



# A Guideline and Checklist for Initiating and Managing Clozapine Treatment in Patients with Treatment-Resistant Schizophrenia

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## Abstract

Treatment-resistant schizophrenia (TRS) will affect about one in three patients with schizophrenia. Clozapine is the only treatment approved for TRS, and patients should be treated as soon as possible to improve their chances of achieving remission. Despite its effectiveness, concern over side effects, monitoring requirements, and inexperience with prescribing often result in long delays that can expose patients to unnecessary risks and compromise their chances of achieving favorable long-term outcomes. We critically reviewed the literature on clozapine use in TRS, focusing on guidelines, systematic reviews, and algorithms to identify strategies for improving clozapine safety and tolerability. Based on this, we have provided an overview of strategies to support early initiation of clozapine in patients with TRS based on the latest evidence and our clinical experience, and have summarized the key elements in a practical, evidence-based checklist for identifying and managing patients with TRS, with the aim of increasing confidence in prescribing and monitoring clozapine therapy.

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## Key Points

Early and sustained treatment with clozapine represents the best available strategy for achieving and maintaining remission in patients with treatment-resistant schizophrenia.

Common side effects including sialorrhea, constipation and weight gain may result in poor adherence to treatment, while the existence of rare severe adverse events and the associated monitoring burden may result in delays in starting therapy.

Strategies for optimizing treatment and managing side effects are summarized and a checklist is provided.

## 1 Introduction

Schizophrenia is a serious mental illness involving positive and negative symptoms, as well as cognitive impairment [1]. It has a median incidence of 287 (uncertainty interval 246–331)/100,000 [2] and median standardized mortality ratio of 2.6 [3]. Therapies targeting postsynaptic dopamine

receptors are not effective in all cases, especially regarding negative symptoms and in patients with treatment-resistant schizophrenia (TRS). TRS is defined as patients who do not respond sufficiently to sequential trials of at least two different antipsychotics administered at appropriate doses, duration, and with adequate adherence from the patient [4–7].

TRS is a major clinical challenge that can occur early in the treatment pathway or develop later in patients who respond initially to antipsychotic treatment [8–10]. Several lines of evidence indicate that it has a different neurobiology to schizophrenia that responds to dopamine D2 receptor blockers [11, 12]. It has been hypothesized that TRS could represent a neurobiologically distinct sub-type of schizophrenia [13, 14]. Some data point to a sub-type of schizophrenia associated with TRS characterized by unaltered dopamine function [15–17], and glutamate dysregulation [18–20], which would explain why these patients do not respond to dopamine D2 blockers [21]. TRS occurs in 20–50% of patients with schizophrenia [22–24], including in community settings [25]. It is associated with higher disease burden [26, 27] and poorer outcomes [28], especially involving persistent positive symptoms despite adherence with treatment [29].

Clozapine is the only drug approved for TRS by regulators in North America, Europe, and many other jurisdictions. It is a tricyclic dibenzodiazepine derivative that interacts with multiple neuroreceptors, including dopamine, serotonin and muscarinic receptors [30, 31]. Its low affinity for D<sub>2</sub> dopamine receptors may explain its relative lack of extrapyramidal side effects [30], whilst its actions to modulate glutamate levels may contribute to its superior efficacy in TRS [32]. Clozapine is more effective than other antipsychotics for TRS [33], and it reduces rates of hospital readmission and all-cause mortality [34–36]. A systematic review and meta-analysis of long-term studies (median follow-up 5.4 years) revealed that continuous clozapine treatment was associated with a significantly lower all-cause mortality rate compared to other antipsychotics (mortality rate ratio = 0.56, 95% confidence interval (CI) = 0.36–0.85,  $P = 0.007$ ) [37], which may be due to reduced suicidality [38].

Real-world evidence has confirmed its effectiveness [39–41]. Meta-analysis of cohort studies found that clozapine resulted in greater symptom improvement compared to other second-generation antipsychotics, fewer treatment discontinuations, and a lower risk of hospitalization [42]. Based on evidence from nearly 50,000 patients, the risk ratio for hospitalization in patients taking clozapine relative to patients taking other antipsychotics was 0.817 (95% CI 0.725–0.920;  $P = 0.001$ ) [42].

A systematic review of evidence-based guidelines for antipsychotic treatment of patients with schizophrenia found that all 17 of the guidelines reviewed recommend

initiating treatment with the antipsychotic drug clozapine when patients are diagnosed with TRS [43].

However, despite this strong recommendation, clozapine is underutilized in this setting [44–46], and many patients initiate clozapine treatment after delays associated with trials of antipsychotic polypharmacy [27, 47, 48]. This may be due to the side-effect profile of clozapine, the monitoring requirements associated with its use, and a lack of prescribing experience [49, 50]. A systematic review that investigated facilitators of guideline adherence in treating TRS identified institutional directives/audits, integrated clozapine clinics, facilitated monitoring, interaction with experts, educational programs, and distribution of educational material as effective strategies for increasing access to clozapine [51]. Delaying initiation of clozapine treatment is associated with higher economic burden [52], and poorer response rates [53–56].

It may be possible to detect or predict TRS at the first psychotic episode [57–60]; however, because of the associated risk of potentially serious adverse effects [61], clozapine is not generally indicated in the first-line treatment of schizophrenia [62, 63]. Moreover, patients receiving clozapine are recommended to have hematological monitoring, particularly in the first 6 months of treatment when the risk of agranulocytosis is highest [64]. Clinicians should also be alert for possible cardiovascular, metabolic, gastrointestinal, and neurological adverse effects, some of which may be managed by reducing the dose or titration rate while monitoring frequently [65].

The objective of this review is to provide an overview and guide for clinicians and researchers on clozapine initiation, and to propose a *practical checklist* for patient selection, clozapine initiation (titration) and maintenance, side-effect monitoring and management, with the aid to facilitate appropriate clozapine use in clinical care.

## 2 Literature Search

In conducting this review, we have searched Medline using the query (((algorithm OR checklist OR tool OR recommendation OR guide\* OR policy)) AND ((review OR systematic OR meta-analysis OR metaanalysis))) AND ((clozapine AND (resistan\* OR refractor\* OR treatment-resistant schizophrenia OR TRS OR "treatment failure"))) to identify systematic reviews, meta-analyses, guidelines, and treatment algorithms related to TRS published in English before March 2022; we manually searched the reference lists of retrieved recent publications for additional relevant publications.

