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Clinical overview

Optimizing clozapine treatment

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Objective: Clozapine treatment remains the gold standard for treatment-resistant schizophrenia, but treatment with clozapine is associated with several side-effects that complicate the use of the drug. This clinical overview aims to provide psychiatrists with knowledge about how to optimize clozapine treatment. Relevant strategies for reducing side-effects and increasing the likelihood of response are discussed.
Method: Studies of clozapine available in MEDLINE were reviewed.
Results: A slow up-titration of clozapine is recommended in order to reach the optimal dosage of clozapine and diminish the risk of dose-dependent side-effects. Particularly, in case of partial response or non-response, the use of therapeutic drug monitoring of clozapine is recommended. Plasma levels above the therapeutic threshold of 350–420 ng/ml are necessary to determine non-response to clozapine. To ease the burden of dose-dependent side-effects, dose reduction of clozapine should be tried and combination with another antipsychotic drug may facilitate further dose reduction. For most side-effects, counteracting medication exists. Augmentation with lamotrigine, antipsychotics, or electroconvulsive therapy may be beneficial in case of partial response to clozapine.
Conclusion: Treatment with clozapine should be optimized in order to increase the rate of response and to minimize side-effects, thus diminishing the risk of discontinuation and psychotic relapse.

Key words: treatment-resistant; schizophrenia; augmentation; antipsychotic; clozapine

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Clinical recommendations

- Psychiatrists should focus on optimizing clozapine treatment in collaboration with the patient and family.
- Plasma levels above 350–420 ng/ml in a period of at least 12 weeks are needed to determine the lack of response to clozapine.
- Augmentation with lamotrigine, electroconvulsive therapy, or another antipsychotic drug may be beneficial in case of partial response to clozapine.
- Most dose-dependent side-effects can be diminished by reducing the dose of clozapine or by using another type of medication to counteract side-effects.
- In case of persistent, dose-dependent side-effects at optimum dosage, combining clozapine with another antipsychotic drug may facilitate further dosage reduction of clozapine and consequently diminish the burden of side-effects.

Additional comments

- The evidence supporting clozapine augmentation is sparse, and positive studies only find minor, if any, benefit for clozapine augmentation
- Clozapine optimization strategies have only sparsely been evaluated in a systematic setting.

Introduction

The optimization of antipsychotic treatment should always take place in a dialogue between the patient and the psychiatrist in order to identify the patient's needs with respect to treatment and attitude to the various side-effects (1). The distressing consequences of a specific side-effect may vary among patients (2), e.g., extrapyramidal side-effects (EPS) may be experienced as more distressing by a guitar-playing patient than by other patients because EPS conflict with the fine motor movements required for playing. Furthermore, the psychiatrist should always ensure that the patient is aware of factors that may worsen their psychosis, such as comorbid substance misuse or stressing psychosocial conditions. Improvements in the patients' psychosocial status, e.g., by obtaining better accommodation, seeking treatment for substance misuse, or taking early retirement, are effective interventions because of their stress-reducing effects (3, 4). Other measures, such as supportive family interventions, social skills training, and cognitive behavioural therapy may also be effective in patients with treatment-resistant symptoms (5–8). Furthermore, compliance should always be assessed as it is a common factor in 'treatment resistance' (4). The degree of compliance may be almost impossible to determine, and partial compliance is common even in patients considered as fully compliant. Therefore, the psychiatrist should always consider the use of observed administration of the medication or a trial of long-acting depot injection before classifying the patient as treatment-resistant.

Clozapine has affinity for several different receptors, and it may thus elicit a wide range of side-effects, such as sinus tachycardia (9), orthostatic hypotension (9), nocturnal enuresis (10), hypersalivation (11), and severe sedation (12), and this complicates the use of the drug. Furthermore, clozapine has been associated with potentially fatal side-effects, such as agranulocytosis (13), cardiomyopathy, myocarditis (14), hypersalivation-induced aspiration pneumonia (15), acute myeloid leukemia (16), as well as potentially life-shortening weight gain and metabolic complications (17). The response rate to clozapine is about 50%, irrespective of non-response or partial response to prior treatment with other antipsychotics (18). In addition to the high response rate and the unique efficacy in patients with treatment-resistant schizophrenia (19), clozapine possesses anti-suicidal (20) and anti-aggressive (21) properties. Despite the wide range of side-effects and complications, clozapine remains the gold standard medication in patients with treatment-resistant schizophrenia.

