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Clozapine Optimization: A Delphi Consensus Guideline From the Treatment Response and Resistance in Psychosis Working Group

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***Background and Hypothesis*: There is limited evidence to guide the approaches to clozapine treatment. Accordingly, an international initiative was undertaken with the aim of developing consensus recommendations for the optimization of clozapine monotherapy. Study Design: We conducted an online Delphi survey among members of the Treatment Response and Resistance in Psychosis (TRRIP) working group comprising experts from twenty-nine countries. The threshold criterion for a consensus recommendation was ≥ 75% agreement ("agree" and "strongly agree" responses) on a question. Agreement of ≥ 50% but < 75% in a second or third Delphi round was deemed to provide guidance. *Study Results*: Forty-nine (first round), 32 (second round), and 48 (third round) of the 91 current TRRIP members participated. Expert recommendations at ≥ 75% comprised second-line treatment with clozapine in cases of persistent positive symptoms with co-occurring extrapyramidal symptoms, tardive dyskinesia, or suicidality/aggression. There was considerable disagreement on myocarditis screening parameters. The management of somatic and neuropsychiatric adverse drug reactions warrants further research for more evidence-based recommendations. Rechallenge with clozapine was recommended for eosinophilia, sinus tachycardia and fever and guidance (agreement ≥ 50%) was reached for pneumonia and thrombocytopenia. *Conclusions*: Given the limited evidence available, this consensus-based series of recommendations and guidance statements supports clinical decision-making to optimize clozapine monotherapy and provides guidance for future research in treatment-resistant schizophrenia.**

Key words: Delphi/schizophrenia/clozapine/consensus

Introduction

Treatment-resistant schizophrenia (TRS) is a subtype of the illness with a poor response to adequate trials of at least 2 first-line antipsychotics.[1] According to a recent meta-analysis of longitudinal cohort studies, 25%–33% of patients with first-episode psychotic disorder diagnosed as schizophrenia already have or go on to develop treatment resistance.[2]

Clozapine is the most effective and only unanimously guideline-recommended[3] antipsychotic for TRS, with reductions in total symptoms,[4] suicidality,[5] hospitalizations,[6,7] reduced risk of discontinuation of cardiometabolic medications,[8] and all-cause mortality,[9] relative to other antipsychotics.

The Treatment Response and Resistance in Psychosis (TRRIP) Working Group—comprising researchers and clinicians with experience and expertise in the area of schizophrenia—previously employed Delphi methods

to clarify the definitions of TRS and clozapine-resistant schizophrenia[1] and provide guidance for the management of clozapine-resistant schizophrenia.[10] To develop further expert guidance around patient selection, clozapine initiation and discontinuation, dosing, rechallenge, monitoring for and management of clozapine adverse drug reactions (ADRs), we conducted a Delphi survey with the TRRIP Working group to build international, expert-based consensus guidelines for clozapine treatment.

Methods

We conducted an iterative 3-round expert consensus Delphi survey of the TRRIP Working Group between February and July, 2022. The online survey was developed and revised by all coauthors and approved by the local data protection officer and the ethics committee of the LMU Munich (*Ref. nr. 21-0341KB*). The 91 members of TRRIP include researchers and clinicians from more than thirty countries across North and South America, Asia, Africa, and Europe with experience and expertise in the area of schizophrenia.[1] A Delphi method of consensus development was used, comprised of three online survey rounds with the licensed software "LimeSurvey" (Version 4.4.12 + 210308).

In the second/third round, an agreement threshold of ≥ 75% for each question/statement/substance was set to define consensus recommendations in accordance with Delphi methods. Agreement rates between 50% and < 75% were deemed to fall short of a consensus and taken to represent a "guidance" rather than a "recommendation."

Results

Participants

In the first round, a total of $n = 49$ TRRIP members participated in the survey with a mean of 27.8 (SD = 10.0) years of clinical experience. They had treated, on average, 181.6 (SD = 164.4) patients prescribed clozapine. The majority of professionals were based in Europe ($n = 22$, 44.9%), followed by North America ($n = 11$, 22.4%), Asia ($n = 12$, 24.5%), South America ($n = 3$, 6.1%) and Australasia ($n = 1$, 2%) (supplementary-B table 1). A total of 32 TRRIP members participated in the second round of the survey and 48 in the third.

