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Letter to the Editor

WHETHER LACK OF CORRELATION BETWEEN DOSE OF ANTIPSYCHOTICS AND EFFECT IS TRULY NONEXISTENT?

Dear Editor,

Clinical trials from the seventies and eighties of the twentieth century mostly agreed that there was no relationship between clinical parameters of schizophrenia and plasma concentration or dose of typical antipsychotics (Modestin and Petrin 1976, Cohen et al. 1980). On the other hand, it is surprising that studies which investigate correlation between dose or plasma concentration of atypical antipsychotics and clinical effects in patients with schizophrenia are very rare and often inconclusive (Mauri et al. 2014). In our study, which was carried out at the long-stay psychiatric Institution for Accommodation of Adults "Male Pčelice", Kragujevac, Serbia, and included 153 patients with chronic schizophrenia (54.9% males, average age 50.8 ± 10.1 years), we explored the relation between total daily dose of antipsychotics and quality of life (as measured by three scales: (1) The World Health Organization Quality of life BREF scale (WHOQOL-BREF), (2) EuroQol Five-dimensions – Five-Level scale (EQ-5D-5L), and (3) Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)) or severity of psychiatric symptoms (as measured by the Brief Psychiatric Rating Scale (BPRS)) and side effects of drugs (as measured by the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU)). About 3.9% of patients were on chronic monotherapy for more than a year with oral typical antipsychotics, 56.2% with oral atypical antipsychotics and 39.2% were on combination of typical and atypical antipsychotic taken orally (9.2% of all patients were using clozapine). Total daily dose of antipsychotic was calculated and expressed as chlorpromazine equivalent.

Significant correlations were found only between total daily dose of antipsychotics and scores on the EQ-5D-5L ($r = -0.182$, $p = 0.024$), the BPRS ($r = 0.260$, $p = 0.001$) and the UKU ($r = 0.294$, $p < 0.001$), which means that increase in daily doses is linked to decrease in quality of life, increase in adverse effects and loss of therapeutic effectiveness.

As majority of our patients were taking atypical antipsychotics, it seems that a clear therapeutic window exists with these drugs: increase of doses above those which achieve plateau of the clinical effect causes more adverse effects and decreases quality of life (Mauri et al 2007, Kane et al 2003). It has been recently shown that quality of life of patients on oral atypical antipsychotics was lower than that of the patients on depot atypical antipsychotics, due to increased incidence of adverse effects with oral dosage forms (Sağlam Aykut et al 2017). Low patient adherence to oral dosing forms may create false impression that an antipsychotic drug is underdosed, pushing psychiatrists to prescribe higher doses, which when taken cause more adverse effects and decrease quality of life. Probable reasons for giving large doses (e.g., average of

the chlorpromazine equivalent was 359.5 ± 289.2 mg) were inadequate choice of atypical antipsychotic or therapeutic resistance (e.g., 45.3% of the study patients could have been qualified as "treatment refractory"), as reflected in relatively high values of the BPRS score (e.g., 32.9 ± 8.7 points). Recent meta-analyses have shed some light on low rate of at least minimal treatment response in multi-episode patients (51%), similar to that observed in our study (Haddad and Correll 2018).

The intent of our letter was to draw the attention of the readership to unresolved issue of correlation between doses of atypical antipsychotics and their clinical effect which, due to many practical implications, requires further research.

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