Aims of the study

This review aims to describe and to discuss strategies for optimizing clozapine treatment in order to increase the likelihood of response and minimize the burden of side-effects.

Material and methods

A clinical overview was chosen because of the sparse systematic data within this field and because of the traditions with use of clozapine. We identified and reviewed studies of clozapine and augmentation, dosage, therapeutic drug monitoring (TDM), side-effects, and optimization strategy available in Medline, Embase, and the Cochrane library. The databases were searched with the term: 'clozapine', 'Clozaril' or 'Leponex,' and the hits were sorted manually based on their title and abstract. All types of publications were reviewed. Only publications in English, Danish, and German and studies published from January 1, 1970, until September 31, 2010, were reviewed. Furthermore, reference lists in all used articles were reviewed.

Results

Practical procedures

Clozapine is licensed for treatment-resistant schizophrenia, and the recommended dosage is up to 900 mg/day. Patients eligible for clozapine are psychotic patients having a suboptimal response to at least two antipsychotic drugs. Treatment with clozapine is associated with a 0.7% risk of agranulocytosis (13), and for this reason, white blood cell count (WBC) and/or absolute neutrophil count are mandatory weekly during the first 18 weeks of treatment and then monthly (the regimen differs between countries) (22). Clozapine may also cause cardiomyopathy and myocarditis (14), and in case of cardiac symptoms, an ECG or other examinations may be warranted.

Therapeutic drug monitoring

The clinical utility of routine monitoring of plasma levels of clozapine is subject to some controversy (23). From a general pharmacological point of view, TDM is recommended for drugs with a narrow therapeutic index, which display a

substantial inter-individual dose–concentration relationship and complex metabolism (24). Clozapine fulfills all three criteria. Clozapine dosage and clinical response are poorly associated mainly because clozapine is associated with large inter-individual variation in dose–plasma concentration levels; extreme cases have shown a 45-fold variation after single-dose administration (25, 26). Owing to the complex metabolism of clozapine and its metabolites, plasma concentrations are influenced by smoking, gender, age, and the concomitant administration of other drugs. The metabolism involves several P450 enzymes, in particular CYP1A2, with contributions from CYP3A4, and, to a lesser extent, CYP2D6. The concomitant administration of CYP1A2 inhibitors, such as fluvoxamine or ciprofloxacine, is found to result in clinically relevant increases in plasma levels (27, 28). So far, no clear therapeutic interval has been established for clozapine, but several studies have identified therapeutic plasma level thresholds above which patients are more likely to respond. The levels vary, but most studies have indicated a threshold of 350–420 ng/ml (29–31), while lower thresholds have also been suggested (250 ng/ml) in cases where the daily dosage was divided into two or more doses (32). If these levels elicit no response from the patient, further up-titration is recommended, provided that the treatment is well tolerated (26). However, clozapine concentrations above 350 ng/ml have been associated with an increased risk of EEG abnormalities and seizures (33) and doubling of side-effects compared with lower levels (34). Conversely, it should be kept in mind that up to one-third of patients treated with clozapine respond at concentrations below 400 ng/ml (28). Patients whose clozapine intake is administered as several doses during the day were found to have up to one-fourth lower clozapine levels than patients receiving a single nighttime dose (32). Genotyping of the CYP enzymes has so far not been of any advantage in dosing of clozapine because the CYP1A2 remain the major metabolic pathway but genotyping of pharmacodynamic or pharmacokinetic mechanisms may be promising in the future (35).

Unless intoxication is indicated, plasma levels should be obtained after steady-state concentration has been achieved (5–7 days) (26). Blood sample should be drawn 12 ± 1 h postdose (36). There have been some discrepancies as to the reporting of plasma vs. serum values. Two comparative studies have reported conflicting data as serum levels were about 10% higher in the study by Kaladijian et al. (37) compared with plasma levels while about 7% lower in Hermidia et al.'s study (38). Depending on the specific method used, reference values may also vary between laboratories. These differences are unlikely to be significant for clinical practice, but it is imperative that laboratory methods document their validity against external quality controls. As some laboratories use SI units for their results, a factor of 3.06 may be used for conversion from ng/ml to nmol/l (39).

