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ORIGINAL PAPER

Open-Label Memantine in Fragile X Syndrome

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Abstract Glutamatergic dysfunction is implicated in the pathophysiology of fragile X syndrome (FXS). The purpose of this pilot study was to examine the effectiveness and tolerability of memantine for a number of target symptoms associated with FXS. Medical records describing open-label treatment with memantine in 6 patients with FXS and a comorbid diagnosis of PDD were reviewed. Six patients received memantine over a mean 34.7 weeks of treatment. Four of 6 (67%) patients showed global clinical benefit on ratings with the CGI-I. Symptom specific rating scales, however, showed no statistically significant improvement. Two patient developed treatment-limiting irritability on memantine. Memantine was modestly effective in several patients with FXS. Further systematic study is warranted.

Keywords Memantine · Fragile X syndrome · Inattention · Hyperactivity · Social withdrawal · Irritability

Introduction

Fragile X syndrome (FXS) represents the most common inherited form of intellectual disability. FXS is the result of a cysteine-guanine-guanine (CGG) trinucleotide repeat expansion (>200 repeats) within the fragile X mental retardation 1 gene (FMR1) located near the long arm of the X chromosome. FXS is inherited via triple repeat expansion from fragile X premutation (individuals with 55–200 repeats) or full mutation mothers. The disorder occurs in approximately 1 in 2,000–6,000 live births. Among all individuals with mental retardation, the prevalence of FXS is estimated to be between 1.9% (Gerard et al. 1997) and 6.0% (Florencia et al. 2006). Additionally, FXS is the most common known cause of autistic disorder, a developmental disorder marked by social impairment, communication delay, and interfering repetitive behaviors. Approximately 1 in 4 (25%) to 1 in 3 (33%) individuals with FXS are thought to additionally meet criteria for autistic disorder (Bailey et al. 2001; Rogers et al. 2001). Up to two-thirds of males with FXS may meet criteria for the broader autism phenotype (Clifford et al. 2007).

FXS is associated with a common genotype and a substantially increased risk, particularly in males, for a particular neurobehavioral phenotype marked by severe interfering behavioral symptoms in addition to cognitive delay. In addition to mental retardation, individuals, disproportionately males, with FXS often suffer from behavioral difficulties out-of-proportion to cognitive level (Berry-Kravis and Potanos 2004). Common behavioral and mood symptoms noted in FXS individuals include anxiety-related symptoms [shyness, social phobia, obsessive compulsive disorder (OCD)-like symptoms], attention deficit hyperactivity disorder (ADHD)-like symptoms (overarousal, hyperactivity, distractibility, impulsivity), and aggressive/self-injurious behaviors (SIB) (Berry-Kravis and Potanos 2004).

Glutamatatergic dysfunction has been implicated in the pathophysiology of FXS (Bassell and Gross 2008; Bear et al. 2008; 2004; Dolen and Bear 2008; Huber et al. 2002;

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Tervonen et al. 2008). Specifically, excessive neurotransmission at the Group 1 metabotropic glutamate receptor 5 (mGluR5) has been associated with failed transcription of FMR1 and subsequent lack of fragile X mental retardation protein (FMRP) (Bear 2005; Bear et al. 2004; Dolen and Bear 2008).

While significant drug development based upon findings in animal and cellular modeling is focused on attenuating excess mGluR5 activation in FXS (Bear 2005; Dolen and Bear 2005, 2008), dysregulated ionotropic glutamate receptor activity may also contribute to the pathophysiology of the disorder (Pilpel et al. 2008). Long-term changes in hippocampal brain development in FXS mice has been associated with an ionotropic glutamate receptor imbalance marked by downregulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and upregulation of *N*-methyl-D-aspartic acid (NMDA) receptors at 2 weeks of life with the difference resolving by 6–7 weeks of age (Pilpel et al. 2008). Hippocampal slices from FXS mice have shown an excess of long term depression (LTD) due to inappropriate AMPA and NMDA receptor internalization (Huber et al. 2002).

