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Assessment of the Effect of Amantadine in Patients with Traumatic Brain Injury: A Meta-Analysis

A Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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ENGLISH ABSTRACT

This thesis aimed to perform a meta-analysis to determine the efficacy of amantadine as a pharmacological therapy for cognitive problems after traumatic brain injury.

We used PRISMA Guidelines to report the steps of meta-analysis. The search included databases in English (PubMed, PsycINFO, Embase, Cochrane Library databases and the Cochrane Controlled Trials Register, ProQuest, ClinicalTrials.gov trial registry). Scientific journals, specialty critical care medicine journals and clinical neurology specialty were searched using www.scimagojr.com. The databases were searched using dates inclusive from their onset until February 16, 2019, for terms reflecting (a) traumatic brain injury, (b) amantadine, and (c) cognitive functions. From 3440 potentially relevant articles, 26 studies were included in the systematic review, of which only 14 clinical trials and 6 cohort and case-control studies were included in the meta-analysis. Data was extracted for a random-effects meta-analysis and a systematic review and quality of the clinical trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias.

Overall 16 studies with 1127 participants were included in the meta-analysis to investigate the effect of amantadine on cognitive function, 7 studies with 677 were included to assess effect of amantadine on the length of hospitalization and 3 studies were included to assess the adverse events of amantadine. There was no visual evidence of funnel plot asymmetry for cognitive function or length of hospitalization, excluding publication bias. Egger's linear regression test showed absence of publication bias (Egger's β_0 (95% CI) = -0.43597 - 2.50833, t(18) = 1.47875, p= 0.15649) and (Egger's β_0 (95% CI) = - 15.534 - 4.473, t(5)= 1.421, p= 0.21451), respectively. However, there was evidence of considerable statistical heterogeneity in meta-analysis assessing the effect of amantadine on cognitive function. This heterogeneity was explained by subgroup analyses and meta-regression. Methodological heterogeneity was mostly explained by choice of design of included studies and risk of bias while clinical heterogeneity was attributed with different onset and duration of treatment, traumatic brain injury severity and age of patients. There was no significant difference between subgroups concerning dose of administered amantadine (Q=1.24, p= 0.27). Starting amantadine in the first week after TBI had the greatest effect on cognitive function (SMD= 0.97; 95% CI 0.45 - 1.49), whereas its effect when administered between 1 week and 3 months was only SMD= 0.45 (95% CI 0.21 - 0.69). When administered after 3 months the effect was the weakest among the 3 subgroups (SMD= 0.41; 95% CI 0.22 - 0.60). Furthermore, amantadine showed a better effect size when administered to patients below 18 years of age or to patients with less severe traumatic brain injury.

When the different clinical parameters; onset of treatment, age and severity of traumatic brain injury, were assessed, meta-regression showed a statistically significant relation between onset of treatment and the effect size of amantadine. The relation between the other two parameters and the effect size of amantadine showed a marginal statistical significance. Baseline risk predicted the majority of the heterogeneity between studies except in the model of onset of treatment.