- Early recognition of TRS and management of psychotic symptoms are critical, as a prolonged duration of untreated psychosis is associated with negative outcomes.
  - It is important to address the preconception that some individuals will not respond to any medication. Instead, it should be reinforced that the proper medication may not have been administered
- TRS is defined as failure to respond to at least 2 antipsychotic medications, each at an adequate dose (i.e., equivalent to  $\geq 600$  mg chlorpromazine per day), with adequate adherence to treatment (i.e.,  $\geq 80\%$ ), and for a minimum treatment duration of 6 weeks (i.e., combined duration  $\geq 12$  weeks). Clozapine-resistant schizophrenia (CRS) is defined as fulfilling the same criteria as above but failing also to respond to clozapine with adequate dosing being verified by achievement of a clozapine blood level within the therapeutic range (i.e., 350-600 ng/mL).
- Ideally, objective symptom measurements should be used to assess treatment response (e.g., BPRS, CGI, PANSS, SANS, SAPS).
  - Evaluate adherence with multiple objective means (e.g., pill counts, supervised medication intake, therapeutic drug monitoring, depot administration).
  - Examine and exclude potential contributing factors for inadequate response (e.g., substance abuse disorders, neurocognitive disorders).

**Fig. 1** Definition and identification of treatment-resistant schizophrenia. TRS treatment-resistant schizophrenia, CRS clozapine-resistant schizophrenia [7]; BPRS Brief Psychiatric Rating Scale, CGI-S-TRS Clinical Global Impressions-Severity TRS Scale, PANSS Positive and

Negative Syndrome Scale, SANS Scale for the Assessment of Negative Symptoms, SAPS Scale for the Assessment of Positive Symptoms (adapted from reference [4], permission not required)

### 3 Patient Selection

The US Food and Drug Administration (FDA) indications for clozapine include TRS and suicidal behavior in patients with schizophrenia or schizoaffective disorder [62], while the European Medicines Agency (EMA) indication includes TRS and schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including second-generation antipsychotics, as well as psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed [63], whereas clozapine is indicated only for treating TRS in Australia, Japan, and Canada [66–68]. Patient selection should begin by confirming the presence of TRS (Fig. 1) [4], (Fig. 2) [7, 69–71], and the absence of contraindications for clozapine treatment, which may differ by country.

Where available, treatment should take place in a context that supports the psychosocial needs of the patient and provides care for psychiatric comorbidities and any medical problems, as well as providing access to psychiatric pharmacotherapy and monitoring [69–71].

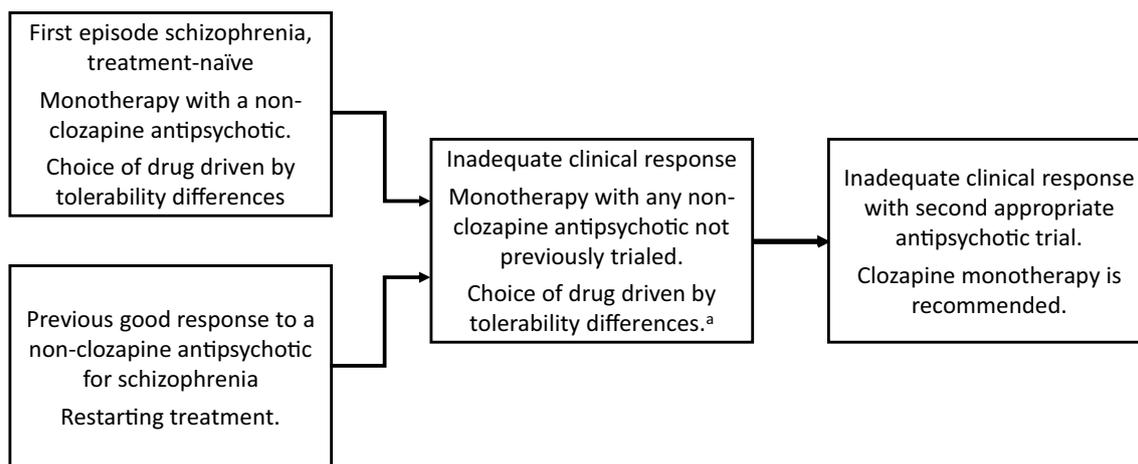
### 3.1 Special Clinical Populations

#### 3.1.1 Pediatric Setting/Early-Onset Schizophrenia

Both the EMA and the FDA state that the safety and effectiveness of clozapine have not been established in pediatric patients [62, 63]; however, guidelines from the UK National Institute for Health and Care Excellence (NICE) [6] and the Canadian guidelines recommend offering clozapine treatment for patients, including children, with early-onset schizophrenia (EOS) meeting criteria for TRS [6, 72]. A systematic review of the efficacy and tolerability of clozapine in this setting revealed that efficacy, tolerability, and dose-blood level relationships are similar to those in adults [73]. Sedation and sialorrhea were reported by most patients treated for EOS. A network meta-analysis established clozapine as more efficacious than other antipsychotics in children and adolescents with schizophrenia [74].

#### 3.1.2 Older Adults

Few geriatric patients were included in studies that informed the FDA label, therefore, caution is warranted regarding the side effects of tachycardia and orthostatic hypotension in patients with compromised cardiovascular functioning, and anticholinergic effects of constipation and urinary retention in older adults in general [62]. The EMA specifically recommends that treatment be initiated at a low dose and titrated



<sup>a</sup>Consider clozapine in severely suicidal patients

**Fig. 2** Algorithm for initial schizophrenia treatment and determination of treatment-resistance schizophrenia (TRS) [7, 69–71] (drawn from published information, permission not required)

slowly [63]. A systematic review of clozapine use in older adults confirmed the lack of controlled studies and reported modest effectiveness based on observational studies, suggesting that the decision must carefully weigh the potential benefits and risks in each individual patient considering their comorbidities and concomitant treatments [75].

### 3.1.3 Pregnancy

Clozapine treatment is not contraindicated by the EMA or FDA for pregnant women who clearly require treatment (FDA pregnancy class B) [62, 63]; however, caution and additional monitoring are warranted because of the relative lack of studies. The World Federation of Societies of Biological Psychiatry does not recommend clozapine treatment during pregnancy because its side-effect profile includes agranulocytosis, metabolic effects, and seizures [76]. A systematic review of outcomes after clozapine continuation in pregnancy based on very limited evidence concluded that a thorough benefit-risk analysis is needed, followed by close monitoring when clozapine is continued during pregnancy [77]. The decision should consider the substantial risks to the mother and fetus/infant from untreated schizophrenia [78]. Clozapine use during breastfeeding is widely contraindicated because clozapine is excreted into breast milk [63, 76, 79–81].

## 4 Clozapine Treatment

### 4.1 Initiating Treatment

Major factors influencing blood clozapine concentrations include those significantly *elevating* clozapine blood levels,

such as female sex (estrogen), older age, Asian/Amerindian ancestry, obesity, inflammation (from infection, rapid clozapine titration), high levels of caffeine use, coadministration of valproic acid, low *CYP1A2* expression, and coadministration of *CYP1A2* inhibitors; conversely, clozapine blood levels are *lowered* by smoking and other *CYP1A2* inducers, including phenobarbital, phenytoin, and topiramate dosage > 400 mg/day (Table 1) [62, 82–86].

Caffeine and tobacco consumption are common and, although their effects on clozapine metabolism can be compensated through drug titration, as with the introduction or removal of concomitant medications, patients should be cautioned about changing their daily intake of these substances. Studies identifying a clinically relevant change in caffeine intake are lacking, but a relevant change may be > 1 cup of coffee or > 2 cans of caffeinated beverages per day in non-smoking patients (> 3 cups of coffee or > 6 cans of caffeinated beverages in smokers) [82].

