

Amantadine: A Review of Use in Child and Adolescent Psychiatry

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Abstract

Objective: To review published literature regarding the pharmacology and use of amantadine in child and adolescent psychiatry. **Method:** A literature search of several databases (PubMed, Psychinfo, CINAHL, Medline, PsycARTICLES, Biomedical Reference Collection and Academis Search Complete) was conducted with the search terms: 'amantadine' with limits: English language, Human trials, all child (aged 0-18 years). The search was later expanded to include 'Adults' and additional relevant articles were selected from reference lists. **Results:** The psychotropic effect of amantadine is related to its antagonism of the N-methyl-D-aspartate (NMDA) receptor. It decreases the toxic effects of the glutamatergic neurotransmitter system which plays an important role in many psychiatric disorders. Two randomized controlled trials (RCTs) of amantadine were identified in children and adolescents. One reported beneficial effects in controlling the symptoms of irritability and hyperactivity in autistic disorder and the other described a significant impact in attention deficit hyperactivity disorder (ADHD). Two open label studies also reported positive effects in ADHD. A pilot study in children with enuresis reported significant reduction in wetting frequency. Studies in adults, with relevance to children and adolescents, reported effectiveness in resistant depression, obsessive compulsive disorder and in counteracting side effects of some psychotropic medications. RCTs found in traumatic brain injury indicated a neuroprotective effect and effectiveness in controlling agitation and aggression. Amantadine is well tolerated in children and adolescents, with an acceptable side effect profile, and considered safe for long term use. **Conclusion:** Amantadine shows potential for use as a safe alternative or as an augmenting agent for treating children with neuropsychiatric and various other disorders. Available data for such use, although promising, require further confirmation.

Key Words: amantadine, glutamatergic system, N-methyl-D-aspartate receptor, pharmacology

Résumé

Objectif: Passer en revue, résumer et discuter la littérature publiée sur la pharmacologie et l'utilisation de l'amantadine en pédopsychiatrie. **Méthode:** Une recherche de la littérature dans plusieurs bases de données (PubMed, Psychinfo, CINAHL, Medline, PsycARTICLES, Biomedical Reference Collection et Academis Search Complete) a été menée avec le mot clé « amantadine » avec des limites: langue anglaise, essais sur des humains, tous les enfants (de 0 à 18 ans). Des articles additionnels pertinents ont été relevés dans les bibliographies. Étant donné la quantité limitée d'information obtenue, la recherche s'est élargie et a inclus « tous les enfants et les adultes », et l'information pertinente a été saisie. **Résultats:** L'utilisation de l'amantadine pour traiter les troubles neuro-développementaux chez les enfants est due à son effet antagoniste au récepteur N-méthyl-D-aspartate (NMDA). L'effet de l'amantadine sur le système glutamatergique des neurotransmetteurs, jouer un rôle important dans de nombreux troubles psychiatriques. La majorité des études relevées étaient des études ouvertes et seulement deux étaient des études contrôlées d'enfants et d'adolescents. Un essai randomisé contrôlé rendait compte des effets bénéfiques du contrôle des symptômes d'irritabilité et d'hyperactivité chez les enfants souffrant d'un trouble autiste. Un autre essai randomisé contrôlé, une étude de comparaison directe avec le méthylphénidate, a constaté un effet statistiquement significatif sur le trouble de déficit de l'attention avec hyperactivité (TDAH). Deux autres études ouvertes constataient aussi des effets positifs sur le TDAH. Une étude pilote sur des enfants souffrant d'énurésie constatait une réduction significative de la fréquence de l'incontinence. Ouvertes pour la plupart, les études sur les adultes, relativement aux enfants et aux adolescents, rapportaient une efficacité dans la dépression résistante, le trouble obsessionnel compulsif et pour compenser certains effets secondaires des psychotropes. Des essais contrôlés sur les traumatismes cérébraux indiquaient un effet neuroprotecteur et une efficacité pour contrôler les