Memantine is an uncompetitive NMDA receptor antagonist used to treat moderate to severe Alzheimer's disease (Reisberg et al. 2003). Memantine exhibits rapid binding kinetics and voltage dependency causing NMDA receptor blockade at low synaptic glutamate levels, and release of blockade at high glutamate levels (Parsons and Gilling 2007). Among NMDA receptor antagonists, memantine has advantages over high-affinity antagonists such as phencyclidine, which have psychotomimetic effects (Mobius et al. 2004).

Memantine use has been the subject of several reports involving persons with idiopathic pervasive developmental disorders (PDDs). In 30 children and adolescents (mean age 8.9 years) with PDDs, Chez et al. (2004) reported on use of memantine (mean dose 8.1 mg/day) over 8-40 weeks of treatment (Chez et al. 2004). Though standardized measures were not used, 16 (53.3%) patients were rated as significantly improved and another 10 (33%) showed milder improvement. Improvement was noted in eye contact, repetitive behavior, attention, and language. In a second report, Chez et al. (2007) described the use of memantine (mean dose 12.67 mg/day) in 151 children and adolescents (mean age 9.31 years) with idiopathic autistic disorder or PDD not otherwise specified (NOS) (Chez et al. 2007). In this analysis, treatment effect was determined by clinician assignment of a Clinical Global Impressions-Improvement subscale (CGI-I) (Guy 1976) score during the initial 4–8 weeks of a mean 9.27 months of treatment. A total of 105 patients (70%) were considered treatment responders, including 34 (23%) rated as "very much improved" and 71 (47%) rated as "much improved" on the CGI-I. Improvement was noted primarily in use of language and social behavior with less significant improvement reported in self-stimulatory behaviors. Erickson et al. (2007) conducted a retrospective open-label study of memantine (mean dose 10.1 mg/day) in 18 persons (mean age 11.4 years, range 6–19 years) with a PDD (Erickson et al. 2007). Over a mean duration of treatment of 19.3 weeks, 11 patients (61%) were considered treatment responders with ratings of "much improved" or "very much improved" on the CGI-I. Significant improvement was primarily seen in social withdrawal and inattention. The majority of subjects received concomitant psychotropic drugs during the trials, and 7 patients (39%) experienced memantine associated adverse effects, including 4 (22%) with increased irritability. In a single case report, memantine (10 mg/day) was associated with decreased irritability during 32 weeks of treatment in a 23-year-old man with autism (Erickson and Chambers 2006). In another study, limited effect of memantine (target dose 0.4 mg/kg) in 14 male youth with PDDs was noted in an 8-week open-label prospective trial (Owley et al. 2006). In this report, only 4 patients (28%) showed minimal improvement, and none were rated as "much improved" or "very much improved" on the CGI-I. Improvement was, though, noted in patient memory and on several subscales of the Aberrant Behavior Checklist (ABC) (Aman et al. 1985), including hyperactivity, irritability, and lethargy. Five subjects (40%) experienced increased hyperactivity during the trial.

Memantine has been the subject of study in many areas outside of its approved use in Alzheimer's dementia and off-label use in PDDs. The drug was not effective in the treatment of major depressive disorder compared to placebo over 8 weeks in 32 adult patients (Zarate et al. 2006), but was associated with similar response to the antidepressant escitalopram in persons with major depressive disorder and comorbid alcohol dependence (Muhonen et al. 2008). In 44 adults, memantine was not associated with significant improvement in a 16-week double-blind placebo-controlled trial targeting symptoms of alcohol dependence (Evans et al. 2007). Memantine did not differentate from placebo in an 8-week trial of adjunctive therapy in 138 adults with schizophrenia (Lieberman et al. 2008). In 16 youth (ages 6–12 years) with ADHD, 20 mg/day of memantine was associated with larger mean improvement in symptoms over 8 weeks of open-label treatment compared to a 10 mg/day dose (Findling et al. 2007). In this pilot ADHD study, memantine was well tolerated with no drug discontinuations due to adverse effects.

