Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2014: 1–12

DOI: 10.1111/acps.12327

Clinical overview

The practical management of refractory schizophrenia – the Maudsley Treatment REview and Assessment Team service approach

Beck K, McCutcheon R, Bloomfield MAP, Gaughran F, Reis Marques T, MacCabe J, Selvaraj S, Taylor D, Howes OD. The practical management of refractory schizophrenia – the Maudsley Treatment REview and Assessment Team service approach.

Objective: To describe a practical approach to the community management of treatment-resistant schizophrenia (TRS).
Method: A descriptive review of an approach to the assessment and management of patients with TRS, including the community titration of clozapine treatment, and a report of the management recommendations for the first one hundred patients assessed by the Treatment REview and Assessment Team (TREAT).
Results: The standardized model for the community assessment, management and titration of clozapine is described. To date, 137 patients have been referred to this service and 100 patients (72%) attended for assessment. Of these, 33 have been initiated on clozapine while fifteen have had clozapine recommended but have not wished to undertake clozapine treatment. Other management options recommended have included augmentation strategies and long-acting injectable antipsychotics.
Conclusion: The service had increased the number of patients receiving community assessment and initiation of clozapine by five-fold relative to the rate prior to the establishment of the service. The large number of referrals and high attendance rate indicates that there is clinical demand for the model. Systematic evaluation is required to determine the clinical and cost-effectiveness of this model and its potential application to other clinical settings.

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Key words: schizophrenia; antipsychotics; health service; treatment; clozapine; community

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Accepted for publication August 5, 2014

Clinical recommendations

- The community assessment and initiation of clozapine for refractory schizophrenia is feasible.
- A standardized approach to the assessment, management, and initiation of clozapine in the community may increase the availability of clozapine for patients with refractory schizophrenia.

Additional comments

- As with many specialized services, there is a risk of disrupting continuity of care by introducing an additional team involved with the patient's treatment, but this may be minimized by coworking arrangements.
- A potential consequence of introducing a specialist team is that general teams may become deskilled in the assessment and management of refractory schizophrenia.

Introduction

Treatment-resistant schizophrenia (TRS) occurs in about one in three patients diagnosed with schizophrenia (1–4). It is defined by guidelines as an inadequate response to sequential treatment with at least two different antipsychotics at adequate dose, duration, and adherence (3, 4). TRS places a significant burden on patient wellbeing. A recent review found decreased quality of life, increased medical costs, and increased rates of serious comorbidities compared with patients with schizophrenia in general (5). The decreased quality of life in this patient population is similar in magnitude to that of patients with end-stage renal disease who are undergoing maintenance dialysis (5). Annual costs for patients with schizophrenia are US $15 500–$22 300 and are 3- to 11-fold higher in TRS (5). A conservative estimate suggests that TRS costs add more than $34 billion in annual direct medical costs in the USA (5), as well as societal costs through lost productivity, carer burden, and social care.

Clozapine has established efficacy and is the only drug treatment licensed for patients with TRS (3, 4). There is evidence that 50% of patients identified as refractory respond to clozapine (6). Furthermore, clozapine is associated with lower rates of readmission to hospital compared with other antipsychotics (7) and is associated with reduced mortality (8). Clinical guidelines around the world advise that clozapine should be offered at the earliest opportunity for patients with TRS (9).

When costs are examined for patients before and after starting clozapine, substantial savings are evident (10, 11). This trend is also demonstrated in randomized controlled trials when clozapine is compared with non-clozapine antipsychotics (12). This is largely due to reduced hospital admissions (10, 11), which account for nearly half of TRS' total health resource costs (5). Cost-effectiveness analyses have demonstrated significant cost reductions after starting clozapine – with savings ranging between £3800 and £10 000 per year per patient (10, 11). As the price of clozapine has decreased since these studies, cost savings are now likely to be even more significant. Therefore, there are both clear health and economic arguments for optimizing the management of TRS.

