

## GUIDELINES ON THE CLINICAL USE OF CLOZAPINE

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Clozapine is an atypical antipsychotic drug used in schizophrenic and schizoaffective patients who do not respond or who do not tolerate the usual antipsychotic therapy.

The use of clozapine is limited because of concern about some Adverse Drug Reactions (ADRs) such as: cardiac events (included myocarditis), dose-dependent seizures and first of all agranulocytosis, a potentially fatal ADR which requires a strict monitoring of white blood cell count and absolute neutrophil count. Despite its efficacy in patients in which this drug represents the last resort and its severe ADRs, there are not yet available guidelines for clinical use and monitoring of this drug.

The aim of our research is to focus on the role of Therapeutic Drug Monitoring (TDM) of clozapine by reviewing the international literature and considering the clinical experience of our Section in the monitoring of clozapine.

TDM of clozapine has proved to be important for its clinical use. In fact, this psychotropic medication shows a multiple mechanism of action, a complex metabolism with substantial interindividual and intraindividual variability (the major focus being on the cytochrome P-450 system) and a narrow therapeutic index.

Regarding plasma levels of clozapine related to therapeutic effects, different studies have found that threshold plasma levels of clozapine in the range of 350-450 ng/ml, which are stable in time, are associated with an increased probability of a good response to the drug, with a major risk of no response or relapse for plasma levels < 250 ng/ml and intoxication for plasma levels > 750 ng/ml.

Furthermore, it has been found that response to clozapine, if there is any, usually appears within six months, but, because of the important inter- and intra-individual variability observed, it is necessary to perform an observation after 1-2 weeks from the beginning of the therapy to be continued for a maximum of one year.

Many different factors can influence plasma levels of clozapine, such as: dose, gender, age, smoking, caffeine intake, drug-drug interaction, and compliance.

We have taken in mind all these considerations, based on a review of the published data, to design an algorithm that can be useful to psychiatrists for the management of patients treated with clozapine.