Tables 1–3 present a summary of the consensus and guidance statements. The following sections highlight the specific findings on which the Tables are based.

Patient Selection for Clozapine

Clozapine as third-line antipsychotic treatment reached a consensus level of agreement (≥75%, hereafter referred to as consensus interchangeably with recommendation) for positive symptoms, catatonia, persistent cognitive dysfunction, and persistent psychosocial dysfunction. Use of clozapine third line reached "guidance" level of agreement for the treatment of persistent negative symptoms. For the clinical scenarios of positive symptoms with: suicidality, aggression, extrapyramidal symptoms, or tardive dyskinesia, consensus on the use of clozapine as a second- or third-line treatment was reached (suppementary-B table 7). There was a consensus that clozapine should not be used in patients who were nonadherent to hematological monitoring, ie, refusing necessary blood draws (supplementary-B table 6). The role of a past history of nonadherence in decision-making was not assessed, so this remains a factor for clinical consideration.

Assessments Pretreatment Assessment and During First Month of Treatment

The recommended pretreatment assessments prior to initiating clozapine treatment appear in table 1. Notably, agreement among international experts was not reached regarding the clinical value of testing cardiac and inflammatory laboratory parameters prior to clozapine initiation, but measurement of C-reactive protein (CRP) and troponin T/I were suggested as guidance by the experts.

In the first 4 continuous weeks of clozapine treatment, daily checks of vital parameters (inpatients) or weekly checks (for outpatients) were recommended as essential. While there was no consensus on the need for cardiac monitoring in the first 4 weeks, weekly CRP and troponin T/I testing and at least 1 electrocardiogram (ECG) to monitor potential cardiac abnormalities (ie, QTc-prolongation, arrhythmia) during this period were suggested as guidance. For monitoring the risk of myocarditis, a median of 4 weeks (mean = 7.3 weeks, SD = 5.7, $n = 32$) of weekly blood draws was considered adequate (supplementary-B table 5). Finally, the suggested guidance included therapeutic drug monitoring: one plasma clozapine level during the first 4 weeks of treatment.

Initiation, Target Dose and Titration

To initiate clozapine monotherapy, a cross-tapering strategy for the existing antipsychotic medication was recommended (supplementary-B table 40). Consensus for first- or second-line treatment of positive symptoms was 300–400 mg/day; for third-line treatment 300–400 mg/day and 400–500 mg/day reached consensus (supplementary-B tables 35 and 36). Consensus was reached for lower target doses in elderly patients, children and adolescents, nonsmokers and patients of Asian ancestry, while a guidance level of agreement was reached for female patients (supplementarty-B table 37). Slower up-titration was recommended for elderly patients, children, and adolescents, and suggested as guidance for nonsmokers. When clinically necessary, a maximum titration of 50 mg/day clozapine was recommended, as was the use of concomitant benzodiazepines (other than by intravenous injection) (supplementary-B table 34). A dose of 300–400 mg was provided as guidance for the

Table 1. TRRIP CONSENSUS Recommendations and Guidance Statements for Clozapine Monotherapy Optimization. Assessments and Monitoring for Clozapine Treated Patients

	General Strategies		Supplemental Tables
	Recommendation	**Guidance**	
Preclozapine assessment			
General	Body weight, BMI, waist circumference, vital signs		B-2
Hematological	WBC, ANC, thrombocytes, eosinophils		
Metabolic	Fasting glucose, HDL and LDL cholesterol, triglycerides, hemoglobin A1c		
Gastrointestinal/Liver	ALT/GPT	AST/GOT	
Cardiovascular	Smoking status, ECG and QTc interval,	C-reactive protein, troponin T/I	
Other	Pregnancy test		
Routine hematological monitoring			
First 4 months	WBC and ANC weekly		B-5
First 6 months	WBC and ANC according to country-specific protocols		
After 5 years	WBC and ANC every 6-months, if no history of neutropenia		

Consensus recommendation: defined as agreement proportion of at least 75% in the second/third round. *Guidance:* defined as agreement proportion of at least 50% in the second/third round. In the third round, four potentially misinterpreted questions with clinical relevance were asked again.
Note: ADR, adverse drug reaction; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BMI, body-mass-index; ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell.

maximum dose of clozapine to be taken as a single daily dose (supplementary-C Table 4).