National clinical guidelines on the management of schizophrenia – including recommending the use of clozapine in people with refractory schizophrenia – were introduced in the UK in 2003 and disseminated widely (3). Nevertheless, clozapine is generally under-prescribed, and there are often long delays, of 4–5 years on average, between meeting criteria for clozapine treatment and being treated with this drug (13, 14). Furthermore, poorly evidenced treatments – such as high-dose or multiple antipsychotic combinations – are often used in preference to clozapine (13, 14). In addition, we found that the long delay before starting clozapine hardly changed in our mental health services in the 10 years following the first NICE guidelines and the use of poorly evidenced treatment strategies in preference persisted (14). Lack of resources and specialist expertise have been identified as factors contributing to delays and challenges in managing TRS (15).

The Treatment REview and Assessment Team (TREAT) was established to address these shortcomings in current treatment. It provides specialist assessment and treatment for patients with schizophrenia who may be treatment refractory. While there are a number of guidelines to inform the treatment of refractory schizophrenia (3, 4, 9), we are not aware of any descriptions of the practical aspects of assessing and managing refractory schizophrenia.

Aims of the study

The current article aims to describe the Maudsley the Treatment REview and Assessment Team service model to provide clinicians with an approach to the practical management of refractory schizophrenia.

Material and methods

Service structure

The main aim of this service is to provide early assessment and management of patients with TRS. Early assessment requires timely identification of patients responding poorly to treatment. This is done by actively working with the community mental health teams (CMHTs), through attending their team meetings and auditing caseloads, to identify patients who may be treatment refractory.

The team is composed of two consultants, one middle grade doctor, two junior doctors, and an administrator. The clinic operates out of the Maudsley Hospital out-patient department (OPD). It is a central location for the areas that the service covers, with good transport links and access to the pharmacy service and medical facilities. It is also close to a general hospital, which is advantageous for close liaison with medical teams such as cardiology and hematology when needed.

Catchment area

The service covers patients in two areas of London (Lambeth – population 303 100, and Southwark – population 288 300) who are already in secondary care. It also accepts referrals and offers assessment of patients admitted to in-patient wards where a management opinion is required.

Referral process

Referrals are accepted from any health professional. A short referral form is used to collect essential patient information, but letters are also accepted to make the referral process as easy as possible. The referrer is then contacted by email or telephone to arrange an assessment or to discuss the suitability of the referral. The latter involves discussion of the patient's current level of symptoms and functioning and past psychiatric history – focusing on past psychiatric medications and history of treatment resistance.

Since the service was configured to cover Lambeth and Southwark in 2012, there have been 137 referrals. Demographic details of those referred along with the reason for the referral are shown in Table 1.

Assessment procedure

The initial assessment is arranged jointly with the care coordinator, where possible, at the OPD. Where there are problems with engagement, every attempt is made to engage the patient with the service. This includes joint home visits with the care coordinator and arranging the initial assessment at community team bases or at the patient's general practitioner's surgery.

The initial assessment is about an hour in length and is completed by a psychiatrist. In addition to the patient interview, collateral history is obtained where possible, and a thorough review of the patient's notes is undertaken. The structure of the assessment is shown in Box 1. Its purpose is first to establish that the illness is TRS, second to determine factors that may influence choice of treatment, and third to provide a baseline measure of illness and function.

Assessment: Establishing that the illness is treatment refractory schizophrenia

Establishing that the illness is TRS requires first determining that schizophrenia remains the correct diagnosis. The psychiatric and medical history is reviewed, paying particular attention to the presence of atypical features that may point to organic causes for psychosis, or an alternative primary psychiatric diagnosis. Significant comorbidities that may underlie or exacerbate the ongoing symptoms are evaluated, such as substance misuse/dependence or the use of medications such as steroids. In addition, a number of routine investigations are organized to exclude potential organic causes, as detailed in Box 2.

Table 1. Referrals to the TREAT service to date

N	137
Age in years (SD)	41.5 (11.5)
Sex (%male)	68
Ethnicity (%)	
White British	26
Black British	24
Black Carribean	15
Black African	14
Asian (India, Pakistan, Bangladesh)	7
European	5
Mixed	4
Other	5
Diagnosis (%)	
Schizophrenia	78
Schizoaffective	13
Other	9
Reason for referral (%)	
Treatment refractory – consider for clozapine	71
Treatment resistance on clozapine	12
Treatment and diagnostic review	12
Other	5

TREAT, Treatment REview and Assessment Team.

