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RESOURCES

Clozapine

Clozapine - A Concise Clinical Overview

Clozapine Titration Schedule

Titration schedule as recommended by the clozapine Summary of Product Characteristics (SPC):

Start therapy at 12.5mg (half a 25mg tablet) once or twice on the first day, followed by 25mg or 50mg on the second day

In some cases clinicians may decide to use a higher starting dose than 25mg/day. This is considered 'off label' (off-license) and therefore should only be considered where the perceived benefits outweigh the risk

If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50mg in order to achieve a dose of up to 300mg/day within 2 to 3 weeks

The daily dose may be further increased in increments of 50 to 100mg at half-weekly or weekly intervals

Doses should be given as divided doses with the larger portion at bedtime (if unequal portions), as clozapine can cause sedation

If the patient presents with numerous and/or severe Adverse Drug Reactions (ADRs) during the titration schedule, the previous dose should be reverted to and a slower titration regime undertaken

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Drug Interactions

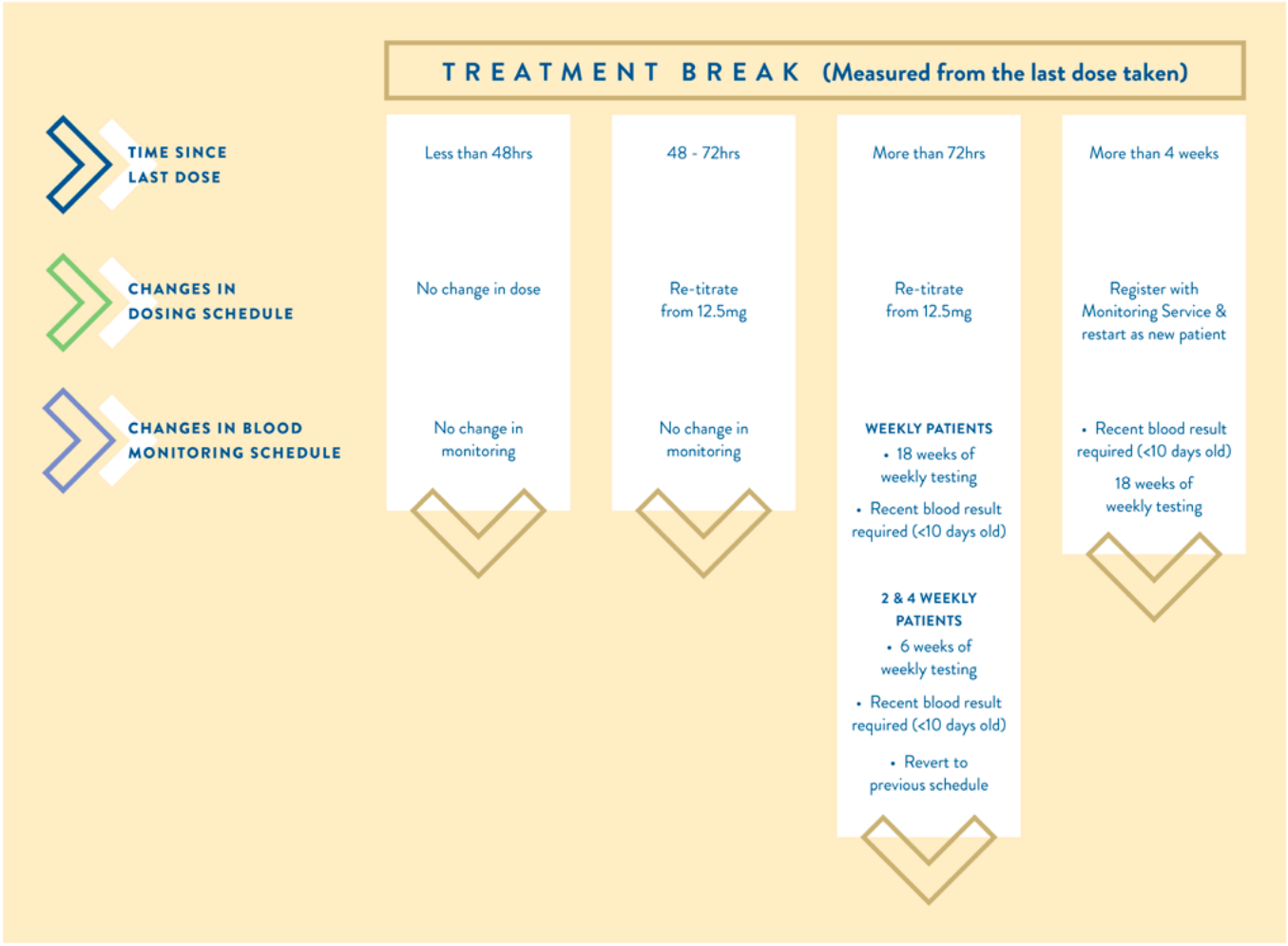
CLOZAPINE DRUG INTERACTIONS			
DRUG	**INTERACTIONS**	**COMMENTS**	**RATIONALE**
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine must not be used concomitantly with other agents having a well-known potential to suppress bone marrow function.	Clozapine and myelosuppressive medications can suppress the bone marrow, which is responsible for the generation of blood cells. This reduction in blood cells can increase the risk of infections, anaemia and bleeding problems. Long-acting depot antipsychotics (which have myelosuppressive potential) must not be used concurrently with clozapine because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia.
Anticholinergics	Clozapine potentiates the action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.	Clozapine is an antimuscarinic agent, as it antagonises muscarinic receptors. There is an additive anticholinergic effect by co-administrating clozapine with other anticholinergics. Consequently, patients are more likely to experience anticholinergic side effects, such as constipation.
Antihypertensives	Clozapine can potentiate the hypotensive effects of these agents due to its sympathomimetic antagonistic effects.	Caution is advised if Clozapine is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.	Clozapine antagonises a-adrenergic receptors. This antagonism inhibits the uptake of catecholamines in smooth muscle cells, causing vasodilation and thus potentially lowering blood pressure. Caution should therefore be exercised with patients taking blood pressure lowering medication, as the concomitant use of clozapine may potentiate the risk of hypotension (low blood pressure).
Alcohol, monoamine oxidase inhibitors (MAOIs), CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if Clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.	Central Nervous System (CNS) depressants, including alcohol, can increase the risk of CNS side effects such as drowsiness when given in conjunction with clozapine. Thus, caution is advised during concomitant use. Benzodiazepines (e.g. diazepam) in combination with clozapine can rarely cause circulatory collapse, which may lead to cardiac and/or respiratory arrest. Consequently, patients should be monitored carefully, especially during dose titration.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause an increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.	Medications such as warfarin and digoxin are highly protein bound. However, the concomitant administration of clozapine can lead to their displacement, and the occupation of protein sites by clozapine. This creates more free warfarin and digoxin in the bloodstream, thus increasing the risk of associated adverse events with these medications.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.	Neuroleptic malignant syndrome (NMS) is a severe life-threatening idiosyncratic adverse reaction to antipsychotic drugs, characterised by fever, altered mental status, muscle rigidity, and autonomic dysfunction. Clozapine and lithium combination can increase the risk of neuroleptic malignant syndrome.
CYP1A2 inducing substances (e.g. omeprazole, phenytoin)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.	Clozapine is metabolised by cytochrome P450 (CYP) enzymes in the liver. CYP1A2 inducers, such as phenytoin, potentiate the metabolism of clozapine, and thus may lead to reduced clozapine plasma levels. Low clozapine levels means that there is likely to be reduced efficacy of clozapine. Patients should thus be monitored for worsening or recurrence of psychotic symptoms and relapse. Higher doses of clozapine may be needed if CYP1A2 inducers are used concomitantly with clozapine.