Routine Hematological Monitoring, and Restarting Clozapine

Table 1 provides recommendations for pretreatment and routine hematological monitoring. Of note, for the requirement of weekly blood draws (absolute neutrophil count: ANC) to monitor risk of neutropenia/agranulocytosis after initiating clozapine, a median of 17 weeks (mean = 15.9 weeks, SD = 5.4, $n = 32$) was considered adequate. If a previously responsive patient has been off clozapine for at least 7 days, reinitiating clozapine with the initial titration protocol and country-specific requirements for weekly monitoring was recommended; however, if prior to discontinuation the patient was on monthly hematological monitoring, then reinitiating clozapine with the resumption of monitoring on a bi-weekly basis was recommended as being sufficient (supplementary-B table 43). For previously responsive patients with ANC ≥ 1500/μL, reinstituting clozapine was recommended; for ANC 1000–1499/μL guidance level of agreement was reached (supplementary-B table 8).

Adverse Drug Reactions

Table 2 provides consensus recommendations and guidance for ADRs according to type and body system. The Delphi process included queries on agreement with general strategies of monitoring or dose reduction, and with the use of adjunctive medications or non-pharmacologic interventions. In general, the strategy of reducing the clozapine dose in the event of clozapine-related ADRs before initiating any side-effect management interventions was supported as guidance (balancing the risk of increased psychotic symptoms with a potential reduction in ADRs). Furthermore, it was suggested guidance that the dosage of other psychotropic co-medications should be reduced before initiating these possible interventions (supplementary-B table 12). For ADRs not requiring discontinuation, opinion was sought on the strategies of clinical monitoring, reducing clozapine dose, or adding medications or other interventions targeting the ADR. These strategies are not mutually exclusive; for a given ADR, a consensus recommendation could encompass more than one strategy.

Special Clinical Situations

Infection. By consensus, the presence of any symptoms of infection indicated an essential need for an urgent physician assessment with white blood cell (WBC) count/ANC. As infection can alter the metabolism of clozapine, obtaining a clozapine level was also recommended (supplementary-B tables 4 and 44); the possibility of clozapine toxicity requires attention.

Clozapine Toxicity. If patients on clozapine become symptomatic with signs and symptoms of clozapine toxicity (ie, sedation, seizures, apathy) without relevant ANC/WBC abnormalities and plasma clozapine levels > 750 ng/

Table 2. TRRIP CONSENSUS Recommendations and Guidance Statements for Clozapine Monotherapy Optimization. Recommendations and Guidance for Clozapine-Induced Adverse Drug Reactions. Dose Reduction is by 25%–50%, and Requires Reassessment

Adverse Drug Reaction	General Strategies		Add-on Medications or Other Interventions		Supplemental Tables
	Recommendation	**Guidance**	**Recommendation**	**Guidance**	
Hematological					
ANC 1000–1499/μL	Monitoring			Lithium	B-14, B-30
ANC 500–999/μL	Discontinue			G-CSF	B-31
ANC < 500/μL	Discontinue		G-CSF		B-32
Metabolic					
Elevated LDL, total cholesterol or triglycerides	Monitoring		Healthy lifestyle instruction/intervention Statin	Metformin	B-14, B-22
Prediabetes	Monitoring		Healthy lifestyle instruction/intervention Metformin		B-14, B-20
Type 2 diabetes	Monitoring		Healthy lifestyle instruction/intervention Metformin Specialist referral	Insulin GLP-1RA	B-14, B-21
Weight gain ≥ 7%	Monitoring		Healthy lifestyle instruction/intervention Metformin	Aripiprazole	B-14, B-19
Weight gain ≥ 14%		Monitoring	Healthy lifestyle instruction/intervention Metformin	Aripiprazole	B-14, B-19
Gastrointestinal					
Liver enzyme elevation	Dose reduction				B-17
Distressing hypersalivation	Monitoring Dose reduction			Sublingual atropine eyedrops	B-14, B-17, B-26
Constipation	Monitoring Dose reduction		High-fiber diet and sufficient fluid intake Lactulose and stimulant/stool softening laxative		B-14, B-17, B-29
Cardiovascular					
Sinus tachycardia		Dose reduction		Cardiac-specific beta blocker	B-17, C-3
Orthostatic hypotension	Dose reduction	Monitoring		Adequate fluid and salt intake	B-14, B-17, B-28
Neuropsychiatric					
Functionally relevant sedation		Monitoring Dose reduction			B-14, B-17
Hypersomnia	Dose reduction	Monitoring			B-14, B-17
OCD symptoms		Dose reduction	SSRI	CBT	B-17, B-23
Epileptic potentials			Anticonvulsant prophylaxis		B-33
One clozapine-related seizure		Monitoring Dose reduction	Sodium valproate Other anticonvulsant		B-14, B-17, B-25
Repeated seizures	Discontinue				B-16
Nocturnal enuresis	Dose reduction			Manage fluid and salt intake	B-17, B-27

