Clozapine Re-Challenge and Initiation Despite Neutropenia and Outcomes from 14 Patients

Edward Silva (✉ ed.silva@nhs.net)

Mersey Care NHS Foundation Trust <https://orcid.org/0000-0002-7254-6307>

Melanie Higgins

Mersey Care NHS Foundation Trust

Barbara Hammer

Arrowe Park Hospital

Paul Stephenson

Mersey Care NHS Foundation Trust

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Abstract

Objective: Clozapine remains the most effective intervention for treatment resistant schizophrenia. But its use is limited because of the risk of neutropenia and agranulocytosis. In the absence of effective alternatives its use after blood dyscrasias is possible. **Methods:** A case series of 14 male patients with treatment resistant schizophrenia treated with clozapine despite previous episodes of neutropenia between 2006 and 2015 is presented. Data were collected during 2015 and 2019. Using routinely collected clinical data we describe the patient characteristics, causes of neutropenia, the strategies used and outcomes. **Results:** Previous neutropaenia was due to varying aetiologies: benign ethnic neutropaenia; clozapine induced; other medication; autoimmune. A range of risk mitigation strategies were used to prevent neutropaenia on clozapine rechallenge: G-CSF; lithium; watch and wait. There were no serious adverse events associated with clozapine or risk mitigation treatments. At follow up during 2019, half of the original 14 patients had improved sufficiently to transfer to conditions of lesser security. **Conclusion:** With careful planning and monitoring, taking into account what is known about neutrophil biology, clozapine can be successfully reinitiated following CIN or in the face of preexisting neutropenia resulting in significant benefits for patients.

Background

Clozapine remains the most effective intervention for treatment resistant schizophrenia (TRS) (1) but remains a third line treatment due to the risk of clozapine induced neutropenia (CIN, ANC(absolute neutrophil count) $<1.5 \times 10^9/L$) and agranulocytosis (CIA, ANC $<0.5 \times 10^9/L$) with rates of 2.7% and 0.7-0.8% respectively. The majority of the abnormalities occur within the first 18 weeks of treatment initiation and almost all within the first year (2) after which the risks become similar to those posed by other antipsychotics. Clozapine may only be used within licence if there is no previous history of neutropenia and with blood monitoring. This risk mitigation regime has been highly effective, with deaths from blood dyscrasias being orders of magnitude lower than those associated with cardiac and gastrointestinal side effects. The MHRA records eight deaths from clozapine induced blood dyscrasias to date as opposed to hundreds from cardiac and gastrointestinal adverse drug reactions (3). In 2006 we were faced with patients who, having had good responses to clozapine, had deteriorated severely when this had been discontinued due to blood dyscrasias and who had failed to respond to multiple alternative regimes; we therefore began to explore both clozapine rechallenge following CIN / CIA and then initiation in the face of pre-existing neutropenia. We present an overview of neutrophil biology relevant to clozapine rechallenge, summarise some of the recent literature relating to rechallenge, the use of lithium and cytokines as support and report the outcomes from 14 cases. In an accompanying article we describe the decision making and practical approaches used (REF).

Mechanisms of CIN and CIA

The mechanisms of CIN and CIA remain elusive and may be distinct (4). Whilst clozapine itself is not directly toxic to neutrophils its metabolites may be (5). Genetic linkage studies suggest both immune and anion transporter gene related mechanisms (6-9) but are not sufficiently predictive to be clinically useful and have predominantly examined European populations, so limiting applicability in other populations (10). CIN and CIA remain idiosyncratic, unpredictable type B adverse drug reactions (ADR). The hypothesis of an immune mediated mechanism is supported by the characteristic timing of both initial adverse effects and the tendency to have faster and more severe problems on rechallenge(11).