Though glutamate dysregulation is clearly implicated in the pathophysiology of FXS, glutamatergic agents have been the subject of limited systematic study. The AMPA receptor-positive modulator (Ampakine) CX516 was not associated with improved memory, language, or attention/

executive function in a 4-week placebo-controlled trial in 49 adults with FXS (Berry-Kravis et al. 2006). The only published trial of an mGluR5 antagonist in FXS utilized single-dose fenobam (50-150 mg/dose) in twelve adults (mean age 23.9 years) with FXS (Berry-Kravis et al. 2009). Half of the subjects showed post-treatment improvement in prepulse inhibition and the drug was generally well tolerated. This pilot study was primarily designed to demonstrate the safety and aspects of the metabolism of fenobam.

Memantine was used in our FXS clinic to primarily treat behaviors commonly seen in FXS including social deficits, irritability, anxiety, and inattention. Our clinical use of memantine began after published studies involving the drug in persons with idiopathic PDDs. The overlap between FXS and PDDs, the exclusion of persons with FXS from autism and related disorder drug trials, and finally the implication of glutamate dysregulation in the pathophysiology of FXS all contributed to our use of memantine. We now report on a pilot open-label investigation of memantine in FXS.

Methods

The study sample consisted of outpatients treated at the James Whitcomb Riley Hospital for Children Child and Adolescent Psychiatry Fragile X Syndrome Clinic (Indianapolis, IN). All patients had a history of testing marked by an expansion mutation in the FMR1 gene with at least partial gene methylation that is consistent with the diagnosis of full mutation FXS by DNA analysis. Individuals in the study also were assessed for the presence of comorbid PDD. PDD diagnosis was made either by a child and adolescent psychiatrist (C.A.E.) using criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association 2000) (2 subjects) or by use of the Autism Diagnostic Observation Schedule (Lord et al. 1994) and Autism Diagnostic Interview-Revised (Lord et al. 1989) (4 subjects). Individuals in the study included all persons with FXS who received treatment with memantine. Memantine was dosed beginning at 5 mg per day, which was increased approximately every 2 weeks in 5 mg increments until clinical response was obtained or side-effects emerged, with a 20 mg maximum daily dose. Patients on concomitant medications had the doses of these medications held constant during the trial of memantine. Each patient's parent or legal guardian provided written informed consent for the treatment. Subject assent was obtained when possible. This study was approved by our local Institutional Review Board and, thus, has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Procedure

Medical records from all patients with a FXS diagnosis who received memantine were reviewed. Collected data included DSM-IV diagnoses (Axes I–III), race, age, gender, target symptoms, memantine dosage and duration, concomitant medications, and any documented adverse effects.

As part of routine care, the treating physician (C.A.E.) prospectively completed the CGI-Severity (S) and CGI-I (Guy 1976) at baseline and all subsequent clinic visits to document any change in target symptoms documented at baseline. The CGI-S item is rated from 1 to 7 (1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill). The CGI-I is also rated from 1 to 7 (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). The CGI-I ratings described change in target symptoms defined at the baseline visit.

All patients also had complete baseline and post-trial ABC data available. The ABC is a 58-item measure of maladaptive behaviors common to individuals with developmental disabilities. The ABC is widely used as a sensitive indicator of drug effects. The ABC is divided into five subscales: social withdrawal (16 items on social impairments), irritability (15 items on tantrums, mood swings, aggression, self-injury), inappropriate speech (4 items on loud, repetitive, or excessive speech), hyperactivity (16 items on inattention, hyperactivity, impulsivity, and noncompliance), and stereotypy (7 items on repetitive behavior). Five patients additionally had complete baseline and post-trial social responsiveness scale (SRS) (Constantino et al. 2003) data available. The SRS is a quantitative measure of autistic traits. Finally, 5 of 6 subjects had pre-trial and post-trial complete ADHD Rating Scale-IV (ADHDRS-IV) (DuPaul et al. 1998) data available.

Patients were considered treatment responders if their post-trial CGI-I rating was 1 or 2. All patients treated in our clinic with memantine before January 1, 2009 were included in the study.