Consensus recommendation: defined as agreement proportion of at least 75% in the second/third round. *Guidance:* defined as agreement proportion of at least 50% in the second/third round. In the third round, four potentially misinterpreted questions with clinical relevance were asked again.
Note: ADR, adverse drug reaction; ANC, absolute neutrophil count; CBT, cognitive behavioral therapy; G-CSF, Granulocyte colony-stimulating factor; GLP-1RA, Glucagon-like peptide 1 receptor agonist; HDL, high-density lipoprotein; LDL, low-density lipoprotein; microL, microliter; OCD, obsessive compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

ml, consensus was reached on a reduction of the clozapine dose by as much as one half (supplementary-B table 4).

Smoking. If after smoking 20 cigarettes/day for at least a year the patient reports he/she ceased smoking 1 day ago (0 cigarette), a decrease of clozapine dose by 25%–33% was recommended (supplementary-B table 41).

Discontinuing Clozapine. For clinical scenarios where clozapine has to be discontinued for reasons not due to

Table 3. TRRIP CONSENSUS Recommendations and Guidance Statements for Clozapine Monotherapy Optimization. Clozapine Therapeutic Drug Monitoring: When to Obtain Clozapine Levels

Treatment Stage	Recommendation	Supplemental Tables
Initiation and stabilization	During or at 4 weeks after initiating treatment	B-44
	After a stable target dose is reached	
	Poor response of positive symptoms	
Ongoing care	When poor adherence is suspected	
	Relevant change in smoking behavior	
	Worsening of symptoms despite a stable dose	
	Co-treatment with a medication interacting with CYP-450	
	Evaluation of possible pseudo-resistance due to sub-therapeutic level	
	Suspected of infection	
	Side effects consistent with a high clozapine level	
	Symptoms of clozapine toxicity	

Consensus recommendation: defined as agreement proportion of at least 75% in the second/third round. *Guidance:* defined as agreement proportion of at least 50% in the second/third round. In the third round, four potentially misinterpreted questions with clinical relevance were asked again.
Note: CYP-450, Cytochrome P450.

life-threatening ADRs, there was consensus that clozapine should be carefully tapered down to reduce the risk of rebound psychosis or other discontinuation symptoms (supplementary-B table 13). Cross-taper and overlap-and-taper strategies reached consensus (supplementary-B table 15).

Rechallenging With Clozapine. For previous clozapine responders with recent poor adherence (<80% of prescribed and recommended dose), reinitiating clozapine was recommended (supplementary-B table 42). Rechallenge with clozapine was also recommended after resolution of the following clozapine-related ADRs: clinically relevant eosinophilia, sinus tachycardia, and fever. Guidance for rechallenge was reached for pneumonia and clinically relevant thrombocytopenia (supplementary-B table 9). There was a consensus for slower clozapine titration for rechallenge, with guidance to reduce the target dose (supplementary-B table 10). Guidance was reached not to rechallenge in case of severe neutropenia (supplementary-B table 9).

Vaccination. Consensus was reached to offer regular flu and Covid-19 vaccinations to patients treated with clozapine and to aim for a low threshold for vaccinations in general (supplementary-B table 11).