Inflammation reduces *CYP1A2* enzyme activity and increases clozapine blood levels; therefore, it is recommended to halve the clozapine dose in people with severe infection, including symptomatic COVID-19, until the patient has been 3 days without fever, after which the prior clozapine dose can be resumed [87].

The minimum trough level for clozapine in plasma associated with a good therapeutic response is generally thought to be 350 ng/mL, whilst levels above 600 ng/mL are associated with higher risk for dose-dependent side effects such as seizures [88, 89]; therefore, the lowest effective clozapine level should be targeted when therapeutic drug monitoring is used (see Sect. 4.6, Therapeutic Drug Monitoring). Some patients only respond to higher clozapine levels, and this may warrant higher dosages, combined with the use of prophylactic anticonvulsive therapy [62, 63].

**Table 1** Clozapine dose adjustment in patients taking concomitant medications [62]

Co-medications (selected examples)	Scenarios	
	Initiating clozapine while taking a co-medication	Adding a co-medication while taking clozapine
	Use one-third of the clozapine dose	Discontinuing a co-medication while continuing clozapine
Strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, enoxacin)	Monitor for adverse reactions. Consider reducing the clozapine dose if necessary	Increase clozapine dose based on clinical response
Moderate or weak CYP1A2 inhibitors (e.g., oral contraceptives, caffeine)	Monitor for adverse reactions. Consider reducing the clozapine dose if necessary	Monitor for lack of effectiveness. Consider increasing clozapine dose if necessary
CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, duloxetine, terbinafine, sertraline)		
Strong CYP3A4 Inducers (e.g., phenytoin, carbamazepine, St. John's wort, rifampin)	Concomitant use is not recommended. However, if the inducer is necessary, it may be necessary to increase the clozapine dose. Monitor for decreased effectiveness	Reduce clozapine dose based on clinical response.
Moderate or weak CYP1A2 or CYP3A4 inducers (e.g., tobacco smoking, omeprazole, dexamethasone, famotidine)	Monitor for decreased effectiveness. Consider increasing the clozapine dose if necessary	Monitor for adverse reactions. Consider reducing the clozapine dose if necessary

CYP3A4 cytochrome P450 3A4, CYP1A2 cytochrome P450 1A2

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When clozapine treatment is started in an in-patient setting, it is recommended to start at 12.5 mg once or twice a day on day one, followed by daily dosage incrementation by 25–50 mg up to a minimum therapeutic dosage (in adults generally 250–450 mg/day depending on sex, race, and smoking status), if tolerated. Older adults should start with 12.5 mg on the first day and daily dosage incrementation by 25 mg [63]. In the community or other settings where patients are not under continuous monitoring, slower titration should be used (see Beck et al. for a community titration schedule [90]).

Most patients with TRS will be switching from a failed antipsychotic therapy. The dosage of the failed antipsychotic should be tapered down during the initiation of treatment with clozapine. Our experience indicates that the best way to cross-taper is to keep the dose of the failed antipsychotic constant during the first week as clozapine titration is initiated, and then to gradually reduce the dose by about 25% per week, depending on the degree of symptomatic stability, the adverse effect burden during the overlap, and the ability to increase clozapine to a therapeutic dose [90]. However, the rate of reduction of the insufficiently effective antipsychotic may need to be adjusted depending on the rate of the clozapine up-titration, the side-effect profile of the failed antipsychotic and overlapping treatment, and how well the patient tolerates and responds to clozapine.

The rate of clozapine titration may influence the occurrence of some adverse events, including benign hyperthermia, tachycardia, orthostatic hypotension, and risk for myocarditis, pneumonia, agranulocytosis, and seizures [65, 82]. More gradual titration combined with careful monitoring may reduce the occurrence and severity of these events. A 2022 guideline proposes personalized titration schedules based on patient ancestry, sex, smoking status and other characteristics that influence clozapine metabolism [82]. These detailed schedules, which include weekly dosing targets and blood clozapine levels during titration are summarized in Table 2. During titration, excessive sedation, orthostatic hypotension, blood clozapine levels exceeding the limit for that week, and signs of inflammation (e.g., elevation in C-reactive protein) are reasons for pausing dosage escalation [82]. See Sect. 5 Side-Effect Monitoring and Management, and follow clozapine clinical monitoring recommendations.

## 4.2 Measuring Response to Therapy

Where possible, use a standardized symptom-rating scale, such as the 30-item Positive and Negative Symptom Scale (PANSS) [91], or a standardized brief psychiatric rating scale, such as the six-item PANSS-6 [92–95] (Table 3) at baseline and subsequently to determine responses to therapy.

## 4.3 Monitoring for Side Effects During the Titration Phase

Clozapine is associated with side effects (e.g., constipation, dizziness, drowsiness, leukopenia, sialorrhea, tachycardia, and weight gain), as well as potentially life-threatening adverse events (e.g., agranulocytosis, myocarditis, cardiomyopathy, neutropenia, agranulocytosis, paralytic ileus, pneumonia, and seizures) that warrant vigilant monitoring following established protocols, especially while titrating up to the therapeutic dose and during the first months of treatment (see Sect. 5) [31]. During this critical period, therapeutic drug monitoring (TDM) provides useful feedback for dosing and confirmation of adherence (see Sect. 4.6). Careful monitoring is also critical for detection and proactive management of side effects before they impact on treatment adherence [65].

## 4.4 Clozapine Trial Duration

After therapeutic plasma levels are achieved, Treatment Response and Resistance in Psychosis (TRRIP) Consensus Guidelines indicate that patients should receive clozapine with careful monitoring for at least 12 weeks, and ideally longer, before evaluating response, unless it cannot be tolerated [7]. In patients with strong negative symptoms, aggression, and/or those at high risk of suicide, a minimum trial duration of at least 16 weeks, and ideally longer, is recommended before evaluating response, unless it is not tolerated [96].

In patients with clozapine-resistant schizophrenia (CRS) [7], various pharmacologic augmentation strategies have been studied and can be tried [97–99]. In a naturalistic, nationwide database study, the only antipsychotic augmentation of clozapine that was superior to clozapine monotherapy for reducing the risk of hospitalization was the addition of the partial D2 agonist aripiprazole [100]. However, the most convincing evidence for efficacious augmentation of clozapine in CRS exists for electroconvulsive treatment [101].

## 4.5 Discontinuing Clozapine

A decision to discontinue clozapine may be based on issues with efficacy, adherence, or tolerability, or on the emergence of life-threatening adverse effects (see Sect. 5). When the decision is not based on an emergency, the clozapine dosage should ideally be tapered over 6 months if possible, with cross-titration to an alternative antipsychotic chosen based on history of response, tolerability, and side-effect profile (Fig. 3) [102]. Regardless of the reason for discontinuation, patients should be monitored closely for the onset or worsening of psychosis, and absolute neutrophil count monitoring should continue for 2 weeks after discontinuation.

