

NMDA ANTAGONISTS ARE USEFUL IN PD: NO

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The search for antiglutamatergic drugs useful in PD is burdened by great expectations and disappointing results.

At least 35 years of literature production can be tracked, and overwhelming theoretical evidence suggests that antiglutamatergic drugs could or should be useful in PD, yet evidence of positive results is restricted to few decent, blinded studies and to a massive presentation of anecdotal reports, never reaching the sufficient impact to generate a reliable meta-analysis.

Among tested drugs, one may quote MK-801, Amantadine, Memantine, Sarizotan, Dextrometorphan, Acamprosate, none of which is endowed with the outstanding evidence that it is (not may be but "is") useful in PD.

MK-801 has undoubtedly the widest background support of experimental pharmacological evidence of its antiglutamatergic activity, yet its toxicity forbade clinical application.

Sarizotan was prescribed as a drug useful to reduce dyskinesias in PD, (as dyskinesias should be reduced by anti-NMDA drugs). Yet the clinical trial ended in a disappointing failure.

Dextrometorphan was tested in PD only in anecdotal reports. It found its role in international pharmacopeia as a cough syrup and only recently, produced in a formulation associated with low dose quinidine sulfate in order to enable its concentration in central nervous system, found a new role for the treatment of pseudobulbar affect. No trials were produced in PD patients.

Acamprosate was recently introduced for the treatment of alcoholism, and supposedly should reduce impulse control disorder (ICD) in PD and, again, supposedly also dyskinesias: yet no studies are supporting these suppositions.

Memantine has been on the shelf as anti-NMDA drug for 30 years: recently it found a role for the treatment of dementia.

Its usefulness in PD or PD with Dementia is, modestly, supported in studies performed in small numbers of patients. As any other drug used for the treatment of cognitive disorders, Memantine is burdened by a lower than 1/7 ratio for Numbers Needed to Treat (NNT): the objection that several other useful drugs are characterized by lower NNTs cannot be accepted in PD, as in this disease the operating physicians are spoiled by direct (not just statistical) evidence of how and when a drug works.

Beyond these putative effects on cognitive disorders, few anecdotal reports evidenced that Memantine might reduce dyskinesias, yet no sufficient evidence was deemed to exist as a support to this hypothesis.

Amantadine is a case apart: born as an anti-flu agent, the discovery of its efficacy in PD was serendipitous. The initially assumed lack of side effects of amantadine finally led to rote rather than scientifically supported utilization of this drug, which is, if we consider the ratio between utilization, prescription and the number of published evidence based studies, probably the most used "evidence unsupported" drug. However, to its defense, one might object that this is a fate shared with L-Dopa, to the dismay of supporters of strict Evidence Based Medicine (EBM) rules.

Beyond PD, amantadine is actually used for the treatment of post-coma patients and, only in Germany, Austria and Hungary, in its intravenously injectable form, for the treatment of Neuroleptic Malignant Syndrome.

In PD amantadine is used for early (before L-Dopa) treatment and to treat dyskinesias. For the first option, no evidence, in terms of designed, reliable studies, of efficacy exists, therefore EBM clearly dismisses its usefulness for treatment in early PD, despite a heap of retrospective studies, which go as far as to suggest that amantadine prevents progression of motor complications and reduces risks of dementia.

For the second options the EBM accepted studies are in the one digit numbers, and, adding to confusion, some of the (inappropriately) quoted studies were performed with intravenous amantadine injection.

Despite these few studies were deemed sufficient to pass EBM ratings, objections can still be raised against amantadine usefulness in reducing dyskinesias: the studies supporting its action were performed in patients receiving a stable dopaminergic drug dose, thus one cannot know whether dopaminergic drug manipulations would achieve similar results as simple amantadine add-on. Furthermore amantadine is (now we know) burdened by several side effects, from

induction of psychosis or confusional states, to induction of livedo reticularis, corneal ulcers, cardiac arrhythmias (these last led recently to a warning from the European Monitoring Agency), thus imposing to any study a load of drop-out cases. Moreover amantadine effect seems to be flawed by tachyphylaxis, which makes some of its effects substantially wane over time, thus explaining the negative bias attached to this drug by many neurologists.

Nonetheless in the quoted European Countries Amantadine is used also as a life supporting treatment for neuroleptic malignant syndrome and for the akin parkinsonian hyperpyrexia syndrome, despite no evidence of its usefulness is, or ever will be, offered.

All in all, because of side effects and tachyphylaxis, Amantadine is a rather difficult drug to study, many variables have to be accounted for, responders and non responders should be reported and analysed, and elegantly designed studies are needed, rather than the lackadaisical anecdotes on its usefulness or uselessness. Unfortunately Amantadine is an old drug, (with no patents forecasting revenues), its production is not particularly expensive, thus returns and costs are uninteresting, and the writer of the present report was constantly faced with denial of any support, by the drug producer company and drug monitoring agencies, to studies on how and why Amantadine works.

However, the few designed studies and the untidy mass of studies based on anecdotal experiences, retrospective analyses or, based on data collected by telephone interviews, show that the study of Amantadine could highlight new research pathways in understanding (and possibly treating) the mechanism of complications of PD due to post-synaptic long term effects, among which one might consider dyskinesias but also ICDs.

To this last devil's advocate argument on Amantadine usefulness, one further objection can be raised: what evidence do we have that Amantadine has any effect because of an anti-NMDA activity?

Is it sufficient to show an antidyskinetic effect in order to conclude that a drug exerts any useful anti- NMDA activity?

Recent (experimental) experience with anti-metabotropic, anti-adenosine receptor designed drugs, old experience with terguride and recent experience with preladenant, suggests that the answer is no.

In conclusion, to the original question "Are anti-NMDA drugs useful in PD?", my answer is no, or, more kindly, for the time, no, as we do not have sufficient clinical evidence of what an anti-NMDA drug could do in PD.