Statistical Analysis

Data were coded and entered into the Statistical Package for Social Science (SPSS) version 13.0 (SPSS Inc. 2005). Descriptive statistics were calculated and presented as means ± standard deviation and range, unless otherwise noted. The Wilcoxan signed rank test (2-tailed) was used to examine differences between baseline and endpoint CGI-S, ABC subscale, SRS, and ADHDRS-IV scores. Statistical significance was set at $p < 0.05$ (2-tailed).

Results

Six patients (mean age 18.3 ± 3.8 years; range 13–22 years) met the study inclusion criteria. Of the six patients, 4 (67%) had a comorbid diagnosis of autistic disorder and the other 2 (33%) had an additional diagnosis of pervasive developmental disorder not otherwise specified (PDD-NOS).

The mean final memantine dosage prescribed was 18.3 ± 2.6 mg/day (range 15–20 mg/day). Mean trial duration was 34.7 ± 36.5 weeks (range 8–104 weeks). Four (67%) patients were receiving concomitant medications during the memantine trial. Target symptoms of treatment included repetitive behavior ($n = 4$), social impairment ($n = 4$), anxiety ($n = 4$), inattention ($n = 2$), and irritability ($n = 2$). All patients had more than one target symptom.

Analysis of CGI-S scores revealed a non-significant change from 4 ± 0.6 at baseline to 3.7 ± 0.8 posttrial ($p = 0.317$). Four (67%) of six patients were deemed responders by ratings of "much improved" ($n = 2$) or "very much improved" ($n = 2$) on the CGI-I. The two patients not responding to treatment had CGI-I ratings of "no change" and "minimally worse". For the sample as a whole, the mean CGI-I score at endpoint was between minimally and much improved (2.5 ± 1.5).

On the ABC, while mean scores on all subscales trended towards improvement, no changes were statistically significant (Fig. 1). Four of 5 (80%) patients with available SRS scores showed improvement, although again the difference was not significant ($p = 0.28$; Fig. 2). Four of 5 (80%) patients with available ADHDRS-IV data also showed improved scores, but once more the difference was not statistically significant ($p = 0.26$; Fig. 3).

Overall, adverse effects during treatment with memantine were recorded in 2 (33%) of 6 patients. Both of these patients suffered from increased irritability that led to premature drug discontinuation. No other adverse effects were recorded during memantine treatment. A comprehensive summary of demographic data and results is presented in Table 1.

The following clinical vignette describing the use of memantine captures some of the positive treatment effects associated with drug response in those patients who tolerated the drug.

Clinical Vignette

Patient 2 is a 19-year-old male with FXS, autistic disorder, and moderate mental retardation. Patient 2 was prescribed memantine to target irritability and social impairment. After beginning 5 mg of memantine daily, Patient 2's dose was increased to 10 mg daily after 2 weeks, 15 mg daily after 4 weeks, and then maintained through 104 weeks of treatment on 20 mg daily. At a 4-week follow-up phone call, Patient 2's caregivers reported improvement in irritable behavior that was previously marked by physical aggression including hitting and biting. His caregivers also reported he was increasingly social and showed willingness to interact more with family and peers in the home and in public. At his 8-week follow up appointment, Patient 2's caregivers continued to report significant improvement, including greater reduction in aggressive behaviors and enhanced social behavior. Prior to treatment with memantine, Patient 2 had begun to refuse to attend a structured employment program. His caregivers had also limited his time outside the home due to his extreme aggressive behavior. During treatment with memantine, Patient 2 was able to leave his home safely on a regular basis and return to his place of employment. Memantine was chosen for Patient 2 given that his behaviors had been refractory to treatment with a number of past agents including chlorpromazine, risperidone, aripiprazole, clonidine, valproic acid, imipramine, and lithium. He remained on stable doses of concomitant drugs including fluvoxamine, mirtazapine, and haloperidol during his treatment with memantine.