Box 1. Initial clinical assessment of patients

- Determine the psychiatric diagnosis.
- Prior treatment history: adherence, dosage, duration and side-effects of previous treatments.
- Evaluate other causes of poor treatment response: e.g. substance or alcohol misuse, and the concurrent use of other prescribed medications.
- Review physical health including side effects of current treatment and potential organic causes for persistent symptoms.
- Standardized rating of symptoms [eg: the Positive and Negative Symptom Scale (PANSS), and Clinical Global impression (CGI)].
- History of prior engagement with psychological therapies.
- Establish whether potential contraindications to clozapine or other treatments exist.
- Full physical examination.

Box 2. Investigations

Organic Causes of Psychosis (59)

- Imaging: MRI head to exclude space-occupying lesion, CVA or other abnormality that could cause psychosis
- Endocrine: Thyroid function tests. Psychosis is a well described feature of both hyper- and hypo-thyroidism
- Biochemistry: B12, Folate, Calcium. Low levels of B12 and folate can cause a presentation similar to both the positive and negative symptoms seen in schizophrenia. Abnormalities in Calcium levels have also been known to cause psychosis.
- Infection and inflammation: Syphilis, HIV, Hepatitis B, Hepatitis C, WCC, CRP, ESR. A wide variety of potential infections can mimic schizophrenia. Normal inflammatory markers are helpful in excluding a wide range of potential infections and autoimmune inflammation. In addition some patients will be at increased risk of having contracted a blood borne virus that may influence choice of antipsychotic.
- Autoimmune: NMDA, VGKC, ANA antibodies. Potential causes of psychosis include an autoantibody mediated encephalitis or systemic lupus erythematous.
- EEG: Indicated if the clinical presentation has features suggestive of epilepsy.

Potential Physical Co-morbidities (4)

- Metabolic: Lipids, Glucose, HbA1c. Antipsychotic treatment can cause a deterioration in metabolic parameters. Even disregarding antipsychotic treatment patients with schizophrenia are at increased risk of metabolic abnormalities (60).
- Haematological: FBC. Any haematological abnormalities may impact on the decision whether to recommend clozapine. In the case of patients with a baseline low neutrophil count the possibility of benign ethnic neutropenia (BEN) should be considered.
- Biochemisty: U + E, LFTs. Renal and liver functioning will have an impact on rate of metabolism of medication. In addition some medications can have hepatotoxic or nephrotoxic side effects. Gamma GT can be helpful in giving an indication of excessive alcohol usage (a contra-indication to some treatments).
- Endocrine: Prolactin. Many antipsychotics have the potential to cause hyperprolactinaemia.
- Antipsychotic plasma concentration: Concentrations can give an indication of current compliance.
- ElectroCardioGram (ECG) – all patients should have an ECG done at least annually to monitor for potential antipsychotic related abnormalities such as QTc prolongation.
- Weight, abdominal circumference, blood pressure: measurements are taken at baseline and frequently when there are changes to medication. BMI is an important factor when weighing the risks and benefits of antipsychotic treatment.

The next point to establish is whether previous treatment has been adequate. To be considered adequate, treatment should be at a therapeutic dose over a sufficient duration and, most importantly, adhered to. This requires reviewing the treatment history to determine which antipsychotics have been used, at what dose, over what period, and with what evidence for adherence. We include psychological treatments in this process. Reasons for stopping treatment are also identified – in particular whether due to poor response, or side-effects. Determining adherence is critical and often the most difficult aspect of this assessment. While one can be confident of adherence where there is evidence that the patient has regularly received a long-acting injection, it is often harder to be certain of adherence with oral medication. We take a conservative but practical approach to assessing adherence to oral medication. As it is reasonable to assume that the majority, although not all (16), patients have adhered to treatment when administration is directly observed (such as on an in-patient unit or during home treatment), we accept this as evidence of adherence. Where patients are taking treatment in the community without direct observation, we look for evidence that prescriptions have regularly been cashed. We inquire about adherence in a non-judgmental and open way to assess how many times a week the patient is not taking the medication as prescribed. We also routinely test plasma concentrations of current oral medication. This provides evidence of recent use, although it does not guarantee that there has been adherence throughout the treatment trial. Finally, it is important to evaluate response to adequate treatment episodes. We base this on

Table 2. Treatment history and response for a typical patient at the TREAT service

