

Memantine: A Review of Possible Uses in Child and Adolescent Psychiatry

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Abstract

Objective: To provide a review of published literature regarding the pharmacology of memantine and potential benefits for use in child and adolescent psychiatry. **Method:** A literature search of several databases (Medline, PsycINFO, CINAHL, PsycARTICLES) was conducted with the search terms: 'memantine' with limits: English language, Human trials, all child (aged 0-18 years). The search was later expanded to include 'Adults' and relevant articles were also selected from reference lists. **Result:** The search did not find any well-controlled studies in children and adolescents except for open label trials, as monotherapy in autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), as well as an augmenting agent in obsessive compulsive disorder (OCD). No study was found in anxiety disorders (AD), the most common psychiatric disorder in children or in mood disorders, both major depressive disorder (MDD) and bipolar disorder (BD). Studies in adults for those disorders with onset in childhood or adolescence, were also mostly open-label and as an add-on therapy. All the studies reported that memantine is a safe drug with minimal drug interactions and a very acceptable adverse effect profile comparable to placebo. **Conclusion:** Memantine has demonstrated beneficial effects in some childhood disorders but the evidence is too limited at present and does not provide enough support of its efficacy to advocate for its regular use in those conditions. Such use remains off-label until further validation of efficacy comes from blinded, randomized, placebo controlled studies.

Key Words: memantine, glutamatergic system, NMDA receptor antagonist, pharmacology, children, adolescents

Résumé

Objectif: Offrir une revue de la littérature publiée à propos de la pharmacologie de la mémantine et des avantages potentiels de l'utiliser en psychiatrie de l'enfant et de l'adolescent. **Méthode:** Une recherche de la littérature dans plusieurs bases de données (Medline, PsycINFO, CINAHL, PsycARTICLES) a été menée au moyen du mot clé « mémantine » avec restrictions : langue anglaise, essais sur des humains, tous les enfants (de 0 à 18 ans). La recherche a ensuite été élargie pour inclure « les adultes » et des articles pertinents ont aussi été relevés dans les bibliographies. **Résultat:** La recherche n'a donné aucune étude bien contrôlée d'enfants et d'adolescents sauf des essais ouverts, comme une monothérapie d'un trouble du spectre de l'autisme (TSA) et du trouble de déficit de l'attention avec hyperactivité (TDAH), ainsi qu'un agent d'augmentation du trouble obsessionnel-compulsif (TOC). Aucune étude des troubles anxieux (TA), pourtant le trouble psychiatrique le plus répandu chez les enfants, n'a été trouvée, ni des troubles de l'humeur, soit le trouble dépressif majeur (TDM) et le trouble bipolaire (TB). Les études chez les adultes de ces troubles, qui sont apparus dans l'enfance ou l'adolescence, étaient également ouvertes pour la plupart, à titre de thérapie d'appoint. Toutes les études rapportaient que la mémantine est un médicament sécuritaire présentant des interactions médicamenteuses minimales et un profil très acceptable d'effets secondaires, comparables à ceux d'un placebo. **Conclusion:** La mémantine a démontré des effets bénéfiques pour certains troubles des enfants, mais les données probantes sont trop limitées à l'heure actuelle et elles ne soutiennent pas suffisamment son efficacité pour en revendiquer l'utilisation régulière dans ces troubles. Cette utilisation demeure non indiquée sur l'étiquette jusqu'à ce que des études à l'insu, randomisées, et contrôlées contre placebo en garantissent davantage l'efficacité.

Mots clés: mémantine, système glutamatergique, récepteur antagoniste du NMDA, pharmacologie, enfants, adolescents

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Introduction

The amino-acid neurotransmitter glutamate is a major excitatory neurotransmitter that impacts negatively on numerous brain circuits. Excessive glutamate activity leads to overactivation of the N-methyl-D-aspartate (NMDA) glutamate receptors, which have been linked with neurotoxicity and neurodegeneration (Kavirajan, 2009). A growing body of evidence points towards a disturbed glutamate neurotransmission in the pathophysiology of some of the major psychiatric conditions in children and adolescents, including autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder, obsessive compulsive disorder, major depressive disorder and bipolar disorder (Zdanys & Tampi, 2008; Sani et al., 2012). Improved treatment of these disorders would rely on drugs that regulate glutamate brain levels and/or modulate its neurotransmission to avoid excitotoxicity (Maeng & Zarate, 2007). This has led to various clinical trials with glutamate modulating drugs such as off label use of memantine in the various psychiatric disorders. This review will focus on its pharmacology, efficacy and safety in those disorders in which it has been studied to date.