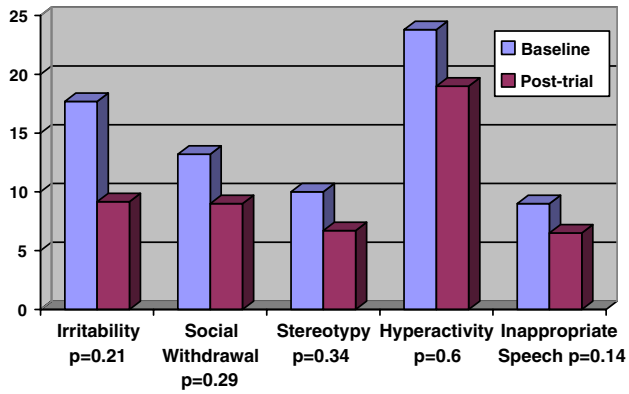

Fig. 1 Aberrant behavior checklist (*ABC*) subscale mean scores. No endpoints had significantly different scores pre- and post-trial

Discussion

In this pilot report, only modest global clinical treatment benefit was noted in 4 of 6 patients, but no statistically significant findings were identified among several outcome measures. For those who tolerated the drug, improvement was primarily noted in social behavior, inattention, and irritability. These results in 4 of 6 patients mirror results found in our previous report on the use of memantine in youth with idiopathic PDDs (Erickson et al. 2007).

In our FXS population, memantine use clinically reduced irritability in two subjects (Patients 1 and 2), but

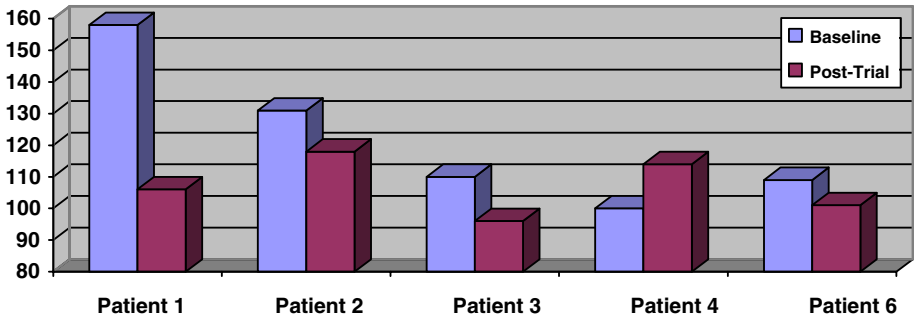

Fig. 2 Individual patient social responsiveness scale (*SRS*) scores (patient 5 did not have available SRS data)

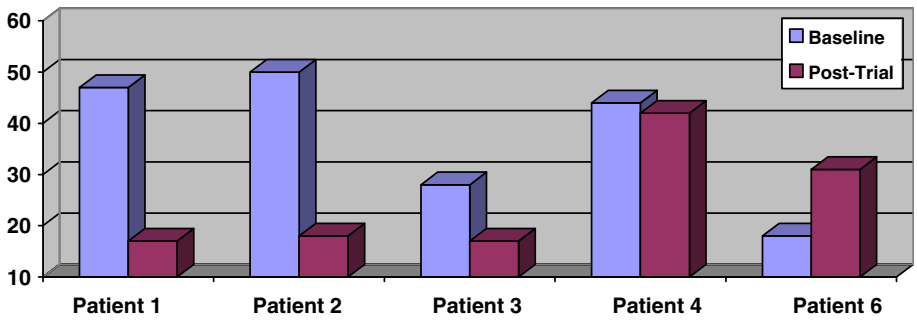

Fig. 3 Individual patient ADHD rating scale-iv (ADHDRS-IV) scores (patient 5 did not have available ADHDRS-IV data)

was associated with potentially causing increased irritability in Patients 5 and 6. The potential for drug-associated behavioral activation noted in this report is consistent with our previous report on the use of memantine in idiopathic PDDs, where 4 of 18 (22%) patients experienced increased irritability (Erickson et al. 2007).

Given the clear evidence of glutamatergic dysregulation in FXS, we hypothesized that memantine could be associated with clinical results exceeding those noted in idiopathic PDDs. This pilot report does not support this hypothesis. This finding may be due to the fact that memantine modulates ionotropic, specifically NMDA, glutamate receptor activity, and dysregulation at metabotropic glutamate receptors has been most clearly linked to the pathophysiology of FXS (Bear 2005; Bear et al. 2004; Dolen and Bear 2008). The lack of robust memantine effect may be due to use of a NMDA antagonist in a population already potentially suffering from excess NMDA receptor internalization (Huber et al. 2002).

Predictors of response to memantine in FXS remain poorly understood. While it is clear memantine may have the potential for positive treatment effect in some persons with FXS, this report does not provide sufficient evidence to make predictions about which patients may best respond to the drug.

Strengths of this paper include prospectively obtained outcome data, including use of the CGI, ABC, SRS, and ADHDRS-IV. Evaluation of this data, though, was clearly confounded by the small sample size. We expect that a larger systematic trial of memantine in FXS may be able to better clarify which specific target symptoms, if any, are most impacted by use of memantine. Among outcome measures, this is the first published report on the use of the SRS in persons with FXS. Clinically, this measure did appear to capture elements of social behavior that are frequently impaired in FXS. For those who improved with the drug, it remains unclear if reduction in SRS scores was due to core improvement in social behavior, or possibly due to reduced hyperactivity, improved attention, and/or reduced anxiety. Based upon this report, the SRS does show potential for use in future FXS drug trials.

The results of this preliminary open-label trial should be weighed against the significant methodological limitations of the report. The small sample size again must be considered. The SRS and ADHDRS-IV were not obtained for all subjects and therefore the subset of patients with available data cannot be considered representative of the whole group. The small sample size did not allow for statistical analysis predictors of treatment response, including presence of comorbid PDD, target symptoms of treatment, use of concomitant medications, or other factors. The high rate of concomitant medication use also adds to the heterogeneity of our sample. Thus it is difficult to extrapolate these findings to memantine montherapy in persons with FXS. Concomitant medication use also limited the investigators' ability to determine if the development of adverse effects was clearly related to use of memantine or due to drug interactions.

Table 1 Clinical demographics and treatment response data for 6 patients with fragile X syndrome (FXS)

Patient no.	Diagnosis	Age (years)	Target symptoms	Memantine dose (mg/day)	Duration of treatment (weeks)	Concomitant psychotropic drugs	Treatment response (CGI-I)	Adverse effects	CGI-S pre/post-treatment
1	FXS, PDD-NOS, moderate mental retardation, bipolar disorder NOS	18.1	Irritability, repetitive behavior, inattention	15	44	Neurontin, propranolol, olanzapine, imipramine	1	None	4/3
2	FXS, autism, moderate mental retardation	19.8	Irritability, anxiety, social impairment	20	104	Fluvoxamine, mirtazapine, haloperidol	1	None	5/4
3	FXS, PDD-NOS, mild mental retardation	13	Inattention, social impairment	20	8	None	2	None	3/3
4	FXS, autism, mild mental retardation	14.6	Repetitive behavior, social impairment, anxiety	20	20	Aripiprazole	2	None	4/3
5	FXS, autism, mild mental retardation	22.3	Repetitive behavior, anxiety, social impairment	20	24	None	4	Irritability	4/4
6	FXS, autism, mild mental retardation	22	Repetitive behavior, anxiety	15	8	Aripiprazole	5	Irritability	4/5

Conclusion

In this preliminary open-label pilot study, memantine was found to be well tolerated and of potentially modest global benefit in 4 of 6 patients. Future larger-scale systematic study is warranted to better understand the impact of memantine in FXS including whether or not specific target symptoms improve. It will also be important to determine if individuals with particular clinical characteristics are vulnerable to clinical worsening. While a modifier of glutamate activity, the specific mechanism of memantine activity (NMDA receptor antagonism) may be responsible for the limited effect of this drug in persons with FXS. Based upon findings in animal models, future study of glutamatergic agents in FXS should focus on modifiers of mGluR5 glutamate receptor activity.

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