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PRACTICAL ISSUES AND UPDATES

Clozapine is the approved option in treatment-resistant schizophrenia and requires careful management

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Abstract
Clozapine is the only agent approved for treatment-resistant schizophrenia, but is underprescribed. Its adverse drug event (ADE) profile and patient monitoring requirements can discourage its use, but the benefits of clozapine generally outweigh its risks, as most ADEs are manageable. Careful patient assessment, gradual titration, minimum effective dosages, therapeutic drug monitoring and checks of neutrophils, cardiac enzymes and ADE symptoms are recommended. Neutropenia is common but does not necessarily warrant permanent clozapine cessation.

Clozapine is effective, approved and underused

Clozapine in adult treatment-resistant schizophrenia (TRS) is not only the sole approved agent in many countries [1], but is universally recommended in 17 expert guidelines [2]. Canada and the UK allow clozapine in paediatric schizophrenia, including TRS [1]. TRS is diagnosed when adherent patients do not adequately respond to correct dosages of two different antipsychotics, prescribed sequentially, each for at least 6 weeks. TRS affects 20–50% of patients with schizophrenia, and has a poor prognosis [1].

TRS may be a schizophrenia subtype, different to disease that responds to dopamine D2-receptor blockers, and possibly associated with glutamate dysfunction [1]. While its detailed pathophysiology is outside the scope of this article, clozapine's benefits may relate to its interaction with serotonin, muscarinic, adrenergic and histaminergic receptors, its relatively low affinity for D2 receptors [3] and its modulation of glutamate levels [1].

Clozapine improves TRS symptoms, including negative and cognitive symptoms, and reduces hospitalisations, suicides and mortality [1, 3]. The all-cause mortality rate ratio for clozapine versus other antipsychotics was 0.56 in a meta-analysis [4]. However, many practitioners are hesitant to prescribe clozapine [1]. Delays contribute to lower likelihoods of TRS remission [1] and reflect factors such as limited familiarity with clozapine, adverse drug event (ADE) concerns and monitoring requirements [1, 5, 6]. These disadvantages of clozapine need to be balanced against its benefits [1]. This article outlines the initiation and management of clozapine in adults with TRS, as reviewed by Correll et al. [1] and de Leon et al. [7].

Metabolism is affected by many factors...

Prescribers need to understand a patient's comorbidities, coadministered medications and demographic and lifestyle factors (Table 1), all of which may affect clozapine's metabolism (Fig. 1).

Clozapine is a substrate for cytochrome P450 (CYP) 1A2, CYP3A4 and CYP2D6 enzymes, among others, and numerous coadministered medications that induce or inhibit these enzymes have the potential to affect plasma concentrations (Fig. 1). CYP1A2 inhibitors are particularly important [1]. While lower clozapine dosages are suggested in patients receiving strong inhibitors (Fig. 1), patient response should be assessed and the dosage increased if needed [8]. Dosage adjustments may not be required for moderate or weak CYP1A2 inhibitors [8]. Inflammation and caffeine, a CYP1A2 substrate, may both increase clozapine concentrations, while smoking, which induces CYPA12, tends to reduce concentrations [1]. Concomitant use of strong CYP3A4 inducers is not recommended, but if unavoidable, dosages may need to be increased, depending on the patient's clinical response to clozapine [8].

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Table 1 Suggested clozapine dosage regimens based on potential clozapine metabolism, as reviewed by de Leon et al. [7]