**Table 2** Summary of clozapine titration schedules based on ancestry and clozapine metabolism [82]

Patient characteristics	Expected dosage, (concentration/ dosage ratio, ng per mL/ mg per d)	First Week	Second week	Third week	Fourth and subsequent weeks
Asia/Amerindian with lower clozapine metabolism <sup>a</sup>	75–150 mg/day (4.7 to 2.3)	First dose 6.25 mg at night <sup>b</sup> Increase daily dosage by 6.25 mg Target 25 mg/day	2 dose increases of 12.5 mg/day Target 50 mg/day TDM < 118 ng/mL on day 7	2 dose increases of 12.5 mg/day Target 75 mg/day TDM < 235 ng/mL on day 14	Target dosage from 75 mg/day for female non-smokers to 75 to 150 mg/day for male smokers <sup>c</sup> TDM < 353 ng/mL on day 21
Asia/Amerindian with average clozapine metabolism	175–300 mg/day (2.1 to 1.3)	First dose 12.5 mg at night Increase daily dosage by 12.5 mg Target 50 mg/day	2 dose increases of 12.5 mg/day Target 100 mg/day TDM < 105 ng/mL on day 7	2 dose increases of 25 mg/day Target 150 mg/day TDM < 210 ng/mL on day 14	Target dosage from 175 mg/day for female non-smokers to 300 mg/day for male smokers TDM < 315 ng/mL on day 21
European/Western Asian <sup>d</sup> ancestry with lower clozapine metabolism	100–200 mg/day (3.5 to 1.75)	First dose 12.5 mg at night Increase daily dosage by 12.5 mg Target 50 mg/day	2 dose increases of 50 mg/day Target 75 mg/day TDM < 175 ng/mL on day 7	2 dose increases of 25 mg/day Target 100 mg/day for female non-smokers; 150 mg/day for others TDM < 263 ng/mL on day 14	Target dosage from 100 mg/day for female non-smokers to 200 mg/day for male smokers TDM < 350 ng/mL on day 21
European/Western Asian <sup>d</sup> ancestry with average clozapine metabolism	250–400 mg/day (1.4 to 0.88)	First dose 25 mg at night Increase daily dosage by 25 mg Target 100 mg/day	2 dose increases of 50 mg/day Target 200 mg/day at the end of the second week. TDM < 140 ng/mL on day 7	2 dose increases of 25 mg/day Target 250 mg/day for female non-smokers; 300 mg/day for others TDM < 280 ng/mL on day 14	Target dosage from 250 mg/day for female non-smokers to 400 mg/day for male smokers TDM < 350 ng/mL on day 21
US patients with non-European ancestries other than Asia/Amerindian with lower clozapine metabolism	150–300 mg/day (2.33 to 1.17)	First dose 12.5 mg at night Increase daily dosage by 12.5 mg Target 50 mg/day	2 dose increases of 25 mg/day Target 100 mg/day at the end of the second week. TDM < 117 ng/mL on day 7	2 dose increases of 25 mg/day Target 125 mg/day for female non-smokers; 150 mg/day for others TDM < 233 ng/mL on day 14	Target dosage from 150 mg/day for female non-smokers to 300 mg/day for male smokers TDM < 291 ng/mL on day 21
US patients with non-European ancestries other than Asia/Amerindian with average clozapine metabolism	300–600 mg/day (1.17 to 0.58)	First dose of 25 mg at night Increase daily dosage by 25 mg Target 100 mg/day	2 dose increases of 50 mg/day Target 200 mg/day TDM < 117 ng/mL on day 7	2 dose increases of 25 mg/day Target 300 mg/day TDM < 234 ng/mL on day 14	Target dosage from 300 mg/day for female non-smokers to 600 mg/day for male smokers TDM < 351 ng/mL on day 21

TDM therapeutic drug monitoring of clozapine concentration, which may be useful for personalizing titration rates

<sup>a</sup>Lower clozapine metabolism, e.g., obesity, oral contraceptives, valproate, use of caffeine (for caffeine-containing beverages, see <https://www.caffeineinformer.com/the-caffeine-database>)

<sup>b</sup>Administer most of dosage at night to avoid daytime sedation and orthostatic hypotension

<sup>c</sup>Increased clozapine metabolism by cigarette smoking

<sup>d</sup>Western Asians are those whose ancestry is from Asian countries west of Pakistan

Drawn from information in reference [82], permission not required

**Table 3** Positive and Negative Syndrome Scale-6 (PANSS-6), comprises three positive and three negative items from the PANSS-30 [91, 92]

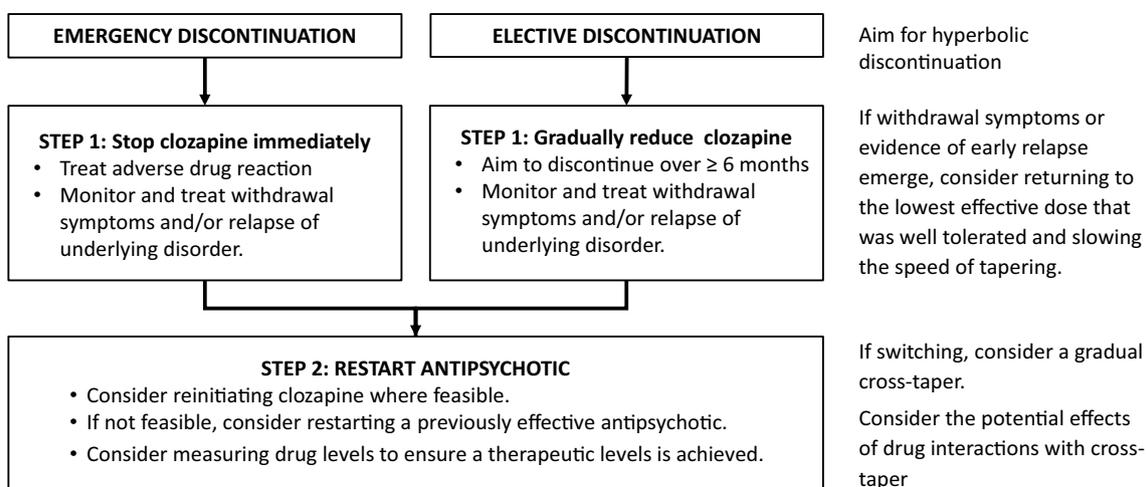
PANSS-30 Item	Item <sup>a</sup>
P1	Delusions
P2	Conceptual disorganization
P3	Hallucinations
N1	Blunted affect
N4	Social withdrawal
N6	Lack of spontaneity and flow of conversation

<sup>a</sup>Each item is scored 1–7 and values are combined; remission corresponds to PANSS-6 total scores < 14 (reproduced from reference [92], permission not required)

## 4.6 Therapeutic Drug Monitoring

TDM is not needed if the patient is tolerating and responding to clozapine. However, it can be useful during initial titration of clozapine and during maintenance when there are signs of relapse, onset of side effects that are known to be dose dependent, or changes in factors known to influence blood levels, such as concomitant medications or cigarette use [103, 104]. Poor adherence to therapy is a frequent cause of non-response that can be detected with TDM; however, low plasma levels may also be due to pharmacokinetic effects. Typical indications for TDM are listed in Table 4 [103].