Medication	Dose	Duration of treatment	Response	Side-effects	Evidence for adherence	Reason for discontinuation
Olanzapine	10 mg	2 months. Feb–Apr 2011	Some decrease in auditory hallucinations but positive and negative symptoms persist to a marked degree and impact on function	Weight gain of 6 kg	Plasma concentration 20 ng/ml	Ineffective
Risperidone	6 mg	6 months. Apr–Oct 2011	Superior to olanzapine but ongoing positive and negative symptoms	Prolactin 900 μg/l Akathisia	Patient and carer report	Akathisia and inadequate response

TREAT, Treatment REview and Assessment Team.

the contemporaneous notes and the history from the patient and their carer. Table 2 illustrates how this is recorded for a representative case.

Assessment: Evaluating factors that may influence treatment choice

The second part of the initial assessment is to ascertain the factors that influence treatment choice. Patient preference is central to this and includes establishing preference for mode of delivery and dosing regimes, as well as concerns about particular side-effects. For community initiation of clozapine, it is vital that the patient has some motivation to engage with treatment. For individuals that are not distressed by their symptoms or have a significant lack of insight, community titration is unlikely to be suitable. It is also important to determine risk factors for side-effects, and whether there are contraindications to clozapine or other treatments.

At the end of the assessment, a variety of investigations are ordered (see Box 2). The initial investigations are indicated to evaluate potential causes of treatment resistance, to monitor antipsychotic side-effects and to see whether any contraindications to clozapine exist. Following this first assessment, the patient's case is discussed at the weekly TREAT meeting where the patient's history and investigations are reviewed and management recommendations agreed.

After the meeting, a report is sent to the patient's community mental health teams (CMHT) that comprises the team's recommendations on diagnosis, treatment options, and a summary of the patient's history and investigations. This is discussed with the team and the patient to decide on the future management.

Management procedure

Following discussion with the patient's CMHT, the management plan is instigated. In the majority of cases, a coworking arrangement is adopted where TREAT will initiate treatment, monitor the patient, and assess response and side-effects, while the CMHT continues to be responsible for other aspects of the patients care. TREAT input is for a defined period, generally 6 months, before discharge back to the CMHT for continued care. Where adherence to antipsychotic treatment has been questionable, our recommendation is often for a period of treatment under direct observation or with long-acting injectable antipsychotics.

Management: Clozapine

Clozapine is indicated for patients with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs (3). It has also been used off-license for refractory affective psychotic disorders, although the evidence base is less well established (17, 18). The decision to initiate clozapine treatment is individualized, based on weighing the potential advantages given the patient's clinical condition against the disadvantages given their risk profile and having regard to the patient's preferences. When making the decision as to whether clozapine should be recommended, we also take into account the benefits that clozapine shows in reducing suicidal behavior (19, 20), reducing aggression and violence toward others (21), and in reducing substance abuse (22).

Table 3. Sample titration chart for 'low support' community initiation of clozapine

Day	AM (mg)	PM (mg)
1	6.25	6.25
2	12.5	6.25
3	12.5	12.5
4	12.5	25
5	25	25
6	25	25
7	25	25
8	37.5	25
9	37.5	37.5
10	37.5	50
11	50	75
12	50	75
13	50	75
14	50	75

The only absolute contraindications to clozapine treatment are a history of prior clozapine induced agranulocytosis or prior clozapine induced myocarditis. Contraindications to community initiation are described below, and in higher risk individuals, clozapine initiation should occur in an in-patient setting.

Although clozapine has well-established adverse effects on glucose metabolism (23, 24), it has been used in individuals with diabetes (25) with favorable results. Likewise although its effects on reducing the seizure threshold are well known, it has been used to good effect in patients with epilepsy (26).

If clozapine is recommended, then we explain to the patient the risks and benefits of clozapine, and provide information on side-effects and the need for regular blood tests. If the patient wants to go ahead with the treatment, we supply them with written and verbal information on the initiation process and document their informed consent. Wherever possible, we seek to involve the patient's family in this process. We explain the likelihood of side-effects and the potential for symptomatic and functional improvements so that they can assist the patient in making his/her decision. The importance of good adherence and the possibility of rapid relapse in the case of unplanned discontinuation are highlighted.

