# Improvement of schizophrenia negative and positive symptoms with amantadine as add-on therapy to antipsychotics: a case series

## *Melhora dos sintomas positivos e negativos da esquizofrenia com o uso coadjuvante de amantadina aos antipsicóticos: série de casos*

Dear Editor,

It has been suggested that glutamate deregulation may be involved in the neuropathology of schizophrenia (SZ), mainly through N-methyl-d-aspartate receptor (NMDA) dysfunction.[1] Memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease, acts as weak non-selective NMDA receptor antagonist. Our group conducted the first randomized placebo-controlled clinical trial with memantine adjunctive to clozapine for the treatment-refractory SZ.[2] To our surprise, the improvement was not only in negative symptoms, and we have also found improvement in positive symptoms and cognition. We report the results of Amantadine, a memantine's derivate, as adjunctive therapy to antipsychotics in four cases of DSM-IV SZ. The four subjects were clinically stabilized, but presented with a pronounced motor retardation, blunted affect, emotional withdrawal and anxiety, scoring at least 3 for each of these items at The Brief Psychiatric Rating Scale (BPRS). The subjects gave informed consent for experimental use of amantadine with the dose increased up to 400mg/day over 6 weeks. Clinical response was assessed using BPRS at baseline and at sixth week and Clinical Global Impression Improvement scale (CGI-I) at the sixth week considering: -3 = very much worse, -2 = much worse,

-1 = slightly worse, 0 = unchanged, +1 = slightly improved, +2 = much improved, +3 = very much improved. The four case series are described in Table 1. These cases illustrate a clinical response to negative symptoms beyond positive symptoms improvement. Some lines of evidence suggest that amantadine would be helpful for the treatment of SZ positive, negative, and cognitive symptom domains. It is capable to increase monoaminergic tonus, through dopamine, noradrenaline and serotonine increase in amygdala and hippocampus conferring an antidepressant profile.[3] Its direct modulation of glutamate, through partial agonism of NMDA receptors has an important role on cognition, learning and new memories recall, contributing for Brain-derived neurotrophic factor (BDNF) cerebral increase and neuronal membrane stabilization.[4] There is evidence that oxidative stress is increased in patients with SZ.[5] As previously reported, memantine may be considered a neuroprotective drug, by increasing BDNF levels and preventing dopamine deficit.[2] Thus, amantadine may act like memantine by chronically reducing neuronal oxidative stress of treated patients, decreasing aggression to neurons and neuronal death. Our findings need to be replicated in a larger sample and over a longer follow-up in order to better evaluate the potential benefits of this adjunctive treatment. However, this report adds to the evidence base supporting a key role of glutamate in the pathophysiology of SZ.

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**Table 1 - Patients with schizophrenia treated with amantadine**

| Patient | Age (years) | Age at onset (years) | Sex | Dose (mg/day) | CGI-I | Concurrent medications (mg/day) | Reported side effects | BPRS Baseline | BPRS Week 6 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | 21 | Male | 400 | Very much improved | Risperidone (2), citalopram (40) | None | 29 | 4 |
| 2 | 30 | 19 | Female | 400 | Much improved | Haloperidol (12.5) | None | 39 | 16 |
| 3 | 32 | 28 | Female | 400 | Very much improved | Haloperidol (30), diazepan (40) | None | 54 | 24 |
| 4 | 24 | 20 | Female | 400 | Very much improved | Haloperidol (10), quetiapine (1000) | None | 70 | 31 |

*CGI-I, Clinical Global Impression; BPRS, Brief Psychiatric Rating Scale*

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|---|---|---|---|---|---|---|---|
| Clarissa Severino Gama | HCPA/UFRGS | FIPE-HCPA*<br>CNPq**<br>CNPq***<br>Stanley***<br>NARSAD***<br>CAPES-GRICES*** | - | AstraZeneca* | - | Actelion Pharmaceutical Ltd. | AstraZeneca<br>Elli Lilly<br>Jansen-Cilag |
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** Modest*
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**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
*Note: HCPA/UFRGS = Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul; FIPE-HCPA = Fundo de Incentivo à Pesquisa, Hospital de Clínicas de Porto Alegre; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; NARSAD = National Alliance for Research on Schizophrenia and Depression; CAPES-GRICES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Gabinete de Relações Internacionais da Ciência e do Ensino Superior.*
*For more information, see Instructions for authors.*

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