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comportements aberrants comme l'agitation et l'agressivité. L'amantadine était constamment désignée comme étant bien tolérée, ayant un profil acceptable d'effets secondaires et étant sécuritaire pour une utilisation à long terme. Son congénère analogue mais plus puissant, la mémantine, a également démontré des effets bénéfiques potentiels pour des troubles semblables, mais aucune étude bien contrôlée n'a été trouvée chez les enfants et les adolescents. **Conclusion:** L'amantadine pourrait être utilisée comme agent de rechange sécuritaire ou agent d'augmentation dans le traitement des enfants souffrant de troubles neuropsychiatriques développementaux ou d'autres troubles qui ont démontré une résistance aux agents psychopharmacologiques d'usage courant. Cependant, les données disponibles pour un tel usage, bien que prometteuses, sont limitées et proviennent surtout d'études ouvertes. Il faut que cette efficacité soit confirmée par des études bien contrôlées.

Mots clés: *amantadine, système glutamatergique, récepteur N-méthyl-D-aspartate (NMDA), mémantine, psychopathologie, psychopharmacologie*

Introduction

Irritability, hyperactivity and mood lability escalating to rage reactions, aggression and self-injurious behaviors seen in children with neuropsychiatric developmental disabilities and executive function disorders, continue to present a challenge in management. There are no specific guidelines to the pharmacological treatment of these conditions. When severe symptoms persist, clinicians resort to off-label medication usage, based on the belief that such behaviors are the result of dysfunctions in the brain circuits and the neurotransmitters involved in self-regulation, including dopamine, nor-epinephrine and serotonin. These monoamines, considered to be modulators of the frontal-subcortical loops involved in the pathogenesis of such disorders, have been the targets of most therapeutic drugs (Hashimoto, 2009). Atypical antipsychotics, stimulants and the selective serotonin reuptake inhibitors (SSRIs) work by regulating these neurotransmitters and are currently the main drugs used to treat those disorders. Challenges with these medications have led to interest in another system of neurotransmitters, the amino acid system, with glutamate as the target neurotransmitter. Glutamate is the major "excitatory" neurotransmitter of the central nervous system and recent data has pointed to glutamatergic dysfunction in mood disorders, anxiety disorders, obsessive compulsive disorder and schizophrenia (Zdanys & Tampl, 2008). Stabilizing the glutamatergic receptor is a new pharmacological target for many disorders in both adults and children. This has led to trials of drugs that modulate glutamate neurotransmission, namely the NMDA receptor antagonists. Two main drugs stand out as effective and safe stabilizers of the glutamatergic system, amantadine and its analogue memantine. The present review focuses on the available evidence regarding the use of amantadine in children and adolescents with challenging behavior and other disorders.

Amantadine (Symmetrel®) is a glutamatergic antagonist that works by inhibiting the NMDA receptor, binding to it to avoid its excessive excitation by the glutamate neurotransmitter. It was originally approved by the US Food and Drug Administration (FDA) in 1976 as an antiviral drug to treat Influenza A, in children one year of age and

older, but is no longer recommended for this purpose. It possesses dopamine enhancing activity and this ability to increase dopamine levels has been shown in an open uncontrolled chart review to reduce problem behaviors related to executive dysfunction (Drayton et al., 2004). Similar beneficial effects have been observed on the challenging behaviors of children with neurobehavioral disorders exhibiting poor executive functioning. Children placed on amantadine have reported improvements in fatigue, distractibility, rigidity and bradykinesia, arousal level, initiation, purposeful movement, attention and concentration, sequencing skills and processing time (Green, Hornyak, & Hurvitz, 2004).