Prior to clozapine initiation, a complete workup is performed by the TREAT service. This includes a physical examination, baseline weight and abdominal circumference, blood tests (FBC, U+E, LFT, TFT, troponin, CRP, BNP and CK), and ElectroCardioGram (ECG). An echocardiogram is performed if indicated, for example, if there is a history of cardiac disease or abnormalities on the electrocardiogram. In addition TREAT will register the patient with the appropriate clozapine monitoring agency and liaise with the patient's GP to obtain a full physical health history.

There are three options for initiation. For a minority of patients, in-patient titration will be the only feasible choice. This will include patients unable to adequately engage with the monitoring requirements due to the severity of mental illness. Physical contraindications to community initiation include myeloproliferative disorders or impaired bone marrow function, uncontrolled epilepsy, previous neuroleptic malignant syndrome, severe cardiac disease, severe renal impairment, and previous history of paralytic ileus. In these circumstances, patients are admitted for titration and closer observation. After discharge TREAT will provide ongoing monitoring and management of side-effects and mental state.

For community titration, there are two options. A 'low support' option is suitable for patients who are able to attend the TREAT clinic on a daily basis for monitoring and where there are no factors that put them at high risk of significant side-effects. Patients attend the TREAT clinic daily for monitoring of observations and side-effects. After the morning dose, the evening dose is taken independently with no monitoring of physical observations. There is no monitoring of observations or side-effects over the weekend. The dose is therefore kept constant from Friday to Sunday. A first dose of 6.25 mg is given on a Monday morning, and the patient remains at the OPD for 3 h. If there is no significant change in observations, the patient is given the evening dose to take home with them and leaves the department. The patient then self-administers their evening dose at home, just prior to going to bed at night. On subsequent days, depending on their physical observations and side–effects, patients will wait in the department for 1–2 h after taking their morning dose. Patients will attend 5 days a week for the first 2 weeks, after which the frequency of attendance can be gradually reduced if it is well tolerated. A sample titration chart for the first 2 weeks is shown in Table 3. For subsequent weeks, dose increases occur at a rate of 25 mg a day, depending on tolerability. After 2 weeks of treatment, clozapine plasma concentrations are checked. Dosage increases should be titrated against tolerability, clinical response, and plasma concentration. One should initially aim to reach a plasma concentration of at least above 200 μg/l (27). The average dose in the UK is around 450 mg/day (28); however, interindividual variability is substantial and the effective dose can range from 150 to 900 mg/day (29).

The 'high support' option is recommended for patients who will be unable to attend for regular monitoring or who need closer monitoring of their mental state or physical health. Patients receive twice-daily visits 7 days a week, to administer medication and to monitor mental state and side-effects, and conduct physical observations. This option requires the assistance of the local home treatment team.

The input of the family is helpful during clozapine treatment. Family members can assist with the management of side-effects. In particular, they can motivate the patient to control their dietary intake and encourage exercise. With simple instructions, families can also assist with monitoring of a wide range of side-effects. With sufficient training, they can perform the monitoring of blood

pressure, heart rate, and temperature. If the family is to play such a supportive role, they will need to have daily phone contact with a clinician during the titration period.

During the titration, patients who are currently taking an oral antipsychotic have this reduced, with the intention to stop over the course of 1–3 weeks as their clozapine dose increases. Exceptions include sertindole, ziprasidone, and pimozide, all of which should be stopped entirely prior to titration due to the risk of QTc prolongation (4). Patients who are prescribed depot medication stop receiving this once their titration has commenced.

Management: Monitoring duration clozapine initiation

One of the primary reasons for premature discontinuation of clozapine is the incidence of side-effects (30). Side-effects can be particularly prominent during the early stages of treatment. Therefore, for the first 2 weeks, side-effects and physical observations are monitored on a daily basis during the week. Following that, ongoing weekly assessment of side-effects in the first 3 months of treatment allows rapid management. The schedule for monitoring is illustrated in Box 3.

Agranulocytosis is perhaps the best-known adverse effect of clozapine. However, with hematological monitoring, the risk of death is extremely low – less than 1 in 10 000 patients (4).