Neutrophil Biology

Neutrophils primarily protect the host from bacterial infections. They are produced in the bone marrow differentiating from pluripotent stem cells over 10-14 days. Mature neutrophils are stored in the bone marrow before being released into the blood where they circulate prior to leaving the circulation randomly into tissues with a half-disappearance time of about six hours. The cells then survive for a further 24 to 48 hours. The bone marrow neutrophil reserve is 10-20 times the number of circulating cells and can be mobilised in acute infection or inflammation. Bone marrow neutrophil production is regulated by cytokines. Recombinant pharmaceutical products are available which are used for the treatment of neutropenia in various clinical settings. Neutrophil counts in blood samples vary regardless of their absolute numbers (12, 13) with diurnal variation peaking in the afternoon/evening in response to variation in Granulocyte Colony Stimulating Factor (G-CSF), one of the cytokines stimulating neutrophil differentiation and release (14, 15). External influences such as exercise and smoking also lead to an increase in circulating neutrophils(16, 17).

The normal neutrophil count is defined mathematically rather than pathologically. The lower limit for neutrophils counts is set at $1.5 \times 10^9/L$, two standard deviations below the normal population mean; this is well above the level associated with a significant risk of infection (less than $0.5 \times 10^9/L$) which is classified as severe neutropenia at which guidelines recommend action for the general or oncology patient (18). Neutropenia is either caused by reduced/ineffective production in the bone marrow or by accelerated cell destruction, sequestration or egress from the circulation and can be inherited or acquired (19). In the haematology literature agranulocytosis is defined as a complete absence of neutrophils but the term is often used to indicate severe neutropenia $ANC < 0.5 \times 10^9/L$ (20).

These processes are important when thinking about the use of clozapine. Clozapine blood testing may be optimised by afternoon blood sampling, ideally after exercise, and this alone has been demonstrated to be sufficient to improve outcomes (21). The Clozaril Patient Monitoring Service (CPMS) categorise neutrophil counts according to a colour-coded system(22).

Table 1

If a patient's neutrophil count is less than $1.5 \times 10^9/L$ (red alert) clozapine treatment must be stopped immediately. A follow-up blood sample should be taken the 2 days following the date of the red alert sample; if either of these follow-up blood counts is in the red alert range then the red alert is confirmed and the patient must not restart clozapine. This provides a significant margin to neutrophil levels below which infection is likely and so in some cases flexibility regarding lower acceptable limits might be considered, especially in cases with low pre-clozapine neutrophil counts.

Benign Ethnic Neutropenia

Asymptomatic or benign reductions in neutrophils are observed in individuals of all ethnic backgrounds. Benign Ethnic Neutropenia (BEN), neutropenia without immune dysfunction or increased liability to infection is due not to a reduced absolute number of neutrophils but increased margination(23). It has been described in various non-Caucasian populations. In studies of Black US populations, clinically significant proportions (4.5%) show neutrophil counts less than $1.5 \times 10^9/L$ or even less than $1.0 \times 10^9/L$ (0.57%) (16). The Duffy Null polymorphism which protects against some types of malaria is predicative of BEN (24) and can be determined simply by a request an extended blood type. It has recently been shown to be associated with the development of clozapine induced neutropenia and withdrawal in clozapine treated UK patients of African genetic ancestry (9) to the extent that there may be the potential to use this readily available genetic investigation in combination with other clinical information, the presence of a fluctuating neutropenia in the absence of infection or other pathology in an affected group, to adjust neutrophil thresholds (25). Since 2002 clozapine monitoring services in the UK have reference ranges $0.5 \times 10^9/L$ lower for patients with haematologically confirmed BEN (see Table 1)(26). Therefore some patients who received clozapine prior to 2002 will have had clozapine discontinued on account of 'red' results that can, in retrospect, be re-evaluated. Afro-Caribbean patients are less likely that their peers to be prescribed clozapine (27) (28).

Clozapine Re-challenge after CIN and CIA

Given the limitations of case reports from populations treated with clozapine and then rechallenged after blood dyscrasia, the available evidence is useful but conflicting. In 2006, the CPMS published the data of all available rechallenges in the UK and Ireland. Of 53 patients presented, 20 patients (38%) experienced a further blood dyscrasia. The second blood dyscrasia was more severe in 17 of these patients (85%), in 12 patients (60%) longer and in 17 patients (85%) it occurred more quickly. Nine (45%) of the 20 cases of dyscrasias were agranulocytosis. Yet 55% of all cases (29 patients) did sufficiently well to continue to