The clozapine dose required to achieve and maintain blood levels in the therapeutic range varies greatly among



**Fig. 3** Provisional protocol for discontinuation of clozapine (adapted from reference [102], permission not required)

**Table 4** Typical indications for therapeutic drug monitoring (TDM) in psychiatric or neurologic patients [103]

### Obligatory TDM for drugs with high levels of recommendation to use TDM

Dosage optimization after initial prescription or after dosage change

### Specific indications for TDM for any drug independent of its level of recommendation to use TDM

Uncertain adherence to medication

Lack of clinical improvement under recommended dosage

Relapse under maintenance treatment

Relapse prevention because of uncertain adherence to medication

Recurrence of symptoms under adequate dosage

Adverse effects and clinical improvement under recommended dosage

Combination treatment with a drug known for its interaction potential or suspected drug interaction

Patient with abnormally high or low body weight

Pregnant or breast-feeding patient

Child or adolescent patient

Older adult patient (> 65 years old)

Patient with pharmacokinetically relevant comorbidity (hepatic or renal insufficiency, cardiovascular disease)

Patient with acute or chronic inflammations or infections

Patient with restrictive gastrointestinal resection or bariatric surgery

Problem occurring after switching from an original preparation to a generic form (and vice versa)

Adapted from reference [103]

patients. There may be high intra-individual variation in plasma levels even in stable patients [105], and some patients only respond after achieving blood clozapine levels above the reference range (350–600 ng/mL) [106].

TDM may be a useful tool for supporting dosing decisions because it provides direct feedback on blood concentrations

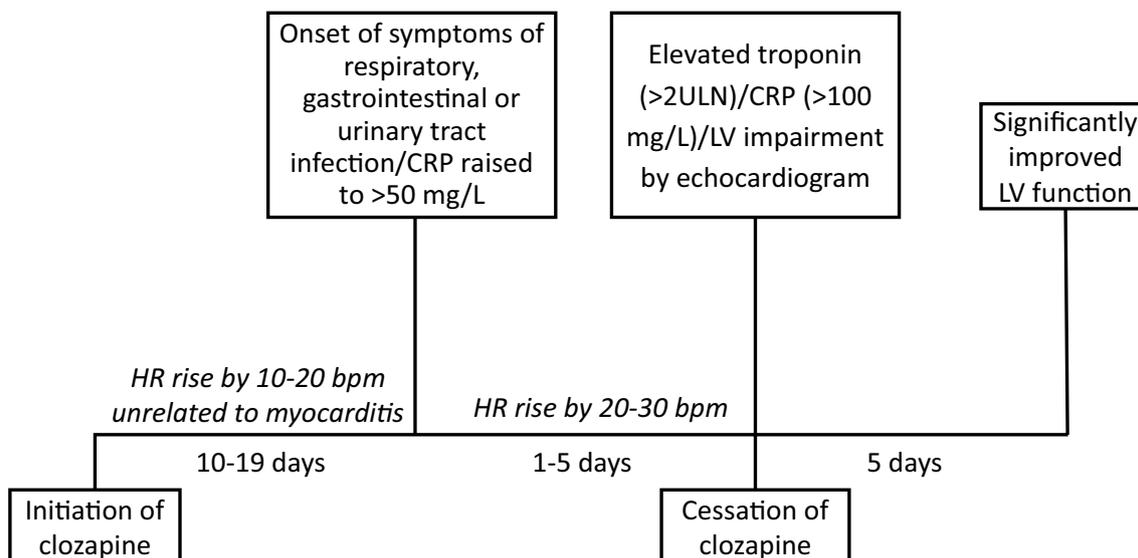
without waiting for symptoms to respond or for side effects to develop [4]. This information can be used to optimize clozapine dosage (Table 5) [104]. Moreover, TDM may potentially increase prescriber confidence [107]. Lower doses/dose reductions may be necessary in patients with clinically significant renal or hepatic impairment (Fig. 4).

**Table 5** Therapeutic drug monitoring (TDM)-informed decision-making algorithm for clozapine-treated patients<sup>a</sup> [104]

Clozapine level <sup>a</sup>	Response	Tolerability	Action
Subtherapeutic (< 350 ng/mL)	Insufficient	Intolerable	Increase dose slowly to reference range and treat side effects if possible
	Insufficient	Tolerable	Increase dose to reference range
	Sufficient	Intolerable	Consider decreasing dose
	Sufficient	Tolerable	No changes needed, continue standard side-effect monitoring
Within reference range (350–600 ng/mL)	Insufficient	Intolerable	Treat side effects and increase dose slowly remaining in the reference range, if tolerated
	Insufficient	Tolerable	Increase dose slowly remaining in the reference range, if possible
	Sufficient	Intolerable	If tolerability does not improve, decrease dose, monitor to remain in the reference range, if possible
	Sufficient	Tolerable	Continue to monitor
Supratherapeutic (> 600 ng/mL)	Insufficient	Intolerable	Consider decreasing dose, monitor. Consider prophylactic anticonvulsant
	Insufficient	Tolerable	Consider cautious dose increase or augmentation. Consider prophylactic anticonvulsant in both cases
	Sufficient	Intolerable	Decrease dose slowly, monitor to remain in the reference range, if possible
	Sufficient	Tolerable	Continue to monitor concentrations. Be vigilant for tolerability issues and consider prophylactic anticonvulsant

<sup>a</sup>Refers to clozapine only, not clozapine plus norclozapine

Adapted by permission from reference [104]



**Fig. 4** The typical evolution of clozapine-induced myocarditis. *bpm* beats per minute, *CRP* C-reactive protein, *HR* heart rate, *LV* left ventricular, *ULN* upper limit of normal [131] (reprinted by permission of SAGE Publications)

## 5 Side Effect Monitoring and Management

Clozapine is associated with side effects of varying severity, including FDA “black box” warnings for severe neutropenia, orthostatic hypotension, bradycardia, and syncope, seizure, myocarditis, cardiomyopathy, and mitral valve incompetence, as well as increased mortality in older adults with dementia-related psychosis (see prescribing information for complete list) [62]. Risk-benefit considerations should be weighed against the fact that clozapine is the only approved treatment for TRS and that clozapine treatment significantly lowers all-cause mortality [34–36].

Adverse effects should be monitored regularly according to local guidelines, which may vary between jurisdictions. Several countries require enrolment in clozapine patient-monitoring registries. Other side effects like nocturnal enuresis or incontinence can be troubling to the patient, and have major consequences if their burden leads to nonadherence and psychotic relapse [108].