The upper limit of dosage or plasma levels of clozapine has received scant attention in the literature. Risk of seizure seems to grow as a function of the plasma level (40–45), and dosages above 600 mg have thus been associated with an increased risk of seizure (42). However, this is not considered as an absolute contraindication; prophylactic treatment with valproate has been used successfully (9). EEG abnormalities have been observed both as a prodrome of central nervous system (CNS) toxicity (24) and in relation to response (33). Although many patients on clozapine exhibit EEG changes (46–54), this did not necessarily predict seizures (46, 55). However, clozapine-induced myoclonus should be considered as a warning sign of increased seizure risk (56). Likewise, cognitive functions, such as vigilance and memory, have been shown to deteriorate with rising plasma levels (57, 58). No dose relationship has been established in connection with other serious adverse events, such as myocarditis (59), cardiomyopathy, and agranulocytosis (60). A Chinese study (61) found that concentrations above 700 ng/ml were associated with diminished rates of response, suggesting an inverted curvilinear concentration–response curve. A retrospective study by Ulrich et al. (62) found plasma levels above 900 ng/ml to be associated with intoxication. Other studies have failed to identify an upper limit of response (29, 30, 63). However, an inverted curvilinear concentration–response curve has been found for nortriptyline, the tricyclic antidepressant drug (64) that also possesses anticholinergic properties. It has been speculated that the decreased response is a result of increased side-effects rather than a true decreased efficacy. In psychiatry, efficacy is measured on psychometric scales, such as the positive and negative syndrome scale (PANSS) and Hamilton depression scales. Some side-effects may be observed as symptoms related to the disease, e.g., sedation is rated as a negative symptom. Similar might be true for clozapine, where hallucinations have been described in cases of overdose (65), probably due to reduced muscarine activity causing a delirium-like state. The clinical response in non-responders with high clozapine levels may

improve upon dose reduction (28). In contrast, therapeutic benefits have been described for concentrations as high as 1200 ng/ml (66), probably due to a reduced cerebrospinal fluid/plasma concentration ratio. Results from retrospective study of 73 acute clozapine monointoxication suggested that dose for a 50% risk of developing moderate or severe intoxication was 900 mg in patients older than 50 years and 14.5 g in patients younger than 50 years (67). Unfortunately, the study did not report plasma levels. It is clear that our knowledge of the relation between response, dose, and concentration is insufficient with regard to such high clozapine levels, and it is not possible to recommend an upper limit based on the current literature. For this reason, the psychiatrist should carefully monitor side-effects and efficacy and be prepared to use the full range of plasma levels in order to increase the likelihood of response.

Dosing of clozapine

Within its therapeutic range, clozapine exhibits linear dose-proportional kinetics, i.e., a doubling of the dose leads to a doubling of the plasma level (68). Clozapine is licensed in dosages up to 900 mg/day, with average dosages of 300 mg/day for women and 400 mg/day for men (28, 69), but a survey found that psychiatrists were reluctant to use more than 600 mg/day (70). Discontinuation rates are high, especially among elderly patients; the risk of discontinuation rises by 33% for every 10-year increase in patients' age at the start of clozapine treatment (13), which suggests better tolerability and response in younger patients. Munro et al. (13) reported a 40% discontinuation rate for clozapine with the highest discontinuation frequency within the first year of treatment. These rates should be seen in the context of the treatment algorithms used as there are no obvious alternatives to clozapine for patients with treatment-resistant schizophrenia. Early discontinuation of clozapine treatment before its benefits are detectable could therefore preclude patients from receiving the best-evidenced and efficient treatment for treatment-resistant schizophrenia. A common mistake when dosing clozapine is to increase the dose too quickly, which may result in dose-dependent side-effects. In particular, autonomic side-effects such as sedation, orthostatic hypotension, and sinus tachycardia may lead to discomfort for the patients and perhaps even discontinuation of the medication. In worst case, rapid dose titration can cause cardiovascular collapse, and in addition to this, concomitant benzodiazepines should be employed with considered caution during titration (71–73). It should be noted that there is little, or even conflicting, documentation for rapid dose titration of antipsychotics with the aim of achieving a quicker response (74, 75). It is important to remember that improvement as a result of up-titration may occur with considerable delay (30). To avoid unnecessary high plasma levels and thereby increase the burden of side-effects (28), the clinical response should not be evaluated until 6 weeks after dose adjustment. A slow-paced titration scheme will allow time for the detection also of lagging responders. After sufficient time has been given for responses, clozapine dosage can be titrated further upward in non-responders. At the lower range of recommended dosage, clozapine can be administered once daily. In order to reduce the impact of the sedation, it is often prescribed for nighttime ingestion, but some patients prefer to take daytime doses as well. This might make it easier to taper off concomitant use of other sedative drugs. Switching to a generic brand or switching within generic brands could lead to altered plasma levels (76, 77), with an increased risk of psychotic relapse (76, 78). However, most of the controlled studies failed to establish different effects among brands (79–85).