receive clozapine. There were no deaths. No clear risk factors for repeat blood dyscrasias were identified. Only one CIA patient was rechallenged and that individual did not go on to develop a further dyscrasia. None of the 20 failed re-challenge patients went on to a third attempt (29). More recently, data from the results of a nationwide pharmacovigilance study in Argentina presented the outcomes of 19 clozapine rechallenge patients; almost 70% of patients did not experience a second dyscrasia and of those that did, the dyscrasia occurred sooner during treatment but unwanted effects were less severe and of shorter duration (30). Evidence from case reports show positive outcomes in more than 60% of clozapine rechallenges post neutropenia (128 positive outcomes from 203 reported cases); fewer attempts are described following agranulocytosis and with less clinical success (3 positive outcomes from 17 reported cases) (31). There is a lack of data relating to the retitration regimes used and the outcome experienced. This is potentially important if immune mechanisms are responsible for the adverse events.

Lithium and neutrophils

Lithium has varying effects on haematopoiesis. It enhances the production of G-CSF and directly stimulates the differentiation of stem cells into neutrophils resulting in increased absolute neutrophil numbers. It also protects neutrophils from the toxic effects of some drugs. In haematological practice it has shown some utility in treating cases idiopathic neutropenia and syndromes in which G-CSF production is reduced (32). The use of lithium to support clozapine rechallenge has been reviewed by both Manu (2012) and Boazak (2018) with high rates of success. However, Boazak noted that, in the few reported cases where lithium was withdrawn following an initially successful rechallenge, a second dyscrasia had followed. As an adjunct to clozapine rechallenge the familiarity psychiatrists have with the use of lithium, patient acceptability, low cost and the attitude of downstream services are all helpful (33-35). There are a number of disadvantages: lithium's effects on neutrophil production, although significant, are markedly less than the alternative of G-CSF; there is a risk of reversible neurotoxicity (36); and case reports of the use of lithium and clozapine include one in which there was fatal agranulocytosis (37) and another by a failure of subsequent G-CSF (38). There is also the concern of poor compliance increasing relapse of affective symptoms, whether or not this has been clearly demonstrated in patients with a specific diagnosis of schizophrenia or schizoaffective disorder opposed to bipolar disorder (39).

G-CSF and neutrophils

G-CSF is a cytokine glycoprotein that stimulates the differentiation, release and survival of neutrophils and other granulocytes. As recombinant products, they have been available for therapeutic use since the early 1990's and were originally used mainly to treat patients with chemotherapy-induced neutropenia for short durations, over time, the indications expanded to include severe chronic neutropenia and for the mobilisation of haematopoietic progenitor cells for stem cell transplantation(20, 40, 41). Filgrastim (G-CSF) is a WHO essential medicine (42) and is used to treat drug induced neutropenia in general (43).

There are multiple case reports in relation to CIN and CIA (40, 44-56) reviewed by Lally et al (57, 58); the general finding being that rechallenge supported by either regular G-CSF or as required (plus rescue) G-CSF was successful in over 70% of initial CIN cases. However, the reported clinical success was markedly reduced and with a risk of repeat agranulocytosis following CIA; in such cases, G-CSF can be safely used to speed recovery following CIA.

The use of G-CSF is not part of usual psychiatric practice. Common side effects of short-term use include flu like symptoms, bone pain, headache, pyrexia and fatigue. Rare complications include splenic rupture, Acute Respiratory Distress Syndrome, glomerulonephritis, alveolar haemorrhage, serious allergic reactions, thrombocytopenia, cutaneous vasculitis and capillary leak syndrome. Long term safety data following short term G-CSF use is available from healthy volunteer donors of peripheral blood progenitor cell (PBPC); approximately 20,000 healthy donors receive G-CSF worldwide yearly (59). Appropriate precautions relating to the longer term use of G-CSF include the management of bone pain with paracetamol as well as regular ultrasonography to monitor for splenomegaly (60). Long-term G-CSF administration predisposes to the development of osteopenia/osteoporosis (61). However, osteopenia is a recognised finding in this patient population and is often present prior to treatment initiation. Regular bone mineral density assessment in patients receiving long term G-CSF is recommended, as it will enable the detection of subtle bone changes and early treatment initiation that can prevent the development of symptomatic osteoporosis. Initial concerns that G-CSF may cause an increased leukaemia risk have been alleviated by long term follow up (62).