The Role of Therapeutic Drug Monitoring or When to Obtain Clozapine Levels. Therapeutic drug monitoring (TDM) reached consensus as a meaningful assessment for the stages of treatment and clinical situations noted in table 3. Should persistent and distressing positive symptoms fail to respond despite an adequate trial of clozapine, with plasma levels > 350 ng/ml but ≤ 450 ng/ml, there was a consensus that the dose should be titrated upwards to achieve a plasma clozapine level > 450 ng/ml, if tolerated by the patient (supplementary-B table 45).

Discussion

For this guidance, 49 experts from the TRRIP Working Group were asked to evaluate and review several strategies for the management of clozapine in terms of the following clinical demands.

Titration Scheme

Our recommended slower uptitration scheme for vulnerable patients (pediatric and elderly patients) is in line ie, with European Medicines Agency (EMA) recommendations for clozapine use in older adults.[11] With regard to the use of clozapine in pediatric patients with early-onset schizophrenia, it should be noted that prescribing information from both the EMA and the United States Food and Drug Administration (FDA) states that the safety and effectiveness of clozapine in such patients has not yet been established.[11,12] Nevertheless, guidelines from the UK National Institute for Health and Care Excellence (NICE) recommend the use of clozapine in children with early-onset schizophrenia meeting criteria for TRS.[13] The recommended titration scheme, with a maximum daily increment of 50 mg, is faster than in clinical practice, but is in keeping with the clozapine SmPC,[12] although it should be noted that rapid titration constitutes a risk factor for the onset of (serious) ADRs[12] and should be performed in the context of a risk-benefit evaluation. For TRS, guidelines recommend either clozapine dosages between 300 and 800 mg per day for at least 8 weeks,[14] clozapine dosages between 100 and 900 mg or blood levels of more than 350 ng/ml,[15] or only refer to the attainment of therapeutic plasma levels (for at least 3 months).[1] Since plasma levels are not always available in real-world settings, the

TRRIP working group recommended 300–500 mg/day as an initial target dose, whereas the FDA recommends 300–450 mg/day (in divided doses) by the end of 2 weeks until a maximum dose of 900 mg/day.[12]

Indication and Dosage

Given clozapine's beneficial properties in the treatment of suicidality and aggression in schizophrenia[16] and its low risk for tardive dyskinesia and EPS,[16] a second-line treatment could be initiated according to our expert consensus. This recommendation is in accord with a recent meta-analysis[17] that suggested that clozapine may be more effective than other antipsychotics when used as first- or second-line treatment.

The second-line use of clozapine in the event of co-occurring acute affective symptoms extends the proposed indication by the EMA where clozapine is indicated in TRS and in schizophrenia with severe, untreatable neurological adverse reactions to other antipsychotic agents, including second-generation antipsychotics[11] and also goes beyond FDA recommendations.[12] It has to be noted that clozapine is approved by the FDA for recurrent suicidal behavior in patients with schizophrenia without meeting TRS criteria, and thus, clozapine can be considered earlier in the course of the disease if indicated.[12] Second-line off-label clozapine treatment in schizophrenia was not recommended for positive symptoms without co-occurring symptoms which is in line with current schizophrenia guidelines[14,15] despite reasonable evidence of efficacy from a few clinical trials.

For first- or second-line treatment of positive symptoms, lower dosages may be effective according to the experts, but this is beyond current Summary of Product Characteristics (SmPCs) since clozapine is only licensed for TRS.[11,12]

That specific populations (eg, elderly patients with TRS) might need lower target doses is not specified in current SmPCs, where only a low starting dose and gradual titration is recommended to minimize the probability of emergent ADRs.[12] Similarly, lower clozapine doses and slower titration speed may be needed according to ancestry status. This adaptive dosing schema has been recommended in a recently published consensus statement,[18] with native American and Eastern Asian populations having poorer cytochrome P450 1A2 metabolizer status, leading to higher plasma clozapine levels relative to its dose than for other ancestries.

Some patients prefer to take clozapine as a single daily dose (eg, at bedtime) rather than 2 or more divided doses. The clozapine SmPC only recommends q.d. intake for dosages ≤ 200 mg/day,[12] while the advice of our experts was not to prescribe daily doses above 500 mg as single doses.