Pharmacology

Memantine (Ebixa®), is a low to moderate affinity, uncompetitive open channel NMDA receptor antagonist approved in Canada for the treatment of moderate to severe Alzheimer's disease (Maeng & Zarate, 2007). The most likely therapeutic mechanism of action of memantine is via the uncompetitive antagonism of the NMDA receptors (Parsons, Danysz, & Quack, 1999). By binding to the NMDA receptors, memantine blocks their pathological activation, excitation and overstimulation by the amino acid glutamate, preventing damage to those receptors while preserving their normal synaptic function and physiological activity (Sani et al., 2012). Through such modulation of NMDA receptor activity, memantine increases or decreases the excitability of those neuronal circuits leading to its clinical effects (Thomas & Grossberg, 2009).

Pharmacokinetics

After oral administration, memantine is quickly and completely absorbed through the gastrointestinal tract with bioavailability close to 100%. Food has no impact on the rate of absorption, with an elimination half-life of 60-80 hours (Kornhuber et al., 2007). The time to reach the maximum plasma concentration (T_{max}) is 3-8 hours after ingestion. Pharmacokinetics follow a linear pattern over the therapeutic dose range of up to 40 mg single dose or 20 mg twice daily dosing (Kavirajan, 2009). Over 80% of the drug is excreted via the kidneys unchanged in the urine and in patients with severe renal impairment the dose should be limited to 5 mg twice daily. Minimal metabolism occurs in the liver and there is little involvement of hepatic microsomal p450 iso-enzymes, except for selective inhibition of cytochrome

CYP2B6 (Kornhuber et al., 2007), with minimal drug-drug interactions. Also due to its modest binding to plasma proteins, clinically significant interactions with drugs that are highly protein bound are unlikely (Kavirajan, 2009).

Memantine is described as a safe drug with a favorable profile of adverse effects. These have been described as mild to moderate comparable to placebo. The most frequently observed adverse effects in adult trials are dizziness, constipation, headache, hypertension and somnolence (Sani et al., 2012).

Clinical Efficacy

Autism Spectrum Disorder

Glutamate levels and NMDA receptors have been reported as increased in the brains of patients with ASD (Owley et al., 2006), with memantine studied for possible beneficial effects. Four open-label trials in children and adolescents reported mixed improvements.

A small eight-week prospective open-label trial of memantine (5-20 mg/day) in 14 children, 3-12 years of age, with ASD reported significant improvements in the behavioral symptoms of hyperactivity, lethargy, irritability and memory (Owley et al., 2006). A subsequent, 19-week, open-label, retrospective study of 18 patients, 6-19 years of age with ASD, treated with memantine to a maximum dose of 20 mg/day, reported significant positive effects on social withdrawal and inattention with moderate effect on irritability (Erikson et al., 2007). Another open-label study of 151 patients, 2.5 - 26 years of age, with ASD, demonstrated significant improvements in receptive and expressive language for 83% of patients as well as a positive impact in social interactions in 71% of patients when memantine 2.5-30 mg/day, was added to their existing medications (Chez et al., 2007). Similarly an open label study, investigating the effects of memantine in four children with ASD, at doses of 20 mg/day for four weeks, found significant improvements in irritability, hyperactivity and inappropriate speech (Niederhofer, 2007). More recently, a ten-week, randomized double-blind, placebo-controlled trial of memantine (RCT) as an add-on to risperidone in 40 children, 4-12 years of age, reported significant improvement in the memantine group in irritability, stereotypic behavior and hyperactivity (Ghaleiha et al., 2012).