Patterns of Clozapine Response

Patients with TRS who do respond to clozapine frequently show this early in treatment, within days or weeks especially when adequate levels have been achieved (63-65); this is consistent with response to other antipsychotics when used first line (66). Persisting with a potentially hazardous treatment in the absence of significant improvement after an adequate trial is not recommended.

Methods

Treating psychiatrists at Ashworth Hospital, one of the four UK high secure psychiatric hospitals, identified patients prescribed clozapine off license despite previous neutropenia, whether due to CIN or any other cause. Routine hospital records were reviewed to identify demographic and clinical details. Data regarding response to treatment, incidents and episodes of seclusion were collected at 04.06.2015 and again on 31.05.2019 regarding transfer out of high secure hospital and continuation of clozapine. By the first data collection point the average length of total follow up was 34.4 months (min 4.1, max 75.1). At the second census date, the average total follow up was 61.4 months (min 17.5, max 122.9); over this period, patients had been followed up on clozapine following neutropenia for an average of 56.6 months (min 0.7, max 119.6).

Results

Patient Demographics:

Fourteen subjects were identified; four had transferred to lesser security by the first census date and a further three by the second. All were male with a primary diagnosis of schizophrenia (ICD-10 F20). The indication for clozapine in each case was treatment resistance. All had been extremely unwell for many years having been in high security for an average 5.1 years prior to the interventions described. All but two patients were being nursed in seclusion or long term segregation (67) at the time of the studied clozapine trial for an average of 486 days; for two patients this was in excess of 2,000 days. These restrictions had been used on account of persistent and at times extreme violence. Three patients had originally been transferred to high security in the context of deteriorations secondary to clozapine discontinuation due to neutropenia.

Previous treatments:

All had failed to adequately respond to multiple non-clozapine antipsychotics (min 3, max 15, average 7.8) alone and as polypharmacy; 12 patients had received these drugs at doses above the recommended UK maxima (**TABLE 2**). Ten had been prescribed clozapine for an average of 394 days (min 35, max 1785) before this had been stopped. Seven patients had shown improvement with clozapine; there was no evidence to suggest the remaining three patients had improved on clozapine although they had taken clozapine on average for 77 days only (min 35, max 150). During previous clozapine treatment a change to an alternative antipsychotic treatment was necessary following a period of neutropenia (N=8) or non-compliance (N=2)

In all cases, a clinical decision was made to trial a period of treatment with clozapine due to the failure of all other antipsychotic treatment regimes and the severity of the patients' psychoses. The risk of possible treatment complications, in particular a further episode of neutropenia, was considered against likely benefits of clozapine treatment. In addition, the anticipated degree of difficulty in maintaining patient and staff safety in the event of a blood dyscrasia resulting in clozapine discontinuation, rebound psychosis and extreme behavioural disturbance was considered.

Aetiology of neutropenia:

All had previous neutropenia (ANC less than $1.5 \times 10^9/L$ due to various aetiologies). Five had previous CIN one of whom had also had agranulocytosis following treatment with another antipsychotic. Two patients had neutropenia associated with other medications (sodium valproate and risperidone) prior to

the use of clozapine and one developed neutropenia related to the use of lamotrigine during clozapine therapy (duration of 1 day with a neutrophil nadir of $0.6 \times 10^9/L$). BEN was present in five cases: two of these patients had pre-clozapine neutrophil counts that were frequently below the BEN adjusted neutrophil cut offs; two had previously been exposed to clozapine prior to BEN having been recognized and clozapine had been stopped when neutrophils fell below the non-BEN levels; and one patient had not had a previous diagnosis of BEN. Another patient had an autoimmune neutropenia. Unfortunately, the data were incomplete as a small number of the adverse events occurred a number of years previously in other healthcare settings; where available, previous clozapine related neutropenic episodes had duration of 7 days on average (min 2, max 21) with an average nadir of $1.0 \times 10^9/L$ (min 0.7, max 1.3) mostly on the second neutropenic day (n=4) (see Table 3). There was one previous episode of agranulocytosis with associated spontaneous infection in the patient who had had both CIN and agranulocytosis secondary to another antipsychotic.

