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Restarting clozapine after a break in treatment

234 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Restarting clozapine after a break in treatment Interruptions in clozapine treatment are commonplace.1 Patients prescribed clozapine should be advised to contact their prescriber if they stop taking the medication. This is partly because, if clozapine treatment is stopped abruptly, there is a need to monitor for symptoms of cholinergic rebound, such as nausea, vomiting, diarrhoea, sweating and headache,2,3 as well as the possible emergence of dystonias, dyskinesias and catatonic symptoms.4–7 If the last dose of clozapine was more than 48 hours ago, it should be re- introduced using a suitable dosage titration schedule.8 Depending on the time since clozapine was last taken, it may be feasible to re-titrate the dose to a therapeutic level more rapidly than is recommended for initial treatment. While there is some evidence to suggest that faster titrations may be safe in those patients naïve to clozapine2 as well as those re-starting it,3 there is the risk that such schedules could lead to drug discontinuation because of adverse effects. The risk of myocarditis, pneumonia, agranulocytosis and seizures, as well as the occurrence of adverse effects such as tachycardia and orthostatic hypotension, are probably reduced with slower initial titration schedules,8,9 and the same may apply to restarting. More cautious dosage titration will be appropriate for certain patients, such as those who are elderly, people with Parkinson’s disease and outpatients starting clozapine who are uncertain about the potential benefits of the medication.10–12 Furthermore, there is some evidence that tolerance to the effects of clozapine is lost after only a few weeks,13,14 so people who have missed clozapine treatment for more than a week should probably restart clozapine as if it were being initiated for the first time. Restarting clozapine after gaps of various lengths should take account of the need to regain antipsychotic activity with clozapine while ensuring safety during titration. Examples of slow, fast and ultra-fast titration schedules are available15 but it is probably best to individualise titration according to patient tolerability. A key element is flexibility: the dosage schedule prescribed for a patient will depend upon how previous dosages within the schedule are tolerated. In broad terms, this means starting with 12.5mg and increasing to 25mg for the next dose if the initial dose caused no adverse effects, such as sedation, increased heart rate or lowered blood pressure. If the 25mg dose is well tolerated then 50mg can be given for the next dose, and so on. In other words, the dose is doubled each time until the target daily dosage is reached (which is likely to be the dose the patient was taking before the break in medication).

Twice daily dosing allows for a faster rate of titration than once daily dosing. Some centres use three times daily dosing, which allows for even quicker titration but may increase the risk of adverse effects caused by accumulation. For example, if a patient were to receive 12.5mg, 25mg and 50mg doses of clozapine on the first day of re- titration, then each successive dose would be added to what remains of previous doses. Thus, the effect of the 50mg dose in this schedule would be greater than a single (i.e. stat) dose of 50mg. The same phenomenon occurs with twice daily dosing, but with 12 hours between doses the contribution of the prior dose is more limited. Where a given dose in the titration schedule is not tolerated, the next dose should usually be delayed and not increased (or possibly decreased). Therefore, it is usually better to prescribe a series of single ‘stat’ doses, one at a time, rather than write up a complete schedule of doses that may then have to be changed.

Revision #1
Created 2026-01-04 20:13:18 UTC by Omar Ayman
Updated 2026-01-04 20:13:18 UTC by Omar Ayman