Myocarditis is another relatively rare but serious complication. Myocarditis tends to occur in the early stages of treatment (median onset 3 weeks after starting clozapine) (31). Frequent monitoring of temperature and heart rate with weekly measurement of troponin and CRP during the first month of treatment allows early detection of a potentially developing myocarditis. Cardiomyopathy occurs with a similar frequency to myocarditis (31) but may present more insidiously; to observe for this, weekly brain natriuretic peptide (BNP) is monitored during the first month of treatment, and an echocardiogram is performed if there is any cause for concern. Tachycardia is a common side-effect of clozapine. If persistent, then ECG, troponin, BNP, and CRP should be checked to exclude incipient myocarditis. If confirmed as a benign sinus tachycardia, then slowing the rate of titration may help. Beta-blockers or ivabradine may be necessary if persistent (32, 33).

As seizures are a dose-related side-effect, caution should be exercised with dose increments, particularly at doses above 600 mg/day (34). Postural hypotension commonly occurs during the initiation of clozapine (35) and carries with it the risk of collapse. For this reason, blood pressure should be monitored and patients should be warned to stand up slowly. For the first 2 weeks, sitting and standing blood pressure are therefore monitored closely. If patients complain of dizziness, or the postural drop is over 30 mmHg, titration can be slowed. Patients are encouraged to maintain good hydration, and if symptoms are particularly troubling, the use of moclobemide with Bovril has been reported to be effective in addressing this issue (36).

Sedation is another side-effect that is more common during initial stages of treatment, but tends to improve with time. Giving the majority of the dose at night or slowing the rate of titration may improve this. Due to the possibility of sedation, postural hypotension, and seizures, patients are advised not to engage in activities where these side-effects may be dangerous, such as driving or operating machinery and to avoid having baths or going swimming. Constipation occurs frequently and can be potentially fatal (37). Regular inquiry,

Box 3. Side-Effect Monitoring

- Baseline: U + E, FBC, LFTs, Lipids, Glucose, BNP, Troponin, CK, ECG, echo if indicated, weight, waist circumference, blood pressure.
- Daily: For the first 2 weeks of initial titration – side-effects, blood pressure, temperature, and pulse are monitored at least daily during the week.
- Weekly: For the first 3 months, all potential side-effects are enquired about on a weekly basis and treated as appropriate. CRP, BNP, Troponin, and CK should be checked weekly for the first 3 weeks. Weight is monitored weekly for the first 6 weeks.
- Monthly:
  - Month 1 – Weight, waist circumference, plasma glucose
  - Month 3 – Weight, waist circumference, lipid levels
  - Month 6 – Weight, waist circumference, lipids, plasma glucose, LFTs
  - Month 12 – Weight, waist circumference, lipids, plasma glucose
- Long term: After the first year, side-effects should continue to be regularly systematically assessed. Weight, abdominal circumference, plasma glucose, LFTs, U + Es, and ECG should continue to be checked on an annual basis.

dietary advice, and prompt treatment with bulk forming and stimulant laxatives when required should prevent it developing into a serious problem.

Hypersalivation occurs in a large proportion of clozapine-treated patients (38). Pharmacological strategies for its management are manifold, and there is little to separate them on the basis of published evidence (39). In clinical practice, hyoscine hydrobromide is a common initial choice, with alternatives such as pirenzepine considered if this proves to be ineffective.

Along with olanzapine, clozapine is associated with a high risk of weight gain (40). Before initiating treatment, advice on diet and exercise is given to all patients, and a referral to a dietician is made if considered appropriate. If significant weight gain still occurs, pharmacological interventions are considered. These may include metformin (41), aripiprazole (42, 43), or reboxetine (44). Treatment may be started prophylactically before clozapine initiation if the patient is already significantly overweight or has multiple metabolic risk factors, such as raised plasma glucose, dyslipidaemia, and hypertension. Weight is measured weekly for the first 6 weeks of treatment and again at 12 weeks when gains are most likely to occur. In the first year of treatment, abdominal circumference and plasma glucose and lipids are measured at 1, 3, 6, and 12 months after treatment. These parameters should continue to be monitored every 6–12 months subsequent to that (3).

Before starting clozapine, an alternative management plan is agreed so that it is clear what will happen should clozapine have to be stopped.