Dosage parameter	Suggested dosages and targets		
	Pts of EWA descent, or pts in the US with non-Amerindian descent (US), and average clozapine metabolism	Pts of AAI descent with LCM	AAIA and other pts with LCM
Starting dose	25 mg at night	6.25 mg at night	12.5mg at night
Suggested dosage ↑[a]			
Wk 1	25 mg/d on several days	6.25 mg/d on several days	12.5 mg/d on several days
Wk 2	50 mg/d on 2 days	12.5 mg/d on 2 days	12.5–25 mg/d on 2 days
Wk 3	25 mg/d on several days	12.5 mg/d on 2 days	25 mg/d on 2 days
Target dosages			
Wk 1	100 mg/d	25 mg/d	50 mg/d
Wk 2	200 mg/d	50 mg/d	100 mg/d (AAIA) and 75–100 mg/d (OLM)
Wk 3	250 mg/d for female non-smokers, 300 mg/d for others	75 mg/d	150 mg/d (AAIA), 100–125 mg/d for female non-smokers (OLM) 150 mg/d for others (LCM)
Wk 4	250 mg/d for female non-smokers, 400 mg/d for male smokers (EWA)	75 mg/d for female non-smokers and 75–150 mg/d for male smokers	175 mg/d for female non-smokers and 300 mg/d for male smokers (AAIA)
	300 mg/d for female non-smokers, 600 mg/d for male smokers (US)		100–150 mg/d for female non-smokers and 200–300 mg/d for male smokers
Target TDM levels			
Day 7	< 140 ng/mL (EWA) and < 117 ng/mL (US)	< 118 ng/mL	< 105 ng/mL (AAIA) and < 117–175 ng/mL (LCM)
Day 14	< 280 ng/mL (EWA) and < 234 ng/mL (US)	< 235 ng/mL	< 210 ng/mL (AAIA) and < 233–263 ng/mL (LCM)
Day 21	< 351 ng/mL	< 353 ng/mL	< 315 ng/mL (AAIA) and < 291–350 ng/mL (LCM)

AAI Asian-Amerindian, *AAIA* pts of AAI descent with average clozapine metabolism, *d* day, *EWA* European or West African, *LCM* lower clozapine metabolism, *pt* patient(s), *wk* week, ↑ increase

[a]In wk 4, ↑ clozapine gradually as needed to achieve target dosage and TDM

... including demographics

Patient ethnicity, age and sex can also affect clozapine's metabolism, although data are limited in special patient groups [1]. Dosage regimens may differ based on likely rates of clozapine metabolism in different patients (Table 1) [7]. Some ethnic groups (Table 1) have relatively low CYP1A2 expression, tending to increase their clozapine plasma levels [7]. Patient age and sex can also affect clozapine metabolism; females and older patients have increased blood concentrations of clozapine through reduced clearance [9]. The European Medicines Agency specifies a lower starting dose and slower titration in older patients [10]. Clozapine's pharmacological profile in paediatric patients appears to be similar to that in adults [11]. It may be the best of limited options in pregnant women, but is contraindicated in breastfeeding [1].

Non-responders may benefit from augmentation

Up to 60% of TRS patients do not respond to an adequate clozapine trial and, provided patients have clozapine levels of ≥ 350 ng/mL, augmentation is suggested for those with persistent symptoms [12]. Consensus guidelines define an effective trial of clozapine in most cases as treatment, subject to tolerability, for at least 12 weeks from the achievement of therapeutic levels. Due to delayed responses, a 16-week trial period is suggested for those with negative or cognitive symptoms. Conversely, a shorter 8-week trial for patients with aggression or suicidality is optimal [12].

Consensus guidelines for augmentation are based on limited evidence and vary with the patient's symptom profile [12]. For positive symptoms, a median 12 episodes of electroconvulsive therapy at a rate of 3 per week, and the