Attention Deficit Hyperactivity Disorder

Glutamatergic dysfunction in ADHD was reported more than ten years ago (Carrey, MacMaster, Sparkes, Khan, & Kusumakar, 2002). Initially, from a study of the available literature, ADHD was considered as a hypoglutamatergic condition affecting primarily prefrontostriatal pathways, (Carlsson, 2000). Later, using short echo magnetic resonance spectroscopy, Carrey et al. provided initial evidence that glutamate concentrations were, in fact, raised in the

left striatum of male ADHD (combined subtype) subjects at baseline as compared to controls, with no increase in the prefrontal cortex (Carrey, MacMaster, Gaudet, & Schmidt, 2007). In 2009, elevated glutamate levels were again reported, this time, both in the prefrontal cortex and striatum of untreated ADHD children (Kavirajan, 2009). Recently, decreased NMDA-mediated transmission was again reported in ADHD, with caution that further reducing it with an NMDA receptor antagonist could worsen the condition (Sani et al., 2012). Whether ADHD is a hyper or hypoglutamatergic condition is not clear. Treatment with a glutamatergic agonist was inconclusive (Carlsson, 2000) but an eight-week, open-label, dose finding trial with memantine in 16 children, 6-12 years of age, diagnosed with ADHD (combined type), using a dose of 10 mg/day in eight children and 20 mg/day in the other eight children, reported a dose dependent benefit in both the inattention and the hyperactivity/impulsivity domains (Findling et al., 2007). The response was minimal at 10 mg/day and significantly better on the 20 mg/day dosage.

Schizophrenia

Abnormalities in glutamatergic neurotransmission have been associated with the psychopathology of schizophrenia, especially the cognitive deficits (Cerullo, Eliassen, & Nasrallah, 2007). This was supported by evidence of decreased cerebrospinal fluid glutamate levels in patients with schizophrenia (Kim, Kornhuber, Schmid-Burgk, & Holzmüller, 1980). As such it was presumed that NMDA antagonists like memantine would have little beneficial effect and may even make certain symptoms worse. However, more recent studies with magnetic resonance spectroscopy (MRS) and proton magnetic resonance spectroscopy have shown increased glutamatergic activity in treatment naive patients with schizophrenia relative to healthy controls, which decreased with treatment (Zdanys & Tampi, 2008). To date, there are no published RCTs on the use of memantine as monotherapy in schizophrenia, except as an augmenting agent to second generation antipsychotics (SGAs).

An eight-week multicenter RCT to assess the efficacy of memantine, 20 mg/day, added to SGAs in 70 partial responders, 18-65 years of age, showed no differences between memantine and placebo (Lieberman et al., 2009). However, a six-week open-label study of seven patients with weekly increasing dose (5, 10, 15, 20 mg) of memantine added to their ongoing antipsychotic treatment reported significant improvement in the negative symptoms (Krivoy et al., 2008). Another double-blind placebo-controlled study of 21 refractory patients, evaluating the efficacy of memantine, 20 mg/day added to clozapine, showed significant improvement of both positive and negative symptoms with memantine over placebo (de Lucena et al., 2009). In patients with catatonic schizophrenia, which has been associated with excessive glutamate function in the striatum, an open label study (Carroll, Thomas & Jyanti, 2006) reported

that memantine produced a rapid and significant reduction in catatonic symptoms.

Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) has been considered a disorder of glutamate dysregulation due to higher levels of glutamate found in the caudate regions of the brain of patients with OCD (Rosenberg et al., 2000). In an MRS imaging study, patients with OCD had elevated striatal glutamate levels which correlated with symptom severity (Kavirajan, 2009). Increased cerebrospinal fluid levels of glutamate were also found in patients with OCD (Chakrabarty, Bhattacharyya, Christopher & Khanna, 2005). Clinical trials in adolescents have shown positive responses to memantine when used as an augmenting agent in resistant cases. A 15-year-old girl, with chronic severe OCD, resistant to several trials of selective serotonin receptor inhibitors (SSRIs) including fluoxetine, sertraline and citalopram up to 80 mg/day, and cognitive behavior therapy, showed significant improvement when memantine was added to a previously ineffective citalopram regimen (Hezel, Beattie & Stewart, 2009). An eight-week RCT of memantine as an add-on treatment to 42 adult patients with moderate to severe OCD reported that all patients in the memantine group met the criteria for partial or complete response (Ghaleiha et al., 2013). Another 12-week open-label trial of 14 adult patients who were SSRI resistant even with augmentation by SGAs showed significant clinical response by week four, when memantine was added (Aboujaoude, Barry & Gamel, 2009). A single-blind, case-control study of a flexible dose of memantine as an add-on to 22 adult patients with severe OCD receiving both CBT and drug treatment showed significantly greater improvement than the 22 control subjects (Stewart et al., 2010).