Patient-compiled side-effect rating scales can provide a starting point for discussing the topic with patients. A systematic review of rating scales for side effects associated with antipsychotic medications suggested that the Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Patients (UKU-SERS-Pat), Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), and the Glasgow Antipsychotic Side-effects Scale (GASS) are useful for this purpose [109]. A validated, clozapine-specific version of the GASS (GASS-C) has been developed [110]. However, several potentially life-threatening side effects are not detected by patient-compiled rating scales. An audit conducted in UK mental health services found that patient-compiled rating scales may be underutilized [111].

### 5.1 Agranulocytosis: Laboratory Tests, Clinical Complications

Clozapine-induced agranulocytosis (severe neutropenia) is a potentially life-threatening decrease in absolute neutrophil count to levels below  $500/\text{mm}^3$  and increases susceptibility to infections [112]. It occurs most frequently during the first month of treatment and affects approximately 1% of treated patients [113, 114]. These reactions are unpredictable and do not appear to be dose dependent [115]. Findings from genomic studies suggest the involvement of multiple genes, including the solute carrier organic anion transporter 1B3/1B7 and members of the human leukocyte antigen complex [116]. People of African, Middle Eastern, or West Indian descent may present with benign ethnic neutropenia (BEN; absolute neutrophil counts  $1000\text{--}1800/\text{mm}^3$ ) [117]. BEN is not associated with frequent or severe

infections, or a higher risk of agranulocytosis with clozapine treatment [118]; however, the lower baseline neutrophil levels require a separate monitoring scheme [62].

#### 5.1.1 Agranulocytosis: Detection and Clinical Complications

Blood cell counts have been successful for preventing fatalities and are required in all treated patients. The FDA requires weekly monitoring during the first 6 months of treatment; if absolute neutrophil count remains  $\geq 1500/\mu\text{L}$  ( $\geq 1000/\mu\text{L}$  for BEN), then monitoring may be reduced to every 2 weeks for the next 6 months, and monthly thereafter (Tables 6 and 7) [62].

The EMA requires weekly monitoring of absolute neutrophil count for the first 18 weeks of treatment, followed by monthly for the duration of treatment [63].

Rechallenge after recovery from clozapine-induced neutropenia is envisioned in guidance from the FDA. A summary of 259 cases of clozapine rechallenge after major adverse events reported a success rate of 63.0% (128/203) for patients with neutropenia, and 17.7% (3/17) for those with agranulocytosis [119]. According to the reviewed cases, rechallenge may be more successful with slow titration and coadministration of low-dose lithium (300–600 mg/day), which stimulates the bone marrow production of leucocytes. Although lithium stimulates leucocyte production, it may also mask the onset of agranulocytosis. Preliminary data suggest that granulocyte-colony stimulating factor, widely used to reduce the incidence and severity of chemotherapy-induced neutropenia, may be useful for stimulating leukopoiesis during clozapine rechallenge [120–123].

### 5.2 Myocarditis and Other Cardiological Adverse Events

Clozapine is associated with the risk of rare myocarditis and cardiomyopathy. Myocarditis is an acute condition involving inflammation of the myocardium that usually occurs during the first month of treatment [124, 125], while cardiomyopathy involves structural changes to the left ventricle that occur over months to years [126]. These conditions do not appear to be dose dependent. In a meta-analysis of cardiac adverse drug reactions among 258,961 people exposed to clozapine, the myocarditis rate was 0.7% (95% CI 0.3–1.6) and the rate of cardiomyopathy was 0.6% (95% CI 0.2–2.3) [127]. The meta-analysis included mainly retrospective studies that used a variety of definitions and markers. Subsequent reports of presumptive myocarditis based on sensitive laboratory tests [128] or retrospectively identified myocarditis (cases defined as flu-like symptoms *plus*  $\geq 1$  symptom/sign of cardiac dysfunction *plus*  $\geq 1$  indicative diagnostic abnormality *and* no evidence of a viral cause) [129], suggest

**Table 6** Clozapine treatment recommendations based on absolute neutrophil count monitoring for the general patient population [62]

ANC level	Treatment recommendations	ANC monitoring
Normal range ( $\geq 1,500/\mu\text{L}$ )	Initiate treatment If treatment interrupted: $\leq 30$ days, continue monitoring as before $\geq 30$ days, monitor as if new patient	Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months
Mild neutropenia ( $1,000\text{--}1,499/\mu\text{L}$ ) <sup>a</sup>	Continue treatment; consider low-dose lithium augmentation to increase white cell count	Three times weekly until ANC $\geq 1,500/\mu\text{L}$ Once ANC $\geq 1,500/\mu\text{L}$ , return to patient's last "normal range" ANC monitoring interval <sup>b</sup>
Moderate neutropenia ( $500\text{--}999/\mu\text{L}$ ) <sup>a</sup>	Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Resume treatment once ANC $\geq 1,000/\mu\text{L}$ ; consider low-dose lithium augmentation to increase white cell count	Daily until ANC $\geq 1,000/\mu\text{L}$ , then Three times weekly until ANC $\geq 1,500/\mu\text{L}$ Once ANC $\geq 1,500/\mu\text{L}$ , check ANC weekly for 4 weeks, then return to patient's last "normal range" ANC monitoring interval <sup>b</sup>
Severe neutropenia ( $< 500/\mu\text{L}$ ) <sup>a</sup>	Recommend hematology consultation Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks	Daily until ANC $\geq 1,000/\mu\text{L}$ , then Three times weekly until ANC $\geq 1,500/\mu\text{L}$ If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC $\geq 1,500/\mu\text{L}$

ANC absolute neutrophil count, BEN benign ethnic neutropenia

<sup>a</sup>Confirm all initial reports of ANC less than  $1,500/\mu\text{L}$  with a repeat ANC measurement within 24 h

<sup>b</sup>If clinically appropriate

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that the incidence may be higher. The risk of myocarditis is higher among patients commencing clozapine treatment while receiving valproate [130]. In a review of case reports, the success rate of clozapine rechallenge after clozapine-associated myocarditis was 64.7% (11/17) [119].

### 5.2.1 Presentation of Early Cardiological Adverse Events

Although rare, cardiological adverse events are potentially life-threatening and their onset can be difficult to diagnose. They may occur more frequently in the first weeks after treatment initiation [124]; however, they are not strictly related to clozapine titration or dosage dependent, therefore vigilance and a proactive attitude are imperative over the entire course of clozapine treatment (Fig. 5) [131].

Signs and symptoms of myocarditis may include fever, malaise, tachycardia/palpitations, arrhythmias, chest pain, and/or symptoms associated with heart failure like dyspnea, tachypnea, and fatigue [63]; however, the clinical presentation is variable and many of the symptoms are not specific to myocarditis [124], highlighting the need for monitoring markers of cardiotoxicity and cardiovascular risk factors (Fig. 5) [90, 131–133]. Troponin I is a sensitive and specific marker for myocardial damage. Echocardiography may be indicated when clinical signs or abnormal biomarkers are present.

Cardiomyopathy often presents with decreased exercise tolerance, peripheral edema, and myocardial congestion, and can lead to the development of malignant arrhythmias, cardiac insufficiency, and pump failure [132]. B-type natriuretic peptide (BNP) and N-terminal proBNP are sensitive and specific markers for heart failure and cardiomyopathy.

