A. Akkermans, N. Rheinheimer, M.M.K. Bruchhage, et al., Frontostriatal functional connectivity correlates with repetitive behaviour across autism spectrum disorder and obsessive-compulsive disorder, Psychol. Med. (Oct 26 2018) 1–9, https://doi.org/10.1017/s0033291718003136.

[2] H.M. Douglass, T.E. Moffitt, R. Dar, R. McGee, P. Silva, Obsessive-compulsive disorder in a birth cohort of 18-year-olds: prevalence and predictors, J. Am. Acad. Child Adolesc. Psychiatr. 34 (11) (Nov 1995) 1424–1431, https://doi.org/10.1097/00004583-199511000-00008.

[3] M.F. Flament, A. Whitaker, J.L. Rapoport, et al., Obsessive compulsive disorder in adolescence: an epidemiological study, J. Am. Acad. Child Adolesc. Psychiatr. 27 (6) (Nov 1988) 764–771, https://doi.org/10.1097/00004583-198811000-00018.

[4] S.M. Meier, L. Petersen, D.E. Schendel, M. Mattheisen, P.B. Mortensen, O. Mors, Obsessive-compulsive disorder and autism spectrum disorders: longitudinal and offspring risk, PLoS One 10 (11) (2015), e0141703, https://doi.org/10.1371/journal.pone.0141703.

[5] G. Baird, H. Cass, V. Slonims, Diagnosis of autism, BMJ 327 (7413) (Aug 30 2003) 488–493, https://doi.org/10.1136/bmj.327.7413.488.

[6] A.S. Carter, D.S. Messinger, W.L. Stone, S. Celimli, A.S. Nahmias, P. Yoder, A randomized controlled trial of Hanen's 'More than Words' in toddlers with early autism symptoms, J. Child Psychol. Psychiatry Allied Discip. 52 (7) (Jul 2011) 741–752, https://doi.org/10.1111/j.1469-7610.2011.02395.x.

[7] J. Virues-Ortega, F.M. Julio, R. Pastor-Barriuso, The TEACCH program for children and adults with autism: a meta-analysis of intervention studies, Clin. Psychol. Rev. 33 (8) (Dec 2013) 940–953, https://doi.org/10.1016/j.cpr.2013.07.005.

[8] J. Parr, Autism, Clin. Evid. (Jan 7 2010), 2010.

[9] E. Lemonnier, N. Villeneuve, S. Sonie, et al., Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders, Transl. Psychiatry 7 (5) (May 9 2017) e1124, https://doi.org/10.1038/tp.2017.101.

[10] B.H. Alfageh, Z. Wang, P. Mongkhon, et al., Safety and tolerability of antipsychotic medication in individuals with autism spectrum disorder: a systematic review and meta-analysis, Paediatric drugs (May 27 2019), https://doi.org/10.1007/s40272-019-00333-x.

[11] L. Fusar-Poli, N. Brondino, M. Rocchetti, et al., Prevalence and predictors of psychotropic medication use in adolescents and adults with autism spectrum disorder in Italy: a cross-sectional study, Psychiatr. Res. 276 (Jun 2019) 203–209, https://doi.org/10.1016/j.psychres.2019.04.013.

[12] S. Patra, N. Nebhinani, A. Viswanathan, R. Kirubakaran, Atomoxetine for attention deficit hyperactivity disorder in children and adolescents with autism: a systematic review and meta-analysis, Autism Res. : Off. J. Int. Soc. Autism Res. 12 (4) (Apr 2019) 542–552, https://doi.org/10.1002/aur.2059.

[13] G. Masi, A. Cosenza, S. Millepiedi, F. Muratori, C. Pari, F. Salvadori, Aripiprazole monotherapy in children and young adolescents with pervasive developmental disorders: a retrospective study, CNS Drugs 23 (6) (2009) 511–521, https://doi.org/10.2165/00023210-200923060-00005.

[14] N. Marrus, H. Underwood-Riordan, F. Randall, Y. Zhang, J.N. Constantino, Lack of effect of risperidone on core autistic symptoms: data from a longitudinal study, J. Child Adolesc. Psychopharmacol. 24 (9) (Nov 2014) 513–518, https://doi.org/10.1089/cap.2014.0055.

[15] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5®), American Psychiatric Pub, 2013.

[16] G. Krebs, I. Heyman, Obsessive-compulsive disorder in children and adolescents, Arch. Dis. Child. 100 (5) (May 2015) 495–499, https://doi.org/10.1136/archdischild-2014-306934.