Major Depressive Disorder

There is growing evidence that disturbances in glutamate function are involved in the pathophysiology of MDD (Sani et al., 2012). Studies with 1H-MRS, currently the most direct way of assessing brain glutamate content, have reported elevated glutamate levels in the occipital cortex (Maeng & Zarate, 2007) and in the cerebrospinal fluid (Levine et al., 2000) of depressed patients. Also trials with the more potent NMDA receptor antagonist ketamine, have shown immediate and significant beneficial effects in severe depression (Berman et al., 2000). However, due to its high level of toxicity, attention has shifted to memantine, a lower affinity NMDA antagonist.

No clinical trials of memantine for the treatment of depression in children and adolescents were found in this search. Studies with contradictory findings were identified in the adult population. The first study, an eight-week RCT of 32 subjects with MDD randomized to memantine, 5-20mg/day or placebo, reported no differences between treatment groups (Zarate et al., 2006). However, a longer 12-week,

open-label, flexible-dose study of memantine's effectiveness in eight patients with major depression reported positive effects as early as week one, reaching maximal improvement by week 12 (Ferguson & Shingleton, 2007). A recent 26-week RCT of 80 patients, 26-65 years of age, comparing the effect of memantine 20 mg/day with escitalopram 20 mg/day in patients with MDD and comorbid alcohol dependence found that both treatment groups improved significantly on the primary outcomes of depression and anxiety severity (Muhonen, Lonnqvist, Juva & Alho, 2008). No significant difference was seen between the memantine and escitalopram groups. One case report of a 47 year old woman with MDD and at least ten recent suicide attempts on polypharmacy, without success, was treated successfully with two infusions of ketamine and subsequently remained stable on oral administration of memantine (Kollmar, Markovic, Thurauf, Schmitt & Kornhuber, 2008).

Bipolar Disorder

There is evidence of elevated glutamate levels in several brain regions and alterations in glutamate receptor function in BD patients. A recent study using MRS found evidence of elevated glutamate in the anterior cingulate cortex and parietal-occipital cortex in patients with acute mania (Kavirajan, 2009). Hence the blockade of NMDA receptors by memantine should result in an anti-manic and mood stabilizing action in BD (Sani et al., 2012).

No studies of memantine were identified in children or adolescents while two open-label studies in adults may be relevant to the adolescent population. A 24-week open-label trial of 18 patients with treatment resistant BD (mean age 42 years) reported significant improvement when memantine was added to ongoing treatment (Koukopoulos et al., 2010). To confirm these preliminary findings, the authors performed another open label study of 40 treatment resistant adults with BP type I and II, and again showed that memantine (10-30 mg) as an augmenting agent was associated with a clinically substantial anti-manic and sustained mood stabilizing effect at 6 and 12 months, with an excellent safety and tolerability profile (Koukopoulos, Serra, Koukopoulos & Serra, 2012). More than 70% of these patients responded or remitted after memantine was added and maintained response at the one year follow-up. In another open label, multicenter dose finding study, 35 adult patients suffering from BD type I (manic or mixed episode) received memantine in three cohorts of 20-30 mg/day, 30-40 mg/day or 30-50 mg/day for a three-week period. All showed positive clinical responses with the greatest improvement occurring on 20-30 mg/day (Keck, Hsu, Papadakis & Russo, 2009).