In most cases clozapine will be discontinued once myocarditis or cardiomyopathy develops, but there may be circumstances where the benefits outweigh the risks. Any decision to rechallenge should be made with the consultation of a cardiologist or heart failure specialist, with the rechallenge attempted at least 6 months after the episode of clozapine-associated myocarditis using a titration in which dosage is increased slowly (e.g., by 25 mg per week) [133].

### 5.3 Gastrointestinal Hypomotility

Clozapine use can cause gastrointestinal hypomotility in any part of the digestive tract and, depending on the location, this can lead to constipation with increased risk of paralytic ileus and pseudo-obstruction, gastroparesis, or dysphagia and aspiration pneumonia and death [134]. A meta-analysis of 32 studies ( $n = 2,013$  patients) showed that the pooled prevalence of constipation associated with clozapine was 31.2% [135]. A comprehensive review of publications up to 2010 revealed a mortality rate for life-threatening gastrointestinal hypomotility of 15.0–27.5% [136], while mortality

**Table 7** Clozapine treatment recommendations for patients with benign ethnic neutropenia, based on absolute neutrophil count (ANC) monitoring [62]

ANC level	Treatment recommendations	ANC monitoring
Normal BEN range (established ANC baseline $\geq 1,000/\mu\text{L}$ )	Obtain at least two baseline ANC levels before initiating treatment, consider low-dose lithium augmentation to increase white cell count If treatment interrupted $\leq 30$ days, continue monitoring as before; if $> 30$ days, monitor as if new patient Discontinuation of treatment for reasons other than neutropenia	Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months  Reduce dose over 1–2 weeks if not urgent For abrupt discontinuation, continue existing monitoring until ANC $\geq 1000/\mu\text{L}$ or $>$ baseline Additional monitoring is required if fever ( $\geq 38.5^\circ\text{C}$ ) within 2 weeks after discontinuation
BEN neutropenia 500–999/ $\mu\text{L}$ <sup>a</sup>	Recommend hematology consultation Continue treatment; consider low-dose lithium augmentation to increase white cell count	Three times weekly until ANC $\geq 1,000/\mu\text{L}$ or $\geq$ patient's known baseline Once ANC $\geq 1,000/\mu\text{L}$ or at patient's baseline, check ANC weekly for 4 weeks, then return to patient's last "normal BEN range" ANC monitoring interval <sup>b</sup>
BEN severe neutropenia $< 500/\mu\text{L}$ <sup>a</sup>	Recommend hematology consultation Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks; consider low-dose lithium augmentation to increase white cell count	Daily until ANC $\geq 500/\mu\text{L}$ , then Three times weekly until ANC $\geq$ patient's baseline If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC $\geq 1,000/\mu\text{L}$ or at patient's baseline

BEN benign ethnic neutropenia

<sup>a</sup>Confirm all initial reports of ANC  $< 1,000/\mu\text{L}$  with a repeat ANC measurement within 24 h

<sup>b</sup>If clinically appropriate

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in patients who develop paralytic ileus was 43.7% [137]. The risk is highest during the first 4 months of treatment, but remains throughout treatment [138]. The risk increases with age and clozapine dose, and is higher in patients receiving concomitant treatment with anticholinergic medications, other medications with anticholinergic properties, or opioids [139].

### 5.3.1 Symptoms and Signs

Symptoms may include abdominal pain or distention, infrequent/difficult defecation, and other well-known symptoms of constipation; however, patients with schizophrenia may not be aware of abdominal symptoms, and detection should not rely on spontaneous reporting. Simply asking the patient whether they are experiencing constipation may not be reliable. Evaluation can use a brief constipation scale such as the eight-item Constipation Assessment Scale (Table 8) [140], or the ROME IV instrument [141].

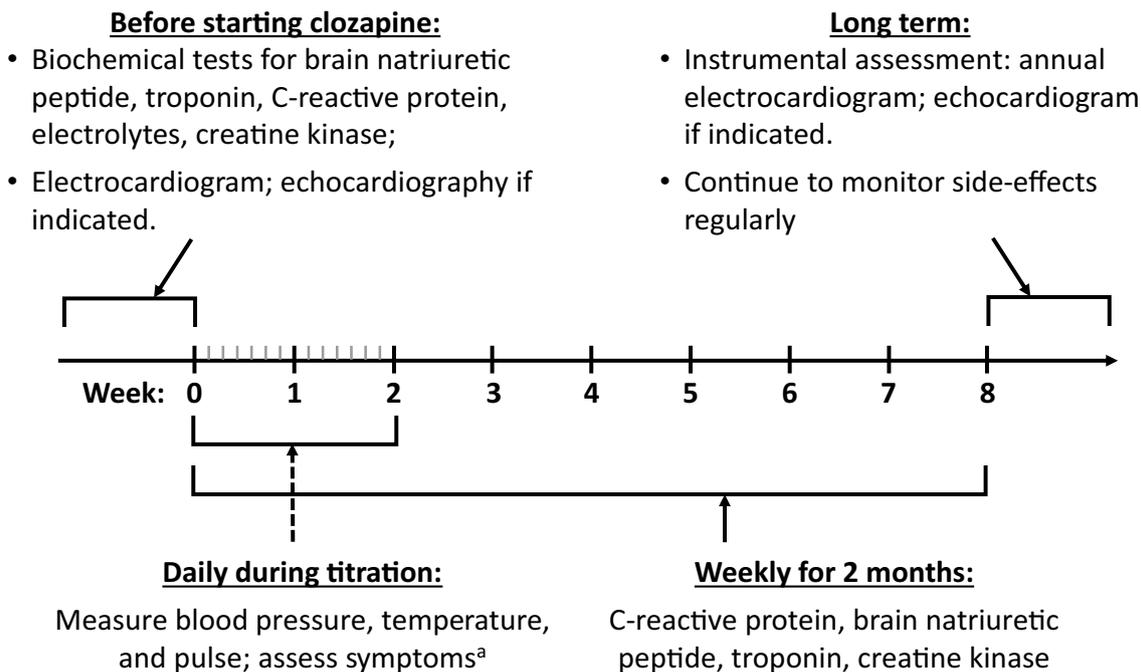
Comparing the results from patient-reported constipation with objective data from gastrointestinal motility testing revealed that self-reporting greatly underestimates the presence of this frequent and potentially life-threatening side

effect, highlighting the importance of educating the patient and family on the need for vigilance [142, 143].

### 5.3.2 Protocols and Procedures to Prevent Gastrointestinal Hypomotility

The best strategy for preventing serious gastrointestinal outcomes is to inform and remind the patient of the potential risks, and counsel them on the importance of a healthy diet, adequate fluid intake, and physical activity. Concomitant medications should be monitored to avoid drugs known to promote constipation or reduce gastrointestinal motility (e.g., opioids, antihistamines, other anticholinergic drugs). This approach should be combined with frequent constipation screening (e.g., weekly administration of a brief scale during the first few months). Abdominal auscultation, palpation, and percussion may be useful for identifying blockage.

