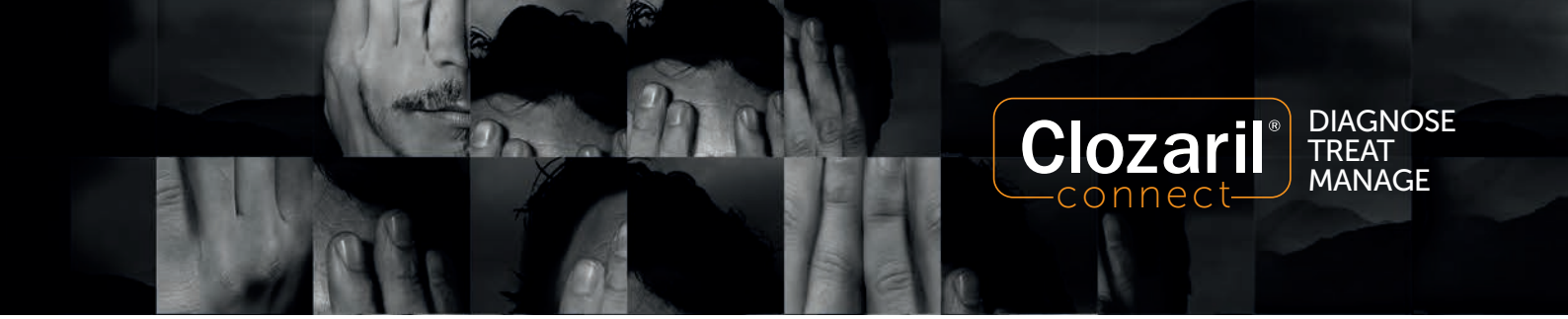


Clozapine and compliance

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

This information is provided for healthcare professionals and should not be used as a patient information leaflet.

Background

Compliance may be defined as the extent to which a person's behaviour coincides with the medical advice he/she has received.[1] Non-compliance is an issue in general medicine and psychiatry and is particularly likely when the aim of treatment is to prevent symptom recurrence or illness relapse. The rate of non-compliance in schizophrenia has been estimated at 33%[2] although some studies give figures as high as 80% for non-compliance with antipsychotic medication.[3]

Compliance with medication may be total, partial, nil or erratic, and non-compliance in schizophrenia may be refusal of treatment, discontinuation of treatment or erratic taking of medication. The reasons for non-compliance in patients with schizophrenia vary and may include depression/lack of motivation, side-effects, forgetfulness, comorbid substance abuse and lack of insight or denial of illness.[4] Severity of illness may also be significant since studies have found that patients with more severe psychopathology are less likely to comply with treatment.[5]

Non-compliance can be detected by several means but it is difficult to get an accurate picture. Patient self-reporting is often unreliable since patients may deliberately give false information. Pill counting may be used but the patient may have the correct number of pills left when they have not taken the medication, and biological analysis such as plasma monitoring may also be of limited use as the patient may be compliant only in the period shortly before the blood test.[6]