Risk Mitigation Strategies:

The relationship between the type of neutropenia and risk mitigation strategy used is set out in **TABLE 4**. A watch and wait approach was taken with the patients who had previous non-clozapine related drug induced neutropenia. For one patient who developed neutropenia during established clozapine treatment when lamotrigine was introduced, two doses of G-CSF were used, lamotrigine was withdrawn and clozapine continued. The patient with autoimmune neutropenia was given clozapine using the BEN reference ranges with provision for G-CSF if required. For the cases of established CIN, prophylactic or rescue G-CSF was used. A variety of approaches including lithium, rescue and prophylactic G-CSF were used taking into account the challenges of the patients with BEN and low neutrophils.

However, as Von Moltke observed, no plan survives first contact with the enemy (68) and so the initial strategies did not all succeed. One patient prescribed lithium did not tolerate this due to sedation and so the alternative of rescue G-CSF was made available. Another patient with BEN and low pre-clozapine neutrophils had a series of neutropenic episodes when clozapine was introduced as planned; these were initially treated with rescue G-CSF but after neutrophils reached a nadir of $0.4 \times 10^9/L$ and there was then a good response to clozapine and G-CSF, both were continued regularly. One CIN case required prophylactic G-CSF following repeated episodes of neutropenia with rescue G-CSF. A further CIN case was switched from prophylactic G-CSF to rescue G-CSF without any further neutropaenia.

Medication and dose:

At the first census date one patient experienced two amber results before a single red result within the first month of treatment reaching a maximum dose of 200mg per day before clozapine was withdrawn. He had reportedly shown some clinical improvement. The remaining patients were able to tolerate

clozapine and at the first data collection point the most recent average dose of clozapine (N=13) was 354mg/day (min 225mg, max 450mg). Hematological advice on the use of G-CSF took into account the patient's body weight, the severity of the previous neutropenia and the effect of clozapine. Where regular G-CSF was used doses varied between 15 and 60 million units per week. One patient was prescribed lithium both for his mental disorder and to stimulate neutrophil counts and so this was at 800mg/day. A lower dose of lithium at 400mg/day was used for another patient when only a neutrophil effect was needed.

Progress:

The treating clinicians considered that all patients had showed a clinical improvement on clozapine. By the first census point all except one remained on the drug and four had been transferred to lesser security. At the second data collection point, of the ten patients remaining in 2015, a further three patients had discontinued clozapine treatment: one patient had died of an unrelated cause; one had refused clozapine for unspecified reasons; and clozapine had been discontinued in another patient due to suspected poor clozapine absorption in relation to an inflammatory bowel condition. A further three patients had remained on clozapine and improved sufficiently to transfer to less secure services. The remaining three patients showed a variable progress but remained on clozapine; one patient had progressed to the extent that very prolonged seclusion had ended.

In summary, by the second census date, half of the original 14 patients had improved sufficiently to transfer to lesser security; one patient was transferred directly to a low secure unit and the others to medium secure facilities. The transfer process was slow, taking on average 40.7 months following initiation of the current clozapine trial (min 17.5, max 54.0); several patients had lengthy periods of decompression from seclusion before this could be contemplated. There followed uncertainty in some receiving units as to whether or not the clozapine treatment initiated in conditions of high security could be continued. The proportion of time spent in seclusion decreased dramatically when assessed at the first census date. Prior to the studied clozapine trial, the 14 men had spent 31% of time nursed in seclusion; this reduced to 13% as at the first census date (paired t-test $p < 0.001$) (**TABLE 5**). The adverse behavioural incidents (including aggression, violence and deliberate self harm) for the ten patients who remained at June 2015 decreased from 30 per 100 days per patient before clozapine initiation to 7 per 100 days per patient after starting clozapine (paired t-test $p < 0.002$) (**TABLE 6**). Seclusion and incident data were not collected at the second census date.

Unwanted effects of treatment:

Four had anomