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Therapeutic reference range for olanzapine in schizophrenia revised

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Therapeutic Drug Monitoring (TDM) is highly recommended for the antipsychotic drug olanzapine, with a proposed therapeutic reference range of 20 - 80 ng/ml. An adjustment towards lower ranges has already been suggested for the oral and long-acting drug formulations.
Based on a self-designed systematic methodology on how to perform a systematic review and evaluate the evidence for a therapeutic reference range on psychotropic drugs, the relevant literature was systematically searched and reviewed for olanzapine oral and long-acting injectable formulations. Eligible studies were evaluated, and population-based concentration ranges were calculated. Clinical routine TDM data from the Central Institute of Mental Health in Mannheim from 2014 to 2018 were analyzed and compared to the findings of the reviewed data.
The association between olanzapine blood levels, clinical effects, and dopamine D_2-receptor occupancy was investigated. 34 studies were detected for qualitative analysis. Of these, 23 studies reported efficacy measures in relation to olanzapine blood levels for oral olanzapine and four for olanzapine pamoate. Seven neuroimaging studies were identified. Based on these studies, conflicting evidence for a relationship between concentration, efficacy or side effects was found (assigned level of evidence low, according to (Hart et al., 2021)). Effective concentrations for 65% and 80% D_2-receptor occupancy of suitable neuroimaging studies ranged from 17 - 44 ng/ml. According to our analyses, we suggest a correction of the therapeutic reference range towards a lower range of 20 - 40 ng/ml for olanzapine oral and long-acting injectable formulations. In this range, optimal treatment response is expected in patients with schizophrenia. Higher olanzapine blood levels are well tolerated and should not necessarily require dose reduction in case of good response and tolerance.
The evaluation of the in-house TDM data revealed higher olanzapine mean blood levels of 45.7 ± 38.8 ng/ml and a mean dose of 19.5 ± 9.2 mg/d with a high interindividual variability. Interquartile ranges revealed that 50 % of the samples fell into a concentration range of 23 - 58 ng/ml. Pharmacodynamically active co-medication was common. Side effects were seen in 14% of the patients, and no correlation between olanzapine blood levels and the occurrence of side effects could be found.