Proactive measures might include the co-prescription of prophylactic laxatives in patients with risk factors (e.g., advanced age, history of constipation). A targeted approach in which laxatives are administered only when needed may avoid unnecessary treatment but requires timely diagnosis of constipation to prevent serious/fatal adverse events.



**Fig. 5** Monitoring for clozapine-induced cardiotoxicity [90, 131–133]. Less or more frequent monitoring may be appropriate depending on the clinical situation and local guidelines. <sup>a</sup>Symptoms may include chest pain, edema, shortness of breath, and other signs associ-

ated with heart failure. If signs or symptoms develop, or cardio markers are elevated, increase the frequency of troponin and C-reactive protein tests until normalized

**Table 8** Constipation assessment scale [140]

Item	No problem	Some problem	Severe problem
Abdominal distention or bloating	0	1	2
Change in amount of gas passed rectally	0	1	2
Less frequent bowel movements	0	1	2
Oozing liquid stool	0	1	2
Rectal fullness or pressure	0	1	2
Rectal pain with bowel movement	0	1	2
Small volume of stool	0	1	2
Unable to pass stool	0	1	2
Total score (severity = sum of scores)			

From reference [140], permission not required

Together, the prevalence and severity of potential adverse outcomes, insensitivity of self-reported screening, and impracticality of screening with gastrointestinal motility test argue for the use of prophylactic laxatives. There are potential side effects with long-term laxative use, and these need to be weighed against the benefits. The FDA recommends “considering prophylactic laxatives in high-risk patients” [62].

**5.3.3 Treatment**

Management includes clozapine dose reduction, osmotic laxative, stimulant laxative, or docusate stool softeners. Patients not responding to these should be referred to gastroenterology. When a bowel obstruction is suspected, stimulants and bulk-forming laxatives should not be used, and the patient should be referred for urgent surgical review.

**5.4 Clozapine-Associated Pneumonia**

The risk of pneumonia is higher with clozapine than with other second-generation antipsychotics [144–146], and pneumonia associated with clozapine has a higher mortality rate than its better-recognized cardiovascular and hematological adverse effects [145, 147]. Several clozapine-associated effects may contribute to increasing the risk of aspiration and the onset of pneumonia, including sialorrhea, sedation, and dysphagia/decreased gastrointestinal motility; moreover, clozapine blood levels may increase once an infection is established, and this may be compounded in smokers who are forced to stop smoking because of pneumonia. A finding of pneumonia may require a reduction or interruption of clozapine therapy until the infection is resolved [147]. This highlights the importance of reducing the chances of side effects by using the lowest effective clozapine dosage, while

remaining vigilant for signs of respiratory tract infection. Update and maintain vaccination against seasonal influenza and COVID-19. Family members and caregivers should be informed of the dangers, risk factors, and signs of aspiration pneumonia.

## 5.5 Sialorrhea

Sialorrhea is one of the most frequent adverse events of clozapine therapy (prevalence up to 90%), and may reduce treatment tolerance and adherence [148, 149]. Clozapine-induced sialorrhea may increase the risk of aspiration pneumonia in fragile patients and should be monitored at every visit. It is addressed in brief side-effect scales (e.g., the GASS-C) and can be further monitored using, for example, the two-item Drooling Severity and Frequency Scale (DSFS) [150], or the five-point Nocturnal Hypersalivation Rating Scale (NHRS) [151].

Treatment may include clozapine dose reduction, when possible, and anticholinergics. A meta-analysis of 19 studies suggests that diphenhydramine, propantheline, chlorpheniramine, and benzamide derivatives can reduce the rates of clozapine-induced sialorrhea, although caution is warranted because some agents (e.g., propantheline) increase the risk of constipation [152]. Thus, locally applied anticholinergic preparations with limited systemic exposure should be used [153, 154], but care should be taken to prevent accidental or intentional ingestion of toxic quantities, and they should be avoided in patients who struggle to follow administration instructions. In severe cases, when other approaches have failed, injection of botulinum toxin B into the salivary glands can be considered [155].

## 5.6 Clozapine-Induced Convulsions

Clozapine may cause EEG changes, but any association between EEG changes and the onset of seizures is unclear and generally prophylactic anticonvulsant therapy is not indicated in the absence of a history of or risk factors for seizures [156]. Clozapine lowers the seizure threshold in a dose-dependent fashion [157], and is associated with seizures at an annual incidence of approximately 5% [158, 159]. Whilst seizures have been reported in patients receiving low doses, the risk is increased at higher doses [160], and the FDA label urges caution when prescribing clozapine in patients with a history of seizures or other predisposing risk factors for seizure (e.g., CNS pathology, medications that lower the seizure threshold, alcohol abuse) [62].

Management of clozapine-induced seizures requires measuring serum drug concentrations and reducing the dose, as well as introducing an anticonvulsant. Consider adding valproate (not in women of child-bearing potential) or lamotrigine as seizure prophylaxis at higher clozapine

doses [159]. Dose reduction and/or addition of antiepileptic therapy allows most patients to continue clozapine therapy [161].

## 5.7 Metabolic Syndrome and Clozapine

Cardiovascular mortality contributes significantly to the reduced life expectancy of people with schizophrenia [162, 163]. Metabolic changes include hyperglycemia, dyslipidemia, and weight gain [62, 164], which predispose patients to diabetes mellitus and cardiovascular disease. Clozapine is the antipsychotic with the highest risk of weight gain and other metabolic effects [164]. Clozapine-associated changes in glucose, insulin, and weight begin within 6–10 weeks of starting treatment [164, 165].

Clozapine's action at numerous receptors has been implicated in these effects [166, 167], and the presence of one component of the metabolic syndrome is a risk factor for the other components [168].

FDA recommendations include regular monitoring of glucose levels, body weight, and symptoms of hyperglycemia (e.g., polydipsia, polyuria, polyphagia, weakness). Hemoglobin A1C levels are more sensitive than fasting glucose levels to detect prediabetes and diabetes, and do not require fasting status [169].

Options for management include considering metformin treatment to improve hyperglycemia, elevated triglycerides, and obesity [170, 171]. Glucagon-like peptide receptor agonists can increase insulin secretion while decreasing glucagon secretion and food intake, and have a larger effect on weight loss than metformin [172]. Lifestyle changes should clearly be promoted [173].

## 6 Conclusion

Patients meeting the criteria for TRS should be treated as soon as possible to improve their chances of achieving remission with clozapine; however, concern over side effects, monitoring requirements, and inexperience with prescribing often result in long delays that can expose patients to unnecessary risks and compromise their chances of achieving favorable long-term outcomes [4]. We have provided an overview of strategies to support early initiation of clozapine based on the latest evidence and our clinical experience, and have summarized the key elements in a checklist. A practical, evidence-based checklist for identifying and managing patients with TRS, such as provided here, should increase confidence in prescribing and monitoring clozapine, reducing treatment delays, and improving outcomes.

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