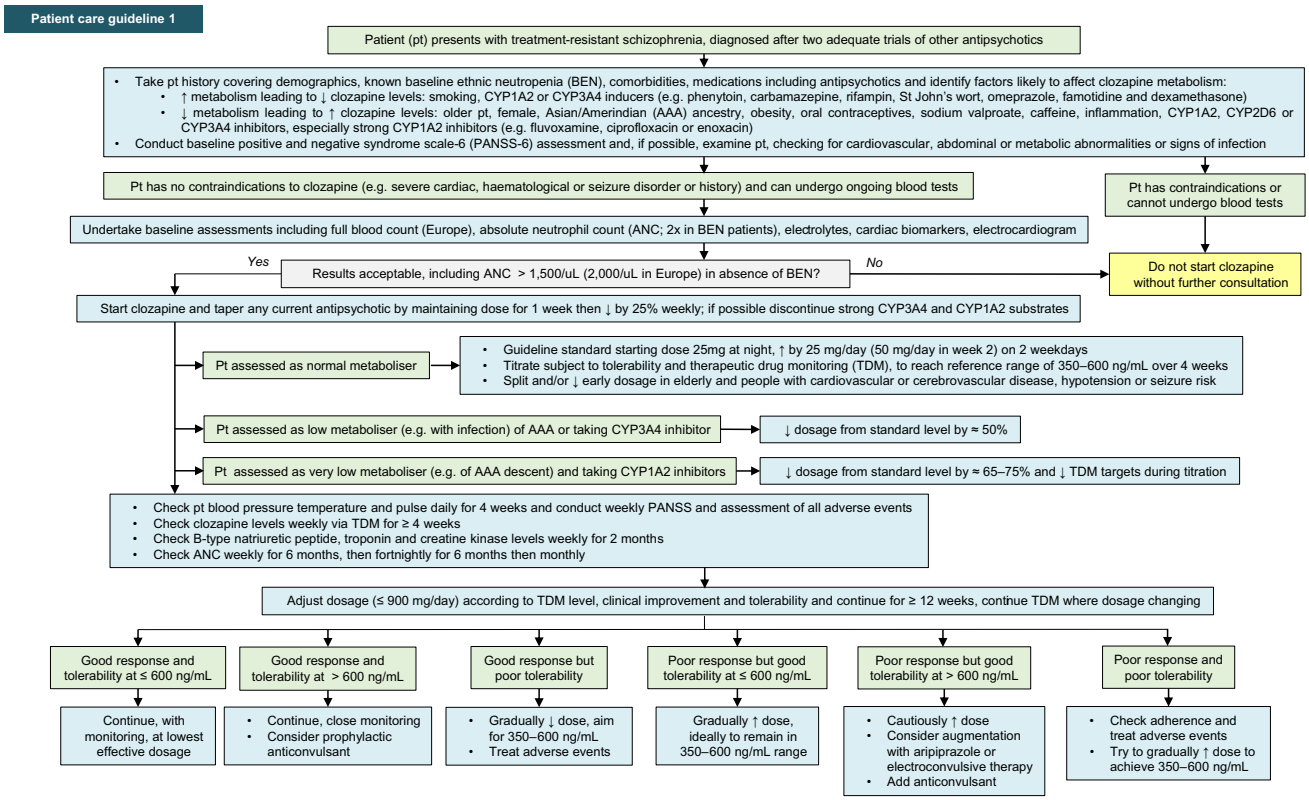

Fig. 1 Suggested initiation of clozapine in patients with treatment-resistant schizophrenia [1, 7, 8]