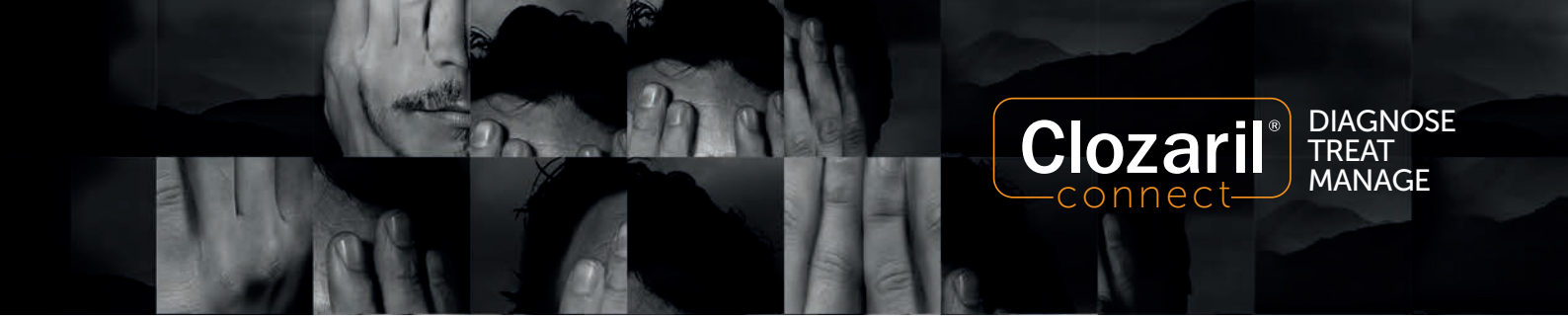
For the patient, the direct consequence of non-compliance is that they may relapse and experience return of symptoms, which may in turn lead to hospital re-admission. Indirect costs of relapse include personal suffering, high morbidity, mortality and an overall reduction in quality of life for the patient and their family members.[6] From a healthcare professional's perspective, the consequences of lack of compliance may include all the costs of a patient deteriorating, for example, re-hospitalisation, additional clinic and staff resources and the cost of additional drugs.

Until all the barriers to compliance are apparent it is difficult to change the patient's behaviour. However, one of the most important positive factors is the existence of a good relationship between the patient and the healthcare professional and establishing rapport and trust is the first step to changing the patient's attitude to their medication.

Clozapine and compliance rates

It has been shown in several studies that patients stabilized on clozapine are largely content with their treatment and as a result adherence to treatment is good.[7,8]

In a survey completed by 570 patients, the majority (62.1%) rated clozapine as much better than their previous treatment, with only 2.7% rating it as slightly or much worse.[7] More importantly from a compliance perspective, 87% of patients in the same study felt that the advantages of clozapine outweighed the disadvantages and 88% of patients stated that they preferred to stay on clozapine rather than change to a different drug.



Compliance with clozapine has been shown to be better than with chlorpromazine or with haloperidol. In a comparative study with chlorpromazine, Claghorn *et al* (1987) showed that psychotic inpatients treated with clozapine had fewer discontinuations due to side-effects.[9] Rosenheck *et al* (2000) also demonstrated greater continuation with clozapine when compared with haloperidol.[10]

Use of clozapine plasma levels to detect non-compliance

Checking plasma clozapine and norclozapine levels and the clozapine:norclozapine ratio may help in detecting recent clozapine non-compliance. The assay should be a trough sample taken either immediately before a normal morning dose or in the morning after an evening dose. The clozapine:norclozapine ratio should normally be in the range of 0.5-2.5. A low clozapine level and a ratio less than 0.5 may be suggestive of non-compliance within the last day or so.[11]

Suggestions to improve compliance with clozapine

To improve compliance, effort should be channelled into supporting patients through the early stages of treatment until the efficacy becomes apparent, early side-effects diminish and a blood taking routine is established.

Assess the patient's attitude to therapy to establish the barriers to compliance and develop an individual care programme including an action plan to be used if symptoms start to return. Make sure that the patient knows who to contact for further advice or in case of emergency. Discuss any misconceptions that the patient may have.

Stress the benefits of treatment and check the patient is aware of the relationship between non-compliance and relapse. Relate being well to staying out of hospital. Discuss the patient's expectations and compare symptoms to those they had six months ago.

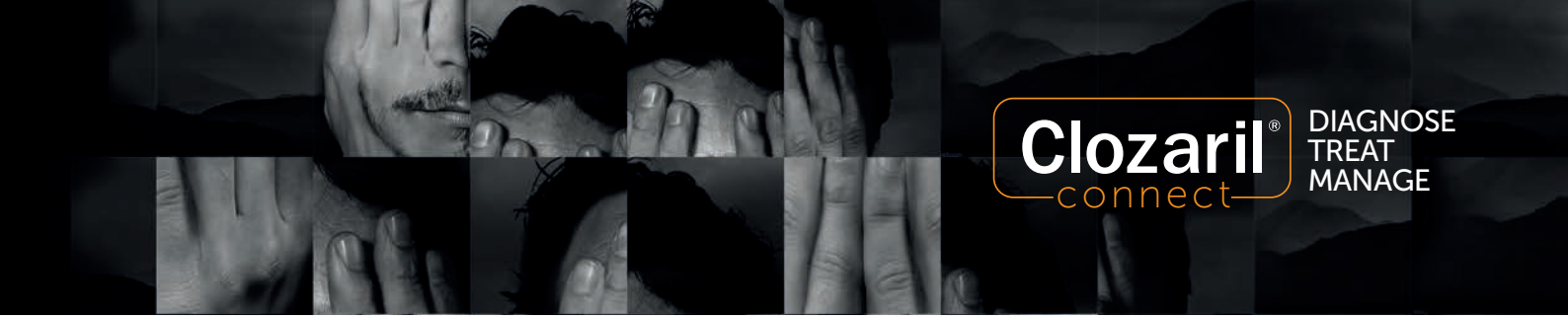
Check that the dose has been optimised and educate the patient on the expected time to response. Treat anxiety or depression where appropriate. Ensure that the current treatment regimen is simple and that explicit written instructions are provided. Use monotherapy wherever possible to reduce the complexity of treatment and reduce the likelihood of interactions. Compliance aids such as monitored dosage systems (MDS) may be useful for some patients. Other strategies include keeping the medication in a visually prominent place, or phone calls or visits to remind patients to take their medication.

Assess the clinic routine and arrangements for blood monitoring and dispensing. If distance to the clinic or waiting times are a problem, consider whether blood sampling at a GP surgery is possible.

Create a relationship where the patient feels that they can report side-effects and assess the impact on the patient. For dose-related side-effects consider reducing or splitting the dose. Check plasma levels where appropriate.

Consider the patient's level of cognitive function since cognitive impairment may reduce the ability to remember to take medication. Provide support and education at a correct level for the patient. Check the patient's support network and provide information and education for carers if necessary.

One strategy which has been effective in improving compliance is compliance therapy, where cognitive-behavioural therapy and motivational interviewing are used to demonstrate the risks and benefits of accepting antipsychotic treatment. Kemp *et al* (1996) compared this with non-specific supportive counselling and found that patients who received compliance therapy had significantly improved compliance from baseline.[12] Another study demonstrated that compliance therapy was more cost-effective than non-specific counselling.[13]



Specific factors affecting compliance with clozapine

Time to first response

Studies have shown up to 30% of patients will show a response by six weeks and 60% will have shown a response by twelve months.[14] Patients should be reassured that it may take some time for clozapine to be fully effective. Looking back with the patient over the course of treatment will enable them to appreciate improvements in functioning and motivate them to carry on until they experience a full effect. The Summary of Product Characteristics (SPC) for Clozaril® (clozapine) recommends that treatment should be continued for at least six months.[15,16]

Blood monitoring

Patients on clozapine require regular blood monitoring and for the majority of them this will require fairly frequent attendance at an outpatient clinic. Although the primary objective of blood monitoring is to detect neutropenia, it also assures regular contact between the therapy team and the patient, which offers frequent opportunity to assess progress and to allay any concerns the patient may have. It also provides an ongoing general health check, helps in the management of side-effects, and enables early detection of patients who may be defaulting from treatment.

Studies have shown that patients generally understand the need for blood monitoring. In a survey of patients taking clozapine, 80% knew why blood tests were needed and 64% felt they were a necessary part of treatment. Less than 2% of patients wanted to stop their therapy due to the blood monitoring.[7] Other studies have found that although patients may object to blood monitoring at the outset, this diminishes over time as they experience the benefits of treatment.[8]

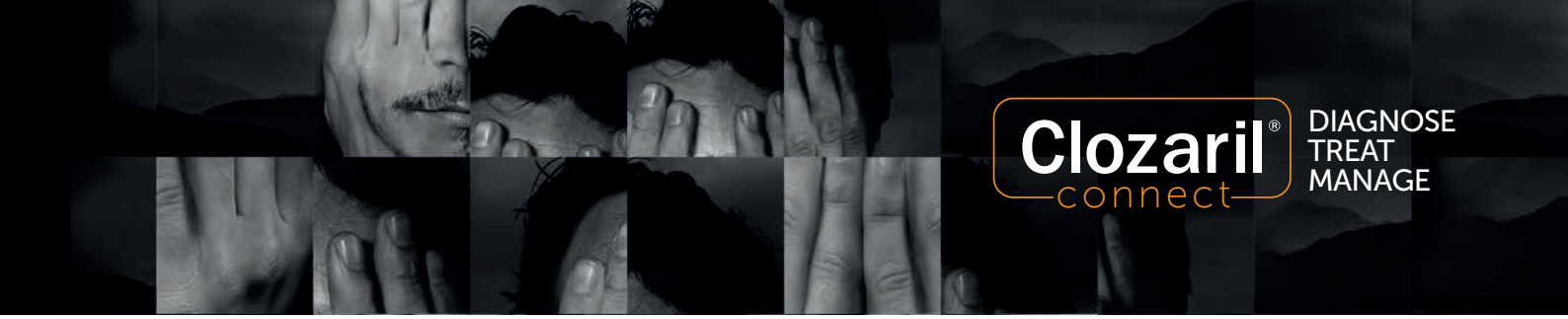
Patients who do not accept the need for blood monitoring easily at the outset may benefit from early referral to the local clozapine clinic, which may help to allay any concerns the patient has and also help the patient to gain confidence from meeting patients established on clozapine.

Side-effects

Clozapine can cause a range of side-effects, many of which diminish over time. The most common side-effects are drowsiness/sedation, dizziness, tachycardia, constipation and hypersalivation. It is often possible to reduce their effect or avoid them altogether by following a few basic principles:

- Tailoring therapy – many side-effects, such as hypotension and tachycardia, are dose-related. By starting with a low dose and titrating the dose slowly the effects of these dose-related side-effects can be reduced. In the case of hypotension, giving the largest part of the dose at night can reduce the effect on blood pressure.
- Proactive approach – it is necessary to take a proactive approach if side-effects, such as weight gain and constipation, are to be avoided. Constipation can be a potentially serious side-effect if left untreated and must be taken seriously. Patients should be counselled prior to commencement and given advice on diet, fluid intake and the importance of seeking advice from their doctor if they become constipated. Similarly, by counselling patients on the importance of a healthy diet and exercise, weight gain may be reduced.
- Monitoring – although the only mandatory requirements are monitoring of the white cell and neutrophil counts, many units conduct baseline and routine monitoring of other parameters such as pulse, BP, ECG, U&Es and LFTs. This can facilitate the early detection of adverse events and provides a baseline should problems arise later in therapy.

For further advice regarding side-effect management please contact your local clinical pharmacist or CPMS.



Restarting clozapine following a break in therapy

In patients in whom the interval since the last dose of Clozaril® exceeds 2 days, treatment should be re-initiated with 12.5mg given once or twice on the first day. If this dose is well tolerated, it may be possible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment.[15,16]

Patients who have been on Clozaril® for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their white blood cell (WBC) count and absolute neutrophil count (ANC) monitored weekly for an additional 6 weeks.[15,16]

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Reporting of side effects
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
UK: Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.
Adverse events should also be reported to Mylan via cpms@mylan.co.uk

Clozaril® (clozapine)

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

CLZ-2018-0154 Date of preparation: July 2018

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