Some patients, especially younger male smokers, may need dosages higher than 900 mg/day to achieve plasma concentrations above the mentioned threshold value (28, 86). In order to reduce the number of daily ingested tablets, a low dose of fluvoxamine (87) or fluoxetine (88) can be added.

Minimizing side-effects

Several of the side-effects observed for clozapine are dose-dependent. Table 1 gives a list of dose-dependent side-effects, most of which are found to induce tachyphylaxis within the first month, thus diminishing the impact of side-effects during maintenance treatment (89, 90). In order to minimize dose-dependent side-effects, the first step is to ensure that patients are given the optimum dose of clozapine. The psychiatrist should keep in mind that the maintenance dose may be lower than the dose at which response was achieved (91). The literature offers little guidance on the optimum dose, partly because clozapine response and tolerability is highly individual and partly because some patients actually prefer a state of mental vulnerability or even the risk of incurring minor psychotic episodes to experiencing

Table 1. Dose-dependent side-effects of clozapine treatment, with treatment suggestions

	Suggested treatment intervention*
CNS	
Seizures (42)	Valproate (93, 94), lamotrigine (94–96)
Sedation (32)	Modafinil (97)†, methylphenidate (98)†
Delirium (99)	Physostigmine (100)
Obsessive–compulsive symptoms (101)	CBT (102), SSRI (103), clomipramine (103)
Cardiac	
Sinus tachycardia (9)	Cardio-selective betablocker (104)
Orthostatic hypotension (9)	Sufficient fluid and salt intake, compression socks (105), fludrocortisone (106)
Other	
Constipation (107, 108)	High-fiber diet and sufficient fluid intake (109), stimulant and softening laxative (109)
Nocturnal enuresis (10)	Desmopressin (110)
Hypersalivation (11)	Sublingually atropine eyedrops (111), sublingually ipratropium spray (112), amitriptyline (113), amisulpride (114), clonidine (115), benztropine mesylate (116), botulinum toxin (117), transdermal hyoscine patch (118), pirenzepine (119, 120), diphenhydramine (121), propantheline (121)

CBT, cognitive behavioural therapy; CNS, central nervous system; SSRI, selective serotonin reuptake inhibitors.

*Before initiating treatment interventions to avoid dose-dependent side-effects, the clozapine dosage should be reduced if possible and the need for concomitant medication reevaluated.

†The risk of psychosis should be assessed.

dose-dependent side-effects, such as drooling, sedation, nausea, and orthostatic hypotension, which significantly compromise their quality of life. The dose adjustment of antipsychotic drugs in patients with schizophrenia can be a sensitive topic for patients, family, and staff as dose reduction increases the risk of psychotic relapse. Before a reduction is initiated, the issue should be discussed with the patient and other relevant persons, including an evaluation of the pros and cons of the adjustment. Except in the case of life-threatening side-effects such as agranulocytosis or myocarditis, clozapine should always be carefully tapered to reduce the risk of rebound psychosis and anticholinergic discontinuation syndrome, e.g., flu-like symptoms (92).

Other interventions to reduce the burden of side-effects and minimize their impact on quality of life should be considered only in connection with dose optimization. An important point in connection with the discussion of side-effects is the fact that clozapine is rarely given monotherapeutically. Furthermore, not all side-effects can be attributed to treatment with clozapine. The concomitant use of benzodiazepines, some mood stabilizers, and other antipsychotics may worsen sedation, a common complaint among patients being treated with clozapine. Tapering off concomitant medication in the effort to reduce the total burden of side-effects is therefore essential.