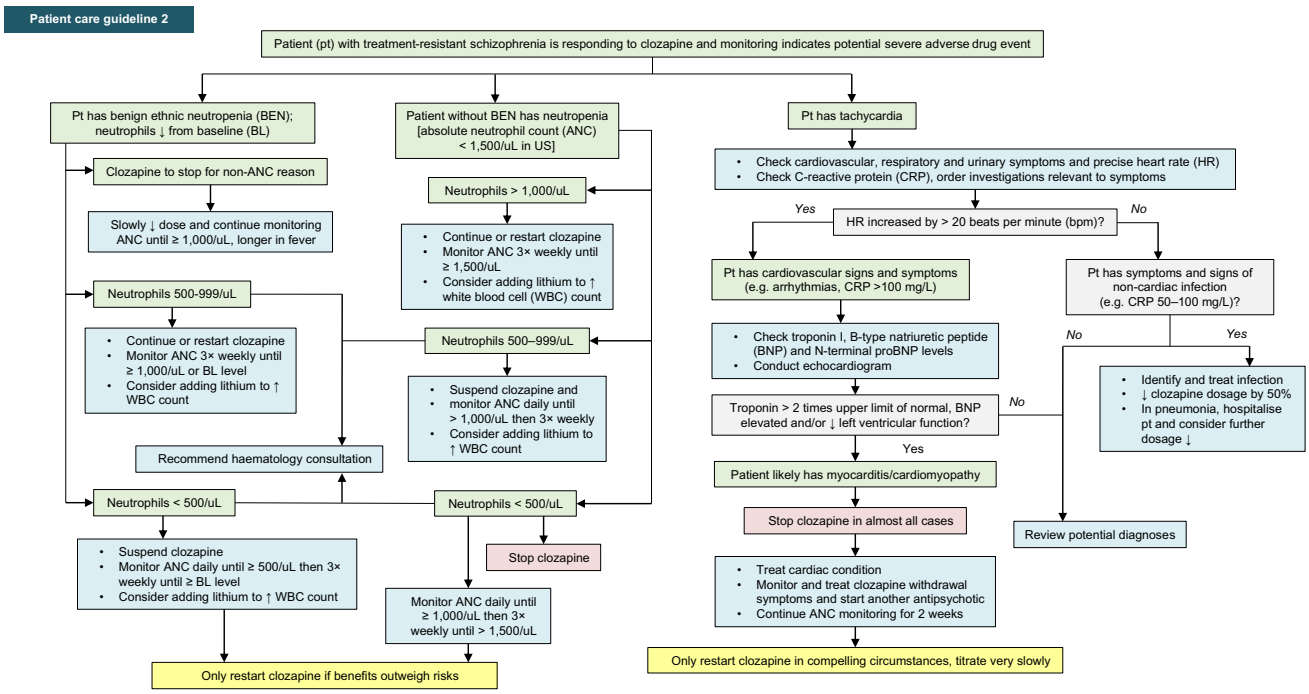

Fig. 2 Suggested management of severe adverse events in patients with treatment-resistant schizophrenia receiving clozapine [1, 7, 8]

Table 2 Common adverse drug events identified in clozapine recipients in clinical trials, as reviewed by Correll et al. [1]

ADE	Comments
Events reported in ≥ 10% of pts in one or more clinical trials [8]	
Drowsiness, sedation	Titrate clozapine slowly [7] and use divided dosages [8]
Hypersalivation	Monitor, especially in less robust pts, to ↓ pneumonia risk and encourage treatment adherence [1]
	Treat by ↓ dose if feasible, prescribe non-systemic anticholinergics in pts who can safely administer them [1]
	In other pts, consider systemic agents, but may ↑ constipation (especially propantheline) [1]
	Consider botulinum toxin B injections into salivary glands where other options fail [1]
Tachycardia	Screen for myocarditis, cardiomyopathy and rare neuroleptic malignant syndrome [8]
Dizziness ± vertigo	Consider ↓ dose to minimise orthostatic hypotension
	Trial fludrocortisone, with electrolyte monitoring, or consider midodrine as second-line option [13]
Constipation	Educate carers and pt on healthy diet, need for adequate fluid intake and exercise, and symptoms [1]
	Elicit symptoms with recognised constipation scale at each visit, as pts may not recognise them [1]
	Consider prophylactic laxatives and GI specialist referral in older pts and those with history of constipation [1]
	Avoid concomitant opioids, antihistamines and anticholinergics [1]
	Treat by ↓ clozapine dosage if feasible, plus laxatives and stool softeners [1]
Nausea ± vomiting	May signal more severe ADEs: check for hypomotility, hepatic or cardiovascular signs [8]
↑ weight	Monitor weight, glucose (via HbA1c) and lipids and check for hyperglycaemia symptoms [1]
	Prescribe metformin or glucagon-like peptide receptor antagonists for metabolic syndrome [1]
Abdominal discomfort, heartburn, dyspepsia	Check for more severe ADEs (e.g. hypomotility or cardiovascular events)
Fever	Mainly in weeks 1–3 of treatment, mostly transient and benign [8]
	Suspend clozapine, screen for neutropenia or infection [8]
Insomnia	Reported by up to 20% of clinical trial pts, but clozapine improved sleep in a subsequent comparative trial [14]
Events reported in 5–10% of pts in one or more clinical trials [8]	
Hypotension	Titrate slowly in divided doses to avoid syncope, especially in elderly pts early in course [7, 8]
	↑ fluid intake, review antihypertensives, especially α1-adrenergic agents, and consider ↓ in clozapine dose [13]
	Trial fludrocortisone with electrolyte monitoring, and midodrine as second-line option [13]
Tremor	Extrapyramidal effect, generally ↓ with clozapine vs other antipsychotics [8]
Dry mouth, headache, visual disturbances, sweating	Undertake any ↓ in clozapine dosage gradually, as sudden ↓ may cause cholinergic rebound, resulting in these symptoms [8]

ADE(s) adverse drug event(s), *GI* gastrointestinal, *HbA1c* haemoglobin A1c assay, *pt(s)* patient(s), ↓ decrease(d), ↑ increase(d)

addition of amisulpride or aripiprazole are suggested. Adding antidepressants is recommended for negative symptoms, with mood stabilisers such as lithium or lamotrigine as augmentation for patients with suicidal ideation. Adding mood stabilisers is also suggested for aggression. Finally, cognitive behavioural therapy may help negative and mixed symptoms [12].