Management: Alternatives to clozapine

In cases where clozapine is not appropriate, alternatives may be considered. Most alternatives to clozapine treatment have limited evidence to support their efficacy in refractory schizophrenia and often carry an increased side-effect burden. Switching of antipsychotics, interventions to improve adherence, and work on exacerbating factors such as substance abuse may show a greater risk–benefit profile than alternatives such as combination and high-dose antipsychotics.

High-dose olanzapine has been shown to have some benefit in patients with a refractory illness, but is associated with greater weight gain than clozapine (45). It is a logical choice in patients who show low olanzapine plasma concentration secondary to increased hepatic metabolism. This may occur in heavy smokers (46). Lamotrigine augmentation is generally well tolerated and is likely to be particularly appropriate if there is an affective component to the patient's presentation. However, evidence for a significant benefit with antipsychotics other than clozapine is fairly weak (47). Omega-3 triglyceride augmentation has some evidence (48) to support it and is a metabolically benign treatment. In addition, psychological therapies should always be considered in patients with ongoing symptoms (49).

Management: Assessing therapeutic outcome and discharge

After treatment has been initiated, the TREAT continue to see the patient regularly to monitor side-effects and to increase dosage until in the therapeutic range. After treatment with a therapeutic dose for a period of 4–6 months, the patient's response is formally assessed by comparing their scores on the standardized symptom ratings [Positive and Negative Symptom Scale (PANSS) and Clinical Global impression (CGI)] to those obtained at baseline and by evaluating patient satisfaction. Families are a valuable resource when it comes to assessing the patient's clinical response. In particular, the family's views on the patient's level of functioning are extremely informative, and these are obtained both at the initial assessment and later when determining response to clozapine. It is important to establish the degree of benefit received from clozapine, to determine whether clozapine is worth continuing.

If clinical response is inadequate, then clozapine plasma concentrations are checked. Plasma concentrations are broadly related to dose. However, significant interindividual variation means concentrations are valuable in determining whether a patient is receiving a therapeutic dose (50). Suggested thresholds for response range from 200 μg/l (27) to 550 μg/l (51). For patients failing to show a response, the dose is adjusted to give a plasma concentration of between 350 and 500 μg/l (4). Once within a therapeutic range, response should be reassessed after a period of 2–6 weeks.

If patients have still failed to respond, a full case review is undertaken. Diagnosis should again be assessed, further investigations may be appropriate, and the possibility of non-adherence must be considered. Pharmacy records and information from family members and carers in addition to the patient's self-report can help clarify the level of adherence. The use of clozapine plasma levels can also assist in the estimation of recent compliance, and the norclozapine–clozapine ratio can further help clarify patterns of adherence (52). If continued treatment is indicated, then doses above

600 mg/day and plasma concentrations >500 μg/l can be considered. There is some evidence that higher doses can lead to clinical improvement (53). However, it is also clear that the side-effect burden increases, and one must be particularly aware of the increased risk of seizures (54). Higher doses therefore need to be carefully discussed with the patient and CMHT, and if the decision is made to proceed, then antiepileptic prophylaxis is recommended. Lamotrigine is frequently used for this purpose due to the evidence suggesting that it also augments the clinical response to clozapine in patients with ongoing symptoms (55). Patients are advised to have showers rather than baths and avoid driving or operating heavy machinery if using doses in this range.

Doses above 900 mg or plasma concentrations >1.0 mg/l are generally not recommended. It is likely that alternative augmentation strategies will be considered if the patient continues to show an inadequate response. Options here include adjuncts such as amisulpride (56), aripiprazole (57) and omega-3-triglycerides (58).

Results

Experience to date

Of the 137 referrals that the TREAT service has received in the 20 months since covering Lambeth and Southwark, 100 have attended for their initial assessment. Of these attendees, thirty-three have commenced treatment with clozapine, while fifteen have had clozapine recommended but have not wished to undertake clozapine treatment. Twelve patients already receiving clozapine have had augmentation strategies recommended. Twelve have been advised to try an alternative oral medication other than clozapine, seven have been advised to try an antipsychotic in a long-acting injectable formulation, and nine have had no changes recommended to their original treatment. Three have solely been offered advice on side-effect management, while two have been advised to reduce their dose of antipsychotic. Seven patients disengaged before treatment recommendations could be made.