[17] C. Westwell-Roper, S.E. Stewart, Challenges in the diagnosis and treatment of pediatric obsessive-compulsive disorder, Indian J. Psychiatr. 61 (Suppl 1) (Jan 2019) S119–s130, https://doi.org/10.4103/psychiatry.IndianJPsychiatry_524_18.

[18] E. Mancuso, A. Faro, G. Joshi, D.A. Geller, Treatment of pediatric obsessive-compulsive disorder: a review, J. Child Adolesc. Psychopharmacol. 20 (4) (Aug 2010) 299–308.

[19] D.A. Drubach, Obsessive-compulsive disorder, Continuum 21 (Jun 2015) 783–788, https://doi.org/10.1212/01.Con.0000466666.12779.07, 3 Behavioral Neurology and Neuropsychiatry.

[20] W.K. Goodman, D.E. Grice, K.A. Lapidus, B.J. Coffey, Obsessive-compulsive disorder, Psychiatr. Clin. 37 (3) (Sep 2014) 257–267, https://doi.org/10.1016/j.psc.2014.06.004.

[21] S.R. Chamberlain, N.A. Fineberg, A.D. Blackwell, T.W. Robbins, B.J. Sahakian, Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania, Am. J. Psychiatr. 163 (7) (Jul 2006) 1282–1284.

[22] T.W. Robbins, C.M. Gillan, D.G. Smith, S. de Wit, K.D. Ersche, Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry, Trends Cognit. Sci. 16 (1) (Jan 2012) 81–91, https://doi.org/10.1016/j.tics.2011.11.009.

[23] J. Naaijen, D.J. Lythgoe, H. Amiri, J.K. Buitelaar, J.C. Glennon, Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: a review of magnetic resonance spectroscopy studies, Neurosci. Biobehav. Rev. 52 (May 2015) 74–88, https://doi.org/10.1016/j.neubiorev.2015.02.009.

[24] D.R. Rosenberg, F.P. MacMaster, M.S. Keshavan, K.D. Fitzgerald, C.M. Stewart, G. J. Moore, Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine, J. Am. Acad. Child Adolesc. Psychiatr. 39 (9) (Sep 2000) 1096–1103.

[25] J. Naaijen, M.P. Zwiers, H. Amiri, et al., Fronto-Striatal glutamate in autism spectrum disorder and obsessive compulsive disorder, Neuropsychopharmacology : Off. Publ. Am. College Neuropsychopharmacol. 42 (Nov 2017) 2456–2465, https://doi.org/10.1038/npp.2016.260, 12.

[26] C.G. Parsons, A. Stoffler, W. Danysz, Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system–too little activation is bad, too much is even worse, Neuropharmacol 53 (6) (Nov 2007) 699–723, https://doi.org/10.1016/j.neuropharm.2007.07.013.

[27] J.W. Johnson, S.E. Kotermanski, Mechanism of action of memantine, Curr. Opin. Pharmacol. 6 (1) (Feb 2006) 61–67, https://doi.org/10.1016/j.coph.2005.09.007.

[28] S. Matsunaga, T. Kishi, N. Iwata, Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis, PLoS One 10 (4) (2015), e0123289, https://doi.org/10.1371/journal.pone.0123289.

[29] K. Mechler, A. Häge, N. Schweinfurth, et al., Glutamatergic agents in the treatment of compulsivity and impulsivity in child and adolescent psychiatry: a systematic review of the literature, Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie 46 (3) (May 2018) 246–263, https://doi.org/10.1024/1422-4917/a000546.

[30] D.A. Rossignol, R.E. Frye, The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review, Frontiers in pediatrics 2 (2014) 87, https://doi.org/10.3389/fped.2014.00087.

[31] S. Hosenbocus, R. Chahal, Memantine: a review of possible uses in child and adolescent psychiatry, Journal of the Canadian Academy of Child and *Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent* 22 (2) (May 2013) 166–171.

[32] A.Y. Hardan, R.L. Hendren, M.G. Aman, et al., Efficacy and safety of memantine in children with autism spectrum disorder: results from three phase 2 multicenter studies, Autism : Int. J. Res. Pract. (Apr 26 2019), 1362361318824103, https://doi.org/10.1177/1362361318824103.

[33] D.M. Hezel, K. Beattie, S.E. Stewart, Memantine as an augmenting agent for severe pediatric OCD, Am. J. Psychiatr. 166 (2) (Feb 2009) 237, https://doi.org/10.1176/appi.ajp.2008.08091427.

[34] S. Lu, H.A. Nasrallah, The use of memantine in neuropsychiatric disorders: an overview, Ann. Clin. Psychiatr. : Off. J. Am. Acad. Clin. Psychiatr. 30 (3) (Aug 2018) 234–248.

