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How to find and validate therapeutic reference ranges for psychotropic drugs

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A key principle of Therapeutic Drug Monitoring is the comparison of individual drug concentrations in the blood of a patient to a reference system, the drug-specific therapeutic reference range. Inconsistent methodologies concerning the way that reference ranges were determined has led to a high variation of ranges reported in the literature. Reported ranges from previous guidelines are more or less considered experts' opinions. Therapeutic reference ranges yield pharmacodynamic information from a reference population on increased likelihoods for the occurrence of desired drug effects and adverse drug reactions. The present work addresses methodological difficulties, which arise when following this concept. Based on examples from the literature, a methodology for finding a therapeutic reference range is introduced. The most robust method to find a therapeutic reference range is a well-conducted systematic literature review including a meta-analysis of prospective data. However, prospective studies, showing concentration/response-relationships, are scarce. For most psychotropic drugs, a relationship between drug concentration and therapeutic response is not well established. For these drugs, a preliminary range for referring individual drug concentrations can be, for instance, computed using population-based concentration ranges. In this context, retrospective data, ideally comprising pharmacodynamic information, can be helpful. The methodology used to estimate the limits of a reference range determines the validity of this range. Valid ranges are not based solely on a single (concentration efficacy) study. Recommendations should also consider in-sights from e.g., pharmacokinetic findings and neuroimaging studies. Ranges for four exemplary drugs have been determined and discussed in the present work. Furthermore, datasets from clinical studies and from TDM databases have been used to verify these ranges.