Pharmacology

The exact mechanism of action of amantadine is not clearly understood. One study performed to investigate the mechanism by which amantadine increases extracellular dopamine levels reported that it does so by inhibiting the reuptake of dopamine and/or blocking the NMDA receptor function (Mizoguchi, Yokoo, Yoshida, Tanaka, & Tanaka, 1994). Initially, it was assumed that amantadine enhances dopamine activity by facilitating presynaptic dopamine release and blocking dopamine reuptake post-synaptically. By increasing dopamine neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic and frontostriatal pathways, amantadine enhances arousal, drive and attentional functions leading to its favorable neurobehavioral effects (Giacino et al., 2012). Lately, increasing evidence shows that amantadine does not act directly on dopamine receptors but enhances dopamine release indirectly via antagonism of the NMDA receptor (Kornhuber, Weller, Schoppmeyer, & Riederer, 1994). Other studies have confirmed that the effectiveness of amantadine results predominantly from this inhibition of NMDA receptors and its ability to stabilize the glutamatergic system (Blanpied, Clarke, & Johnson, 2005). By binding to the NMDA receptors and blocking glutamate access to the cells, amantadine exerts a neuroprotective effect to the excitotoxic damage induced by glutamate.

In humans, amantadine is readily absorbed following oral administration. After oral administration of a single dose

of 100 mg, maximum blood levels are reached in about 3.3 +/- 1.5 hours (range 1.5 to 8 hours). The half-life is about 17 hours (range of 10 -25 hours) and steady state serum levels can be achieved within 48-72 hours (Endo Pharmaceuticals Inc., 2007). Amantadine is primarily excreted via the kidneys and in renal impairment the half-life may increase two to three fold or greater (up to 7-10days). Patients with kidney problems or poor renal clearance may require a lower starting and daily dose. Clinical efficacy is usually seen within days or weeks but can be as early as day one or two (Endo Pharmaceuticals Inc., 2007). Interactions with other drugs are uncommon (Aoki, Sitar, & Ogilvie, 1979), unless administered concurrently with drugs that interfere with the central nervous system or renal clearance. For best results, it is recommended to start amantadine at a low dose of 25 mg/day and increase gradually by 25 mg every 4-7 days until a therapeutic response is obtained, with an average dose of 200 mg/day but not exceeding 400mg/day. Amantadine only comes as a syrup (10mg/ml) and 100mg capsules. Starting at low doses can be an issue and availability may be a problem.

Efficacy Data

Autism spectrum disorders (ASD)

Children in the autism spectrum exhibit a range of aberrant behaviors that are often distressing necessitating the use of psychotropic medication. The FDA has only approved risperidone (Risperdal®) and aripiprazole (Abilify®) to treat the irritability in children with autism (Elbe & Lalani, 2012), while Health Canada has not approved any medication for such use. Atypical antipsychotics are not without short and long term side effects and do not address the core deficits of autism. Glutamatergic dysfunction seems to play an important role in the pathophysiology of autism. Based on neuroanatomical and neuroimaging studies, autism is described as a hypoglutamatergic disorder and treatment is advocated with a dopamine agonist (Carlsson, 1998). However, a hyperglutamatergic hypothesis has also been considered since the brain areas exhibiting cellular abnormalities in autism demonstrate a higher degree of NMDA binding sites (Reiff, 2001). Amantadine, as a weak non-competitive NMDA receptor antagonist, was tested in a double blind placebo controlled study of 39 autistic children, 5-19 years of age (King, Wright, Handen, et al., 2001). According to the parents ratings, the percentage of responders for the reduction of irritability and/or hyperactivity on the Aberrant Behavior Checklist-Community Version (ABC-CV) scale were slightly higher in the amantadine group but the difference over placebo was not deemed statistically significant ($p=0.511$). On the other hand, the clinician ABC-CV ratings showed statistically significant improvements on the hyperactivity scale (amantadine -6.4 versus placebo -2.1; $p=0.046$) and inappropriate speech (-1.9 versus 0.4; $p=0.008$). On the Clinical Global Impression-Improvement

(CGI-I) scale, twice as many subjects in the amantadine group were considered to be responders, 53% versus 25% on placebo ($p=0.076$). King et al. associated the improvement to amantadine's antagonistic action on the NMDA glutamatergic receptors rather than its effect on the dopaminergic system.