[35] A. Modarresi, M. Sayyah, S. Razooghi, K. Eslami, M. Javadi, L. Kouti, Memantine augmentation improves symptoms in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a randomized controlled trial, Pharmacopsychiatry 51 (6) (Nov 2018) 263–269, https://doi.org/10.1055/s-0043-120268.

[36] A. Häge, T. Banaschewski, J.K. Buitelaar, et al., Glutamatergic medication in the treatment of obsessive compulsive disorder (OCD) and autism spectrum disorder (ASD) - study protocol for a randomised controlled trial, Trials 17 (1) (Mar 17 2016) 141, https://doi.org/10.1186/s13063-016-1266-8.

[37] L. Scahill, M.A. Riddle, M. McSwiggin-Hardin, et al., Children's Yale-Brown obsessive compulsive scale: reliability and validity, J. Am. Acad. Child Adolesc. Psychiatr. 36 (6) (Jun 1997) 844–852.

[38] NIMH, Special feature: rating scales and assessment instruments for use in pediatric psychopharmacology research, Psychopharmacol. Bull. 21 (1985) 839–843.

[39] W. Guy, ECDEU Assessment Manual for Psychopharmacology, US Department of Health, and Welfare, 1976, pp. 534–537, 1976.

[40] D. Shaffer, M.S. Gould, J. Brasic, et al., A children's global assessment scale (CGAS), Arch. Gen. Psychiatr. 40 (11) (Nov 1983) 1228–1231.

[41] J. March, O. Karayal, A. Crisman, The pediatric adverse event rating scale, in: Proceedings of the 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, 2007.

[42] Z. Marinova, D.M. Chuang, N. Fineberg, Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder, Curr. Neuropharmacol. 15 (7) (2017) 977–995, https://doi.org/10.2174/1570159x15666170320104237.

[43] S.E. Stewart, E.A. Jenike, D.M. Hezel, et al., A single-blinded case-control study of memantine in severe obsessive-compulsive disorder, J. Clin. Psychopharmacol. 30 (1) (Feb 2010) 34–39.

[44] N. Nikvarz, J. Alaghband-Rad, M. Tehrani-Doost, A. Alimadadi, P. Ghaeli, Comparing efficacy and side effects of memantine vs. Risperidone in the treatment of autistic disorder, Pharmacopsychiatry 50 (1) (Jan 2017) 19–25, https://doi.org/10.1055/s-0042-108449.

[45] C.A. Erickson, D.J. Posey, K.A. Stigler, J. Mullett, A.R. Katschke, C.J. McDougle, A retrospective study of memantine in children and adolescents with pervasive developmental disorders, Psychopharmacology 191 (1) (Mar 2007) 141–147.

[46] J.S. Buckley, S.R. Salpeter, A risk-benefit assessment of dementia medications: systematic review of the evidence, Drugs Aging 32 (6) (Jun 2015) 453–467, https://doi.org/10.1007/s40266-015-0266-9.

[47] M.G. Aman, R.L. Findling, A.Y. Hardan, et al., Safety and efficacy of memantine in children with autism: randomized, placebo-controlled study and open-label extension, J. Child Adolesc. Psychopharmacol. 27 (5) (Jun 2017) 403–412, https://doi.org/10.1089/cap.2015.0146.

[48] C.A. Erickson, J.E. Mullett, C.J. McDougle, Open-label memantine in fragile X syndrome, J. Autism Dev. Disord. 39 (12) (Dec 2009) 1629–1635, https://doi.org/10.1007/s10803-009-0807-3.

[49] L. Bliznak, R. Berg, A. Hage, R.W. Dittmann, High rate of non-eligibility: methodological factors impacting on recruitment for a multicentre, double-blind study of paediatric patients with major depressive disorder, Pharmacopsychiatry 46 (1) (Jan 2013) 23–28, https://doi.org/10.1055/s-0032-1314806.

[50] L. Niemeyer, K. Mechler, J. Buitelaar, et al., Include me if you can"-reasons for low enrollment of pediatric patients in a psychopharmacological trial, Trials 22 (1) (Mar 1 2021) 178, https://doi.org/10.1186/s13063-021-05119-6.

[51] R.W. Dittmann, Rothenberger, Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie 47 (6) (Nov 2019) 489–494, https://doi.org/10.1024/1422-4917/a000690. Psychopharmakologieforschung in der Kinder- und Jugend- psychiatrie - Entwicklungen, Herausforderungen, Perspektiven.