TDM should, if possible, be broadly implemented in routine practice with clozapine monotherapy. This is to ensure optimal safety and efficacy, especially since reaching plasma levels ≥ 350 ng/ml over a period of 12 weeks is recommended for multiple symptom domains in TRS in order to rule out pseudo-resistance and optimize treatment response.[10] However, recent evidence suggests that plasma clozapine levels above 600 ng/ml cannot be presumed to be associated with superior response rates,[19] and there is a lack of evidence on response rates with a threshold level of 450 (but below 600) ng/ml, which was recommended in our expert survey.

Complications—and When to Discontinue Clozapine

Clozapine is associated with rare, but potentially life-threatening ADRs (eg, severe neutropenia/agranulocytosis, myocarditis, paralytic ileus) that warrant vigilant monitoring following established protocols.[20,21] For myocarditis screening, the recommendation for regular checks of vital parameters is in keeping with clinical guidelines. Heart rate elevation of 120 bpm, or an increase by > 30 bpm compared with baseline, or fever, can be considered *soft signs* for potential myocarditis.[22] Weekly CRP and troponin T/I testing in the first four weeks suggested as guidance, is also in keeping with current clozapine monitoring guidelines.[22] According to our experts, weekly myocarditis screening for a median of four weeks (mean = 7.3 weeks) is warranted which is in line with a current myocarditis monitoring protocol, where monitoring up to day 28 is proposed.[22] According to the available protocol from Ronaldson et al., discontinuation of clozapine is warranted if troponin T/I is elevated to at least twice the upper limit of normal or CRP is elevated to > 10 mg/dl.[22] The SmPC recommends clozapine cessation in any event of myocarditis or cardiomyopathy.[11,12]

Agranulocytosis is another rare ADR that might occur during clozapine treatment, most frequently during the first month; it is probably immune-mediated.[23] FDA currently requires weekly monitoring of absolute neutrophil count (ANC) during the first 6 months of treatment[12] and the EMA requires weekly monitoring for the first 18 weeks of treatment.[11] In our survey of experts, weekly ANC monitoring for at least 16 weeks was considered adequate.

The suggestion from our experts to reinstitute clozapine at an ANC count ≥ 1500/μL is in keeping with United Kingdom and some European regulations[24] and stricter than FDA regulations where—as mentioned above, clozapine can be reinstituted at an ANC of at least 1000/μL.[12] It has to be noted that our experts recommended lithium as an intervention prior to the cessation of clozapine for ANC count between 1000 and 1499/μL. Furthermore, the FDA also advises that for individuals with Benign Ethnic Neutropenia who are subject to lower ANC levels, a different monitoring

scheme should be used.[12] Our experts recommended discontinuation of clozapine in severe neutropenia according to current regulations[11,12] and proposed the use of granulocyte-colony stimulating factor (G-CSF), which is used to reduce the incidence and severity of chemotherapy-induced neutropenia and accelerates the return to ANC counts.[25] Our experts suggested as guidance the use of G-CSF for ANC counts < 1000/μL, and there is increasing evidence for the use of G-CSF when undertaking clozapine rechallenge after neutropenia.[26] This guidance is not evidence-based since no controlled studies are available.

Of note, the management of other severe complications that should prompt immediate discontinuation of clozapine according to SmPCs, such as QTc-prolongation and ileus,[27] were not asked about in our expert survey; only rechallenge after return to baseline was discussed as an option.

Somatic ADRs

Multiple ADRs can occur during clozapine monotherapy and the cardiometabolic burden associated with clozapine treatment is one of the worst, compared with other second-generation antipsychotics.[28]