Clozapine has significant anticholinergic properties, and concomitant medication, such as tricyclic antidepressants (TCA) and anticholinergic drugs used for treating EPS, adds to this burden. The blocking of the muscarine receptors leads to reduced parasympathetic activity and consequently shifts the balance toward the sympathetic nervous system. Antagonism of muscarine receptors is responsible for side-effects such as dry mouth, constipation, urinary retention, and cognitive deterioration. The development of anticholinergic-induced psychotic symptoms or delirium has been described at low doses of clozapine as well with subsequent improvement after dose reduction (122). Furthermore, a reduction in the anticholinergic load has been found to improve cognitive abilities (123), a symptom domain strongly linked to the patients' quality of life. The concomitant use of anticholinergics and drugs with anticholinergic affinity should be avoided, and the need for treatment with such drugs reevaluated. Clozapine use is associated with a low EPS risk, which diminishes the need for concomitant anticholinergic treatment. However, anticholinergics are often prescribed with the aim of reducing clozapine-induced hypersalivation, although the supporting evidence is sparse (11). The treatment effect is often insufficient, especially at night because plasma levels peak during the night and because sleep suppresses the swallowing mechanism. Treating clozapine-induced hypersalivation is complicated and several treatment options, including anticholinergics, clonidine, and amisulpride, have been suggested (11). Applying a locally acting anticholinergic drug in the oral cavity, such as ipratropium spray or atropine eyedrops, may diminish the systemic effects of the anticholinergic drug, but our knowledge of systemic absorption is insufficient (11). The merits of anticholinergic treatment for clozapine-induced hypersalivation should be carefully evaluated and discussed with the patient.

In cases where optimizing the clozapine dose is not found to reduce the side-effects, other interventions are available. Although evidence is sparse and recommendation is based on clinical experience, the addition of another antipsychotic drug may facilitate further dose reduction of clozapine (114, 124–126). Hypersalivation may be alleviated by adding amisulpride, followed by a reduction of the clozapine dosage (114). In an open-label study, Reinstein et al. (125) found that the clozapine

dosage could be reduced by letting 2 mg of quetiapine substitute for 1 mg of clozapine. Over a 6-month period, an average weight loss of 4.2 kg was achieved. For a wide variety of dose-dependent side-effects, other treatment-specific interventions exist, some of which are mentioned in Table 1.

Agranulocytosis and neutropenia occur in approximately 1% and 3% of patients treated with clozapine and should lead to discontinuation of clozapine. Lithium (127), filgrastim (128), and granulocyte colony-stimulating factor (129) have successfully been used to manage neutropenia. Patients with agranulocytosis should not be rechallenged with clozapine (127).

The development of metabolic syndrome is an especially challenging side-effect. Henderson et al. (17) found average weight gains of approximately 13 kg, with 34% of patients having developed diabetes over the 10-year period of their study. A recent study found that treatment with clozapine increased the risk of developing type II diabetes by 2.3 times (130). Several counter-strategies have been suggested, such as adding metformin to promote weight loss (131, 132). Wu et al. (131) found a combination of metformin and lifestyle interventions to be more effective than either of them on their own. Combining the two led to a 4.7-kg weight loss, and a BMI reduction of 1.8 in the 12-week study period. Low-dose topiramate may also promote weight loss (133). Even without dose reduction of clozapine, aripiprazole as a supplement to clozapine may improve metabolic parameters such as waist circumference and weight (134). In a study by Leon et al. (135), treatment with 100 mg of clozapine was found to be weight neutral. It remains unclear whether this property is preserved when combining the treatment with the administration of a low-risk metabolic antipsychotic drug. However, the augmentation of aripiprazole with low-dose clozapine has been suggested as an alternative to clozapine monotherapy in order to reduce the burden of side-effects (136). Giving low doses of clozapine has also been shown efficacious in Parkinson patients with L-dopa-induced psychosis (137), indicating that clozapine can be efficacious below the established therapeutic plasma threshold.