Elicit adverse events at every follow-up

Once clozapine is started, systematic monitoring for ADEs, which cause around 17% of patients to discontinue treatment [3], is required (Tables 2 and 3; Fig. 1). Diarrhoea, rash, fatigue, extrapyramidal and urinary symptoms also occurred in 1–4% of clozapine recipients in the 2-year InterSePT™ study [8]. These may be self-limiting, and urinary incontinence may also respond to treatment with ephedrine [3].

Gradual clozapine titration appears to reduce the incidence of many ADEs (Tables 2 and 3) [7]. Alleviating common ADEs, such as constipation, hypersalivation, weight gain and tachycardia (Table 2) may reduce more severe sequelae, such as bowel obstruction, pneumonia and cardiovascular disease (Table 3) [1, 7]. Weight gain usually starts within 6–10 weeks of initiating clozapine, but the progression of associated metabolic abnormalities to ketoacidosis, severe hyperglycaemia, or significant increases in cholesterol or triglycerides was uncommon in one database review [3] (Fig. 2).

Table 3 Severe clozapine adverse drug events in treatment-resistant schizophrenia, as reviewed by Correll et al. [1] and de Leon et al. [7]

ADEs, total deaths (mortality)[a]	Comments
Common serious ADEs affecting 1–5% of pts in clinical trials [8]	
Leucopenia, neutropenia, agranulocytosis, 550 (2%)	Mild or moderate neutropenia, leucopenia or ↓ in white blood cells affects ≤ 3% of pts, usually in mo 1 of treatment; not DD[b]
	Monitor all pts as per protocol (e.g. US Food & Drug Administration): ANC wkly for 6 mo, then fortnightly (for 6 mo if ANC ≥ 1500/μL or ≥ 1000/uL in BEN, or more frequently if not), then monthly, ongoing [8]
	Suspend clozapine if ANC < 1,000/μL (< 500/μL in BEN) but continue ANC monitoring [1]
	Consider adding lithium 3–600 mg/day or granulocyte-colony stimulating factor to ↑ leucocyte production in neutropenia or rechallenge; note lithium may mask agranulocytosis
	Clozapine rechallenge was successful in 63% and ≈ 18% of pts with neutropenia and agranulocytosis, respectively [15]
Seizures, 308 (5%)	Prescribe clozapine at minimum effective dosage and cautiously in pts with history of seizures; DD[b] [1]
	Monitor clozapine levels, but consider prophylactic anticonvulsant such as lamotrigine only in high risk pts (e.g. with high alcohol intake, medications that ↓ seizure threshold and/or seizure history, or pts requiring high clozapine dosage) [1]
	If seizures occur, ↓ clozapine dose and add anticonvulsant [1]
Rare serious ADEs affecting < 1% of pts [7]	
Pneumonia, 2077 (30%)	Aspiration pneumonia can result from dysphagia, sialorrhoea and drowsiness, ↑ by infection-related ↑ in clozapine levels [1]
	Preempt infections via influenza and COVID-19 vaccinations, and use of lowest effective clozapine dosage [1]
	Educate pt about comorbidities and smoking
	Treat infection, ↓ or suspend clozapine to prevent undesired ↑ in concentration, especially if smoking also ↓ or stops
Cardiac arrest or sudden death, 1449 (90%)	May not be clozapine-related; sudden deaths are four times more common in all pts with schizophrenia vs background population [7]
	May be related to arrhythmias [7]
HF, acute myocarditis or cardiomyopathy, 539 (12%)	Myocarditis usually occurs in mo 1 of treatment, and is associated with faster titration and sodium valproate [1, 7]
	Cardiomyopathy occurs over mo/years
	Myocarditis may be over-diagnosed in Australia [7], which has 50% of global cases, or underdiagnosed elsewhere [1]
	Titrate clozapine slowly and avoid concomitant valproate [1, 7]
	Check troponin I levels in suspected myocarditis and BNP and N-terminal proBNP in suspected HF or cardiomyopathy [1]
	If cardiac biomarkers ↑, undertake echocardiogram [1]
	Stop clozapine in confirmed cases; rechallenge not recommended [8], but was successful in ≈ 65% of pts in a case series [15]
↓ GI motility, 326 (12%)	Usually in first 4 mo of treatment, especially in inpatients [7], but with persistent DD[b] risk of gastroparesis, pseudo-obstruction and dysphagia; paralytic ileus has a 44% mortality rate [1]
	↑ in older pts and recipients of anticholinergics, opioids or antihistamines [1]
	Be vigilant for and manage constipation and, if response inadequate, refer pt early to GI specialist [1]
	Do not use bulk-forming laxatives in suspected bowel obstruction, refer immediately to GI surgeon [1]
Arrhythmias, 319 (5%)	↑ risk in older pts and females, which appears DD[b] [7]
Syncope, 229 (7%)	↑ risk in older pts, may be related to rapid titration [7]
	Consider temporary ↓ clozapine dose, treat hypotension, avoid adrenaline which may cause paradoxical severe hypotension