Drug Interactions Continued...

CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, perazine or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.	Clozapine is metabolised by cytochrome P450 (CYP) enzymes in the liver. CYP1A2 inhibitors, such a caffeine, block the breakdown of clozapine, and thus may lead to elevated clozapine plasma levels. High clozapine levels means that there is increased potential for side effects. Lower doses may be used if cytochrome P450 inhibitors are used in conjunction with clozapine. Care must be taken when such inhibitors are initiated or withdrawn, as the clozapine dose may need to be adjusted. For example, on cessation, levels will be lower than what is effective, posing a risk of relapse. A dose increase would be required in this situation.

MANAGING TREATMENT BREAKS

Clozapine patient undergoes a break in treatment



Clozapine Brands & Formulations

COMPANY	BRAND NAME	BLOOD MONITORING SERVICE	WEBSITE Only registered HCPs can access the blood monitoring websites	TABLET STRENGTHS	ORO-DISPERSIBLE TABLETS	LIQUID FORMULATION
Leyden Delta	Leydex®	ZTAS	www.ztas.co.uk	N/A	12.5mg, 25mg, 50mg, 100mg, 200mg	N/A
Viatris	Clozaril®	CPMS	www.clozaril.co.uk	25mg, 100mg	N/A	N/A
Clonmel	Denzapine®	DMS	www.denzapine.ie	25mg, 50mg, 100mg, 200mg	N/A	50mg/ml (100ml bottle)

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