Weight gain is a burdensome ADR than can occur during clozapine treatment,[28] along with an increased risk of the metabolic syndrome, prediabetes and diabetes, and dyslipidemia, all of which rather preclude the use of clozapine as a first-line antipsychotic.[15,20] Should emergent problems with clozapine include ≥ 7% weight gain, significantly elevated LDL or total cholesterol or triglycerides, and prediabetes and diabetes, healthy lifestyle instruction and healthy lifestyle interventions were recommended in line with state-of-the-art evidence to avoid unfavorable metabolic outcomes in severe mental illness.[29,30] Metformin as an add-on treatment, which was recommended for ≥ 7% weight gain, prediabetes, and onset of type 2 diabetes, can be effective in treating antipsychotic-induced weight gain,[31] but recommendations differ regarding metformin's place in the hierarchy of different management options.[32,33] The preferable use of metformin as early intervention strategy for antipsychotic-induced weight gain was strongly recommended in a recent guideline despite limitations of off-label use.[32] Of note, the advent of glucagon-like peptide receptor agonists (GLP-1RAs), such as ie, semaglutide might have an impact on future recommendations for antipsychotic-induced metabolic dysregulations, since they are presumed to have a larger effect on weight loss than metformin.[34] However, since this intervention has not been endorsed by our experts, which may suggest that the evidence available thus far is insufficient to support a recommendation for routine use.

One frequently occurring cardiac ADR, sinus tachycardia, is being reported in up to 25% of people treated with clozapine[35] and is mostly reported as a transient phenomenon during clozapine titration. Despite the lack of published evidence, the use of cardiac-specific beta-blockers was recommended in our expert survey, in light of high clinical relevance of this problem and the persistent and distressing nature of the symptoms.[35]

Hypersalivation which might be due to elevated plasma clozapine levels[36] is a frequent clinical phenomenon that is potentially associated with aspiration pneumonia in patients treated with clozapine.[37] According to meta-analytic evidence, several add-on agents might be beneficial,[38] but evidence from high-quality randomized controlled trials is lacking.[16] Locally applied anticholinergic agents such as sublingual atropine drops might be beneficial for some patients,[39] but no consensus was established in our expert survey. Nevertheless, in order to prevent respiratory complications, regular flu vaccinations and a low threshold for vaccinations in general are recommended for patients on clozapine given the increased rates of pneumonia compared to other antipsychotics.[37]

Further, clozapine is associated with gastrointestinal hypomotility[40,41] which affects approximately up to 75% of patients.[42] The risk of serious morbidity/mortality is substantial,[41–43] which calls for active monitoring of bowel function and treatment with laxatives[42] to prevent serious outcomes, such as paralytic ileus. The recommendation to reduce the clozapine dose is in keeping with available evidence where a dose-dependent effect is presumed.[41] Most importantly, high-fiber diet and sufficient fluid intake, the application of lactulose and treatment with a stimulant and softening laxative (ie, macrogol) reached consensus in our survey, which aligns with the state-of-the-art recommendations for the management of chronic constipation which also comprise physical exercise.[44] It has to be noted that an evidence-based guidance already exists on how to manage clozapine-induced constipation in a step-wise manner with increasing doses over time of various laxatives according to response (eg, the Porirua protocol).[45]

For the management of orthostatic hypotension, sedation during the day and hypersomnia, evidence is sparse[16] and this was reflected in the expert opinion in our survey, where recommendations or suggestions were not postulated. Similarly, this was also the case for the ADR of nocturnal enuresis. Here, according to a recent meta-analysis, review of concomitant medications that may exacerbate nocturnal enuresis and urinary incontinence, such as benzodiazepines or other sedating medications, and consideration of clozapine dose reduction may be effective.[46]

In addition to under-investigated domains of ADRs, some rare reactions associated with clozapine might be still overlooked, such as the relevance of eosinophilia in myocarditis or clozapine-related drug reaction with eosinophilia and systemic symptoms syndrome.[47]

Neuropsychiatric Side Effects

The prevalence of OCD in people with schizophrenia treated with clozapine is presumed to be as high as approximately 50%[48] after a decade or more of treatment and the occurrence appears not to be related to clozapine dose.[48] Since selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for OCD symptoms, our recommendation of add-on treatment with an SSRI for clozapine-induced OCD symptoms appears worth considering. CBT treatment can be offered in line with evidence[49] and evidence-based recommendations for schizophrenia.[13]

Of note, clozapine is the only antipsychotic that carries a "Boxed Warning" by the FDA regarding its risk of inducing seizures[12] and daily doses above 450 mg may increase seizure risk.[11] Since SmPCs point out that the risk is dose-related, low starting dose and gradual titration are recommended as preventive actions, as is divided clozapine dosing.[12] Clinicians should be cautious when prescribing clozapine to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). The initiation of an anticonvulsant as prophylaxis in the emergence of epileptic potentials and as treatment in the emergence of at least one seizure (or repeated seizures) should follow a risk-benefit evaluation, where the clinician should aim to prescribe the lowest possible clozapine dose, take into consideration the pharmacological properties of the anticonvulsant of choice and perform a close monitoring of plasma levels.