ADE(s) adverse drug event(s), *ANC* absolute neutrophil count, *BEN* benign ethnic neutropenia, *BNP* B-type natriuretic peptide, *DD* dose-dependent, *GI* gastrointestional, *HF* heart failure, *mo* month(s), *pts* patients, ↓ decrease(d), ↑ increase(d)

[a]All clozapine-related deaths and relative mortality since 1975 in WHO pharmacovigilance database, as at July 2019 [7]

[b]Described as DD, but given inter-patient variation, may be more accurate to describe as concentration-dependent [7]

While severe neutropenia is a high-profile ADE and is the reason for clozapine's US risk evaluation and mitigations strategies (REMs) status (Fig. 1), pneumonia is the event most likely to increase mortality in clozapine recipients (Table 3). New neutropenia (Table 3, Fig. 1), the precursor of agranulocytosis, needs to be distinguished from benign ethnic neutropenia (BEN) [1]. BEN is a chronic low ANC of 1000–1800/μL that may occur in people of African, Middle Eastern and West Indian descent (Fig. 1), which is not associated with increased risks of agranulocytosis or severe infections [1]. Neutropenia definitions differ in Europe and the US (Fig. 1) [8, 10].

Other ADEs may be very rare or medically benign [3, 8], but the latter can lead to clozapine discontinuation if they are distressing to the patient [1]. Nocturnal enuresis can be treated by limiting evening fluids, emptying the bladder before bedtime and bathroom alarms, with aripiprazole a potential pharmacological option [16]. Desmopressin is a second-line option requiring monitoring for hyponatraemia [16]. Conversely, priapism is an urological emergency and responds to goserelin acetate, which may be continued

to allow patients to maintain their clozapine treatment [3]. Gradual clozapine titration may reduce the likelihood of benign hyperthermia as well as several more serious ADEs (Tables 2 and 3) [1, 7].

If clozapine is discontinued for > 2 days, then restarted, a 12.5 mg starting dose once or twice daily is recommended to reduce risk of bradycardia, hypotension and syncope [8]. Depending on tolerability, upward titration can sometimes be faster than the initial treatment titration [8]. In the absence of an emergency, when a decision is made to stop clozapine, a very slow discontinuation over 6 months, with another antipsychotic cross-titrated, is recommended [1].

Overcoming barriers to clozapine use

Two systematic reviews considered the barriers to clozapine prescription, which result in unmet needs for many patients, especially in certain countries [5, 6]. Both highlighted the complexity of blood monitoring, which in one review was the biggest barrier in most studies [6]. Insufficient provider training and education, ADEs, poor patient adherence and difficulty identifying suitable patients were other concerns, as were administrative and healthcare systems [5, 6].

Suggestions for increasing the level of prescribing of clozapine included better prescriber education (e.g. via clozapine certification during training; the US REMs status requires certification for prescribers and pharmacists [5]), integrated care (via clozapine clinics and interdisciplinary teams [5]) and simplified blood monitoring (e.g. via finger prick tests [6]). Overcoming practical, resource-based barriers, such as obtaining baseline blood tests and access to staff and facilities (especially at the time of clozapine initiation), would also be helpful [6].

Take home messages

- Offer clozapine early to patients with treatment-resistant schizophrenia, i.e. those who have not responded to adequate trials of two other anti-psychotics.
- Obtain a careful medical history before starting clozapine, including demographic and lifestyle factors (e.g. race, smoking and caffeine consumption). as these can affect clozapine metabolism.
- Disadvantages of clozapine include the variable relationships between dosage, plasma concentration and clinical response, the need for blood monitoring, and serious ADEs (e.g. pneumonia, agranulocytosis and cardiac conditions).
- Gradually titrate, with initial lower dosages, particularly in patients assessed as likely to metabolise clozapine more slowly, as well as TDM and active management of ADEs before they lead to severe sequelae.
- Well-structured guidelines for starting clozapine in different patient groups and for monitoring and managing ADEs are readily available.

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