Discussion

The TREAT service model aims to identify and treat patients with refractory symptoms quickly and effectively to prevent delays in the effective management of refractory schizophrenia. Proactively working with community teams enables identification and engagement of patients. Regular systematic assessments are performed to monitor treatment response, while regular side-effect assessment and management encourages adherence and minimizes medication side-effects. The TREAT closely coworks with all professionals involved in the patients care to make community treatment with clozapine possible.

The number of referrals and the fact that 100 (73%) of patients referred attended the service indicates that there is clinical demand for the TREAT service. Of the first one hundred patients to be assessed, clozapine was recommended for 48 patients, other management recommendations were made for forty-five patients (including twelve who were already receiving clozapine), and seven patients disengaged before receiving recommendations. In the forty-eight patients in whom clozapine was recommended, thirty-three (69%) elected to start clozapine, and all successfully went on to clozapine. This is equivalent to approximately 20 patients per year, which compares with a rate of less than 4 community clozapine initiations per year in our hospital prior to the introduction of the TREAT service (14). This provides preliminary evidence for the effectiveness of the service in enabling treatment-resistant patients to receive clozapine. Further work is needed to evaluate the clinical and cost-effectiveness of this service model.

This service model has been developed in an inner-city setting, and it operates in an environment where a variety of services are able to provide additional support if required. However, the elements that compose the service can be adapted so as to be suitable for clinicians working in other settings. So long as patients are able to attend a daily appointment on weekdays and seek help if they become unwell over the weekend, then there is no reason that the procedures described cannot be implemented by clinicians working in less supported settings, including psychiatrists practicing independently.

Potential advantages of a dedicated service for refractory schizophrenia

A specialist team allows the initial assessment, pre-clozapine workup, and initiation of treatment to be completed quickly. This means action can be taken as soon as the patient makes a decision and so improves engagement and commitment to the treatment plan. It allows evidence-based treatment plans to be constantly tailored to the Individual patient's needs. Once clozapine is identified as the most suitable management option, the service can allow patients to have a low intensity clozapine titration in the community which is much less time

consuming and invasive than a hospital admission or home treatment team intervention. This option may encourage a patient to consider clozapine medication where they may have not wanted to before.

Potential disadvantages

There are disadvantages to adding an extra service into a potentially already complicated setup. It can be hard for the patient to attend multiple appointments with different teams, and they can become confused about each team's role. Providing a specialist treatment refractory team can potentially lead to a loss of skills within the community team. Furthermore, it can cause confusion among the clinicians about their individual roles and responsibilities. There is also a risk that continuity of care can be threatened. The TREAT model has attempted to minimize these by involving CMHTs at all points, inviting care coordinators to attend the assessment and discharge meetings, and encouraging close communication with the responsible clinicians through regular email or phone contact. Through this, discussion about management allows education about the latest management options and decreases the risk of community team members losing skills. Referrers are asked to provide anonymous feedback to allow identification and attention to problems. An additional service also has cost implications. Based on evidence that treating refractory patients with clozapine reduces overall cost (10, 11), it is anticipated that such a service would reduce the absolute cost of managing these patients. However, this is not certain and requires a cost-effectiveness study, which is currently being conducted.

In conclusion, the TREAT service provides a new practical model of how to assess and manage patients with TRS to prevent unnecessary treatment delays. However, this service has only recently been established, and further research is required to evaluate outcomes and determine cost-effectiveness.

Acknowledgements

This was funded by a Medical Research Council (UK) grant to Dr Howes (grant number: MC-A656-5QD30) and a Maudsley Charity Grant (number 666) to Dr Howes.

Declaration of interest

Dr Gaughran has received fees for lectures/advisory work or research support from BMS, Sunovion, Roche, Lundbeck, Abbvie and has family professional links to GSK and Lilly. Dr Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by Astra-Zeneca, BMS, Eli Lilly, Jansenn, Lyden-Delta, Servier, and Roche. Neither Dr Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company. Professor Taylor has received consultancies fees, lecturing honoraria and/or research funding from AstraZeneca, Janssen, Roche, Lundbeck, Otsuka, Novartis, Sunovion, Eli Lilly, and Wyeth. Drs Beck, Bloomfield, MacCabe, McCutcheon, Reis Marques and Selvaraj have no conflict of interests.

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