Rechallenge

Another controversial debate in clozapine is rechallenge. Our experts' general recommendation was that the titration of clozapine dose for rechallenge should be slow and gradual. For low ANC counts, coadministration of low-dose lithium (300–600 mg/day) was not recommended or suggested by the experts, despite the evidence that lithium is presumed to stimulate the bone marrow production of leucocytes according to some case reports,[50–52] because of the risk that the use of lithium may mask the development of agranulocytosis.

Reports of successful and safe reinitiation of clozapine after neutropenia,[53,54] eosinophilia,[55] neuroleptic malignant syndrome (NMS),[56,57] and myocarditis[58] are documented in the literature, but whether clozapine rechallenge is a reasonable clinical option after return to baseline for patients depends on country-specific prescribing regulations and guidelines. Even though rechallenge after severe neutropenia is not recommended by SmPCs,[11,12] according to our experts, there is flexibility with regard to overruling ANC-based treatment recommendations to continue or restart clozapine in individuals where the benefit outweighs the risk for severe neutropenia in consultation with hematology.[12,52]

Opposition to the rechallenge of patients with a history of clozapine-induced myocarditis was at the level of guidance rather than expert recommendation level. There are some encouraging case reports[52] but the evidence is limited. Our experts only recommended rechallenge for clinically relevant eosinophilia, sinus tachycardia, and fever. For other ADRs, such as clinically relevant thrombocytopenia and pneumonia, rechallenge was suggested as guidance by the experts, but not for NMS, ileus, and severe cardiac ADRs.

Conclusion

Whereas the superior efficacy of clozapine in TRS is clearly established, the handling of ADRs related to clozapine are underinvestigated and the published guidelines for monitoring clozapine treatment lack internationalization and harmonization. Limitations of our approach, which have already been described in more detail elsewhere,[10] include the low quality of evidence for expert opinions according to the Grading of Recommendations Assessment, Development and Evaluation system[59] and the nonpluralistic, nonrepresentative consensus approach. Nevertheless, our consensus-based recommendations are based on the first international Delphi survey among international experts and provide state-of-the-art consensus statements in order to promote optimal treatment for individuals with TRS and stimulate future research strategies.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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E. Wagner has been invited to advisory boards from Recordati. D. Siskind reports no conflict of interest. P. Falkai is on the advisory boards and receives speaker fees from Janssen, Lundbeck, Otsuka, Servier, and Richter. O. Howes is a part-time employee and stock holder of Lundbeck A/s. He has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organized by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Recordati, Roche and Viatris/ Mylan. Dr Howes has a patent for the use of dopaminergic imaging. C.U. Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma and Quantic. J. Lee has received honoraria from Sumitomo, Lundbeck, Otsuka and Janssen. W.G. Honer has provided consultation to AbbVie. J.M. Kane has served on advisory boards or received honoraria for lectures from Alkermes, Boehringer Ingelheim, Cerevel, Dainippon Sumitomo, HLS Therapeutics, Intracellular Therapies, Janssen, Johnson and Johnson, Lundbeck, Merck, Minerva, Newron, Novartis, Otsuka, Roche, Saladex, Sunovion, Takeda, Teva. He has received grant support from Janssen, Otsuka, Lundbeck and Sunovion. He is a shareholder of LB Pharma, Health Rhythms, North Shore Therapeutics and the Vanguard Research Group. E. Fernandez-Egea has received consultancy honoraria from Boehringer-Ingelheim (2022), Atheneum (2018-2022), received training and research material from Merz (2020) and is director of a private practice company (cambridgepsychiatry.co.uk). T. R. E. Barnes has served on an advisory board for Gedeon Richter. A. Hasan has received speakership fees from Lundbeck, Otsuka, Janssen, and Recordati and was member of advisory boards of these companies and as well for Rovi.

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