Attention deficit hyperactivity disorder

The search for alternate medication to the stimulants has been ongoing for years. In 1980, in an open label trial, eight boys and one girl, 10-13 years of age, were taken off the stimulants for one week and tried on amantadine, 100 mg bid, for one month. On the Conners questionnaire, amantadine's efficacy was rated as intermediate between stimulants and no medication, with two children achieving 80-90% of the improvement obtained on methylphenidate (Mattes, 1980). Interest in amantadine for the treatment of ADHD was rekindled with the publication of the book "Delivered from Distraction" (Hallowell & Ratey, 2005) as it stated that Dr. William Singer and Dr. Roger Cohen from Harvard University successfully treated over 400 children suffering from ADHD with amantadine. Since amantadine's dopaminergic agonistic activity on the prefrontal cortex is somewhat parallel to the stimulants, it could potentially show similar beneficial effects.

A six week, open-label study of 24 stimulant naïve ADHD children (5-13 years of age) given amantadine as a single dose of 50-150 mg in the morning, showed modest efficacy on the parent and teacher ADHD rating scales (Donfrancesco, Calderoni, & Vitiello, 2007). This effect was stated to be less robust than that of stimulant medications. Response rate was 58% based on parents and 46% based on teachers ratings. The study concluded that amantadine has an acceptable acute tolerability at single doses up to 150mg/day, with the most common side effect being transient appetite decrease. A subsequent six week double blind randomized controlled trial (RCT) of 40 patients (28 boys and 12 girls, 6-14 years of age) treated with amantadine at a dose of 100-150mg/day compared with methylphenidate 20-30mg/day reported similar efficacy. The small differences in scores were considered non-significant. On the parent rating scale, the percentage of responders for amantadine was 50% versus 55% on methylphenidate, while the teacher rating scale indicated 30% responders for amantadine versus 35% for methylphenidate, with the amantadine group reporting fewer side effects of decreased appetite and restlessness compared to the stimulant group (Mohammadi et al., 2010). This study was criticized for the lack of a placebo group and the short duration of the study effect (Yang, Mao, Li, & Zhao, 2011) but the authors argued that the use of an active agent, known to be effective in this disorder, as a control group is an acceptable alternative.

Fetal alcohol spectrum disorders (FASD)

Although FASD is considered a neurodevelopmental disorder (e.g. Alcohol Related Neurodevelopmental Disorder) no study, open-label or RCT, focusing on amantadine for the treatment of this condition was identified. There is presently no well-established pharmacotherapy for the treatment of aberrant behaviors or the intermittent explosive outbursts seen in the context of the FASD. Both the glutamatergic and nigrostriatal dopaminergic neurotransmitter systems have been implicated in the production of impulsivity and hyperactive behaviors that are common in these children, and amantadine, a dopamine agonist and an NMDA receptor antagonist, is likely have a positive impact on such behaviors by enhancing frontal lobe function. One open-label trial of impulsive and aggressive behaviors in eight hospitalized children (4-12 years of age) with developmental disabilities (seven with neurodevelopmental disorders), refractory to other treatments, reported improvement in all the children with marked clinical improvement in four children on amantadine (King, Wright, Snape, & Dourish, 2001). More studies are needed to evaluate amantadine's effectiveness in this condition.

Other disorders

A growing body of evidence, mostly open label studies, has pointed to the involvement of the glutamatergic system in the etiology of depressive disorders (Ferguson & Shingleton, 2007). Amantadine has been used successfully as an augmenting agent in resistant unipolar depression (Stryjer et al., 2003; Rogoz et al., 2007) as well as in obsessive compulsive disorder (Pasquini, Berardelli, & Biondi, 2010) possibly due to the glutamatergic dysfunction described in these disorders. Other open label studies have reported effectiveness in counteracting the sexual dysfunction induced by the SSRIs (Shrivastava, Shrivastava, Overweg, & Schmitt, 1995) as well as drug induced neuroendocrine side effects of neuroleptics including elevation in serum prolactin levels, galactorrhea, gynecomastia, breast tenderness, decreased libido and amenorrhea (Correa, Opler, Kay, & Birmaher, 1987; Siever, 1981). A four week open label study of six primary enuretic children treated with amantadine reported a significant reduction in wetting frequency (Ambrosini & Fried, 1984).

Amantadine has also been reported as useful in counteracting the excessive weight gain in children and adolescents on atypical antipsychotics. An open label trial of eight boys and one girl, 9-16 years of age, receiving amantadine 100 mg bid or tid for weight gain from psychotropic medications reported stabilization of the weight gain (Gracious, Kryslak, & Youngstrom, 2002). The weight loss and decreased body mass index were strongly correlated with the length of amantadine treatment. Other studies have also supported the effectiveness of amantadine in reducing the weight gain induced by olanzapine (Correa et al., 1987; Floris, Lejeune, & Deberdt, 2001). Although this was contradicted by an

open label study of 25 adults (Bahk et al., 2004) and a systematic review with meta-analysis of 32 studies of several agents including amantadine (Maayan, Vakhrusheva, & Correll, 2010), a 12 week RCT of amantadine on 21 adults, who gained at least 2.3 kg on olanzapine, reported that it induced weight stabilization (Graham, Hongbin, Lieberman, Harp, & Perkins, 2005). Significantly fewer subjects taking amantadine gained weight.

Amantadine has been described as having neuroprotective properties (Kornhuber et al, 1994) and safe even in vulnerable patients with a history of brain injury undergoing neuro-rehabilitation. In traumatic brain injury (TBI), amantadine showed beneficial effects in two patients with agitation and aggression recovering from acute injury. It was considered a preferred treatment for patients with behavior problems in the acute stages of recovery from coma (Chandler, Barnhill, & Gualtieri, 1998). A retrospective, case-controlled study of amantadine in 54 pediatric patients, 3-18 years of age, with TBI demonstrated subjective improvements in the majority of patients and it was reported as well tolerated in the pediatric population (Green et al., 2004). Exposure to amantadine was associated with a more rapid emergence of cognitively mediated behaviors. Through its neuroprotective effect and by stabilizing the excitatory neurotoxic effects of glutamate, amantadine is likely to exert similar beneficial effects on the agitation, aggression and other cognitively mediated deficits in children with neurobehavioral or neuropsychiatric disorders. More controlled studies are required to confirm such an effect.

Safety data

Amantadine is well tolerated in children, as those taking amantadine did not report more side effects than those on placebo (King, Wright, Handen, et al., 2001). Side effects reported in other studies include suicidal ideation and attempts (some fatal) with and without a history of psychiatric disorders. The actual incidence (although quite rare) and the pathophysiologic mechanism are not known. Deaths have also been reported from deliberate overdoses with amantadine, two in the United States and one in Canada (Cook, Dermer, & McGurk, 1986). The lowest acute lethal dose has been reported as 1000mg (Endo Pharmaceuticals Inc., 2007). Maximum plasma concentrations are directly related to doses up to 200mg/day. Higher dosages may result in greater than proportional increase in maximum plasma concentrations elevating the risk of toxicity. Parents should be advised to keep the medication out of the reach of children and prescriptions should not be written liberally in large quantities.

Side effects reported most frequently (5-10% incidence) include nausea, dizziness (lightheadedness) and insomnia. Less frequently reported adverse reactions (1-5%) include confusion, somnolence, anorexia, dry mouth, constipation, headache, orthostatic hypotension, agitation, irritability and

hallucinations. Rarer side effects (0.1-1%) include psychosis/paranoia, delusions, abnormal thinking, slurred speech, hypertension, urinary retention, livedo reticularis (a skin reaction) and skin rash (Endo Pharmaceuticals Inc., 2007). Patients with a history of epilepsy or seizures should be observed closely for possible exacerbation, due to decreased seizure threshold. Sporadic cases of neuroleptic malignant syndrome have been reported in association with dose reduction or discontinuation of amantadine. Rare instances of elevation of liver enzyme levels have been reported in some patients. In every case, the side effects were reversible by either decreasing the dosage or by stopping the drug. Laboratory findings have shown elevation in creatinine phosphokinase (CPK), blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase, Lactic dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT) and bilirubin (Endo Pharmaceuticals Inc., 2007). Careful monitoring is required when amantadine is administered concurrently with central nervous system stimulants. A switch to mania has been described in vulnerable bipolar patients (Sodre, Bucker, Zortea, Sulzbach-Vianna, & Gama, 2010; Rego & Giller, 1989).

Discussion and recommendations

Amantadine has an impact on both the monoaminergic and the glutamatergic systems. Together with its safety profile and neuroprotective effect, it offers some advantage in the management of children with neurodevelopmental disorders. The only well controlled study in autism (King, Wright, Handen, et al., 2001) rates the level of effectiveness as modest even though the clinicians reported statistically significant improvements in hyperactivity, inappropriate speech and to a lesser extent on stereotypy. The large placebo response could be related to the short duration of the study as well as the dosage used. The maximum dose of amantadine used was 5 mg/kg/day with a mean dose of 168.3 mg, while an average dose mentioned in many studies is 200 mg/day. A better response, separating it from placebo may have been achieved at higher doses and a longer duration of the study. The discrepancy between parents and clinicians ratings on the ABC-CV is a weakness of this study, which needs to be repeated with a different evaluating tool and dosage regimen. However, on the CGI, twice as many subjects showed moderate to marked improvement over placebo, with the clinicians reporting significant improvements in behavioral ratings. Amantadine shows beneficial effects in the symptomatic treatment of children with autism spectrum disorders. Whether autism is a hypo- and hyper-glutamatergic disorder is unresolved and further studies are needed to clarify the issue and whether amantadine has any impact on the core deficits.

In ADHD, a head to head RCT between methylphenidate and amantadine, (Mohammadi et al., 2010), reported equal efficacy. The results showed a promising level of evidence

as it used a first line medication as comparison. However, with two other open label studies (Mattes, 1980; Donfrancesco et al., 2007) not reporting similar efficacy between amantadine and methylphenidate, Mohammadi's study needs to be replicated, with a placebo group if possible, to better appreciate the impact of each drug. If the results are similar, amantadine may offer the advantage of a non-stimulant medication to treat the attention difficulties and hyperactivity in children with ADHD without upsetting the mood balance. It could represent a less expensive alternative when atomoxetine (Strattera®), the only non-stimulant approved by Health Canada for the treatment of ADHD, is not successful or is prohibitive due to cost. It could also be used as an alternative to stimulant medications when there is a history of tics (Tourette syndrome), irritability or mood lability (bipolar disorder), intolerance to other medications or when there is concern over growth trajectory. With its excellent safety profile, it also offers an alternative medication in hyperactive preschoolers when parents are concerned over the use of stimulants (Master's, 1997). Vulnerable patients with an associated or undiagnosed bipolar disorder may require close monitoring while taking amantadine to avoid a manic switch, likely due to the increase in monoamines in the amygdala and hippocampus.

Glutamatergic dysfunction especially excessive glutaminergic activity in some brain areas is seen as toxic and an important contributor to various other psychiatric disorders including OCD and depression. As a stabilizer of the glutamatergic system, amantadine offers an alternative to patients who have been unresponsive or resistant to more effective but possibly less safe drugs. It can be used safely as an augmenting agent due to its lack of interactions with most drugs, without fear of enzyme induction or inhibition, as it is excreted mainly by the kidneys. It may also be of major benefit in the management of severe depression especially if augmentation with amantadine does hasten recovery and shorten the delay in response to an SSRI (Stryjer et al., 2003). Further confirmatory evidence is required.

Conclusion

The search for medications with alternate mode of actions led to the glutamate neurotransmitter and the NMDA receptor as pharmacological targets, with amantadine being studied for use in child and adolescent psychiatry. This review found that amantadine is fairly safe in children when used properly and offers a broad range of clinical utility with positive therapeutic effects in various conditions, although its use in such conditions is strictly off label. In order to draw valid conclusions regarding its true efficacy in any of the conditions mentioned, and to advocate for its broader use, further well-controlled studies are needed.

Acknowledgements / Conflicts of Interest

The authors have no financial conflicts to disclose.

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