Augmentation

Augmentation is the addition of a drug to an existing drug in order to increase efficacy. From a pharmacological point of view, the patient should exhibit at least partial response before augmentation is considered. Otherwise, switching may be a more appropriate option. The benefits of augmentation with other antipsychotics have been questioned in recent meta-analyses that reviewed randomized, placebo-controlled augmentation studies, which found only minor or no advantages of augmentation with an antipsychotic drug (138–140). Nevertheless, augmentation with antipsychotics is a common procedure although the literature does not favor any particular antipsychotic drug as an augmenting drug. Neither does it support specific augmentation strategies for specific domains of the schizophrenia disease, e.g., positive symptoms or negative symptoms. Despite the disappointing results from the meta-analysis, some partial clozapine responders may benefit from augmentation with an antipsychotic drug, and because the evidence-based alternatives are sparse, augmentation may be worth trying (141, 142). In addition to this, the benefits of augmentation should always be carefully evaluated against an increased burden of side-effects; although clozapine has a low risk of EPS, its augmentation with risperidone is known to have caused EPS (143) and hyperprolactinemia (144). If possible, augmentation should not be tried until after the first 3–6 months of treatment with clozapine to avoid the risk of confusing the effect of the augmenting drug with any late-onset effects of clozapine. Furthermore, a worsening of psychotic symptoms has been described after augmenting drugs were introduced (145, 146). It is therefore recommended to carefully monitor patients using a psychopathology scale, e.g., the PANSS scale, because worsening or lack of response may occur. Deterioration, or the absence of improvement in mental state, should lead to discontinuation of the augmenting drug. The duration of the augmentation is largely unresearched. Patients with treatment-resistant schizophrenia may require longer response times. A meta-analysis by Paton et al. (147) showed that augmentation trials with a duration of more than 10 weeks were associated with an increased likelihood of response, but this finding was not confirmed in Taylor et al.'s (138) meta-analysis. The most well-researched augmenting antipsychotic drugs are amisulpride, sulpiride, risperidone, and aripiprazole (148–153).

Other non-antipsychotic augmentation strategies exist: Two systematic reviews of five double-blinded, placebo-controlled augmentation studies involving lamotrigine suggests that augmentation with lamotrigine is generally well tolerated and more effective than placebo in reducing positive

symptoms (154, 155). Augmenting clozapine treatment with electro-convulsive therapy (ECT), in some cases followed by maintenance ECT, seems particularly promising with respect to the reduction of catatonic behaviour and positive symptoms such as aggression, delusional thinking, and hallucinations (156, 157).

A careful evaluation of the case for continued treatment with clozapine should be undertaken if no response has been obtained after 12 or more weeks of clozapine at sufficient plasma levels (> 420 ng/ml), either alone or in combination with other drugs or ECT. As treatment with clozapine is often associated with significant weight gain and diabetes, it should be discontinued in case of non-response. A study by Taylor et al. (158) found that despite non-response to clozapine, the patients stayed on the medication.

Discussion

Clozapine remains the drug of choice for treatment-resistant schizophrenia despite the widespread use of atypical antipsychotics (159) and the extensive pharmaceutical research for more than 40 years, the successor has not been found yet.

Treatment with clozapine requires specialized knowledge and especially complex cases should preferably occur in specialized clinics with sufficient knowledge of and experience with clozapine (160). It is essential that focus on side-effects is maintained. Several strategies to reduce the burden of side-effects exist. A slow up-titration scheme is recommended in order to reduce the burden of side-effects and ensure that patients are treated at the lowest efficient dosage. TDM may assist on finding the optimum dosage but should only be considered as guidance. A threshold for response at 350–420 ng/ml has been suggested. If only a partial response is detected, the clozapine dosage should be increased slowly until intolerability occurs. The augmentation of clozapine with ECT, lamotrigine, or antipsychotics is recommended in case of persistent, partial response to clozapine, although the supporting evidence is sparse. The effect of the augmentation should be carefully monitored, e.g., using a standardized psychopathology rating scale, because worsening may occur. Further studies are needed to optimize clozapine treatment, with regard both to minimizing the burden of side-effects and to improve the rate of response.

The suggested addition of an antipsychotic to facilitate dose reduction of clozapine is not supported by clinical data but mainly from clinical experience. However, one should have in mind that most patients receiving clozapine are complex patients that have tried all evidence-based interventions and is often treated with high dosages and polypharmacy at the expense of dreadful side-effects. In addition to this still tormented by hallucinations and delusions and for these reasons, any treatment that potentially could improve the quality of life of these patients should be considered.

With this clinical overview, we aimed to increase the focus of psychiatrists to use clozapine at an earlier state and to equip them with the necessary knowledge for how to optimize the treatment. As already mentioned, this manuscript is a clinical overview, and the evidence for some of the optimization strategies is sparse and more based on empirical findings and traditions. For these reasons, the interventions should more be seen as suggestions rather than definite answers.

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