On the other hand, augmentation with memantine did not demonstrate any positive impact when added to lamotrigine, an anticonvulsant which decreases presynaptic glutamate release and has been shown to be effective in about 40-50% of patients with bipolar depression. An eight-week

placebo-controlled study of 29 patients, 18-65 years of age, failed to show a statistically significant benefit when memantine at a maximum dose of 20 mg/day was added to a stable dose (100 mg or more/day) of lamotrigine (Anand et al., 2012).

Other Disorders

Glutamatergic mechanisms mediated by NMDA receptors have been implicated in feeding and abnormal eating behaviors (Sani et al., 2012). Excessive glutamate activity has been reported in the hypothalamic arcuate nucleus contributing to overeating and obesity (Kavirajan, 2009). An open-label, 12-week, prospective study of 16 patients (13 women and men, mean age 42.7 years), with binge eating disorder reported that memantine, at a flexible dose of 5-20 mg/day, was associated with significant reductions in the frequency of binge days and episodes as well as severity of illness (Brennan et al., 2008).

It has been mentioned that drugs modulating glutamate activity may be helpful in treating anxiety disorders (Cortese & Phan, 2005). Unfortunately, in a 12-week open-label study of memantine, seven patients with generalized anxiety disorder (18-64 years of age) demonstrated no clinically significant response on 10 mg of memantine administered twice daily (Feusner, Kerwin, Saxena & Bystritsky, 2009). More recently, a ten-week, open-label, study of memantine (5-20 mg/day) added to the treatment regime of 15 adult partial responders, resulted in clinically significant reduction in anxiety symptoms compared to baseline (Schwartz, Siddiqui & Raza, 2012).

Discussion

Memantine, as a glutamatergic modulator, has the potential for use as an effective and safe medication in many childhood disorders but research to support such use has been limited. The trials carried out in ASD showed beneficial effects, but, as they were all open-label studies without a placebo group it is hard to attribute any changes to memantine alone. In the only RCT in ASD, memantine added to risperidone showed a significant effect on irritability, stereotypic behaviors as well as hyperactivity. This combination may have future use in the more challenging cases. In ADHD, the only small open-label study of memantine, showed a dose-dependent beneficial effect.

In MDD, there are no studies on the use of memantine in children and adolescents. With the use of SSRIs remaining controversial in children, a drug with a different mode of action like memantine may be useful, if effective. However, depression in adults often has onset in adolescence. Extrapolating from the studies in the adult population, one RCT identified found no significant clinical effect, while a different RCT of citalopram in patients with MDD and co-morbid alcohol dependence, as well as a small open-label study, reported beneficial effects within one week, sustainable up

to 26 weeks. Since there were no control group in the latter two studies, memantine's usefulness in depression remains inconclusive. Similarly, memantine, on its own, has not demonstrated a strong anxiolytic effect, but it has shown benefits as an augmenting agent, with a possible preferential efficacy in OCD. In eating disorders, memantine has shown a strong effect mainly in binge eating disorder. In schizophrenia, where there have been controversies that the use of a glutamate antagonist could make things worse, symptomatic improvements have not been demonstrated even when memantine is used to augment the SGAs. A significant effect was, however, demonstrated when memantine was added to clozapine. Memantine is also effective as an add-on in catatonia and is reported to have a positive impact on negative symptoms. Studies in BD have been more encouraging as memantine showed significant efficacy in the management of acute manic episodes but not for depressive episodes.

Conclusion

To date, studies of memantine in child and adolescent psychiatry have been too limited to validate its usefulness. The benefits reported in ASD, ADHD and the other disorders need further validation from well-controlled studies before advocating for its general use. In two very important conditions in children and adolescents, anxiety and depression, the evidence from existing studies coming mostly from the adult population is inconclusive. Memantine has shown some significant beneficial effects as an add-on therapy especially in OCD and in the manic phase of BD. More rigorous clinical trials are needed to confirm whether it is truly and consistently effective in these conditions. If efficacy is demonstrated, its excellent safety record and tolerability make it a desirable medication for use in children and adolescents.

Acknowledgements/Conflicts of Interest

The authors have no financial conflicts to disclose.

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This is a great opportunity for those wanting to gain exposure and practice writing journal articles, and publications always look great on your CV. You don't even have to do it all yourself - the section editors are willing to partner with you to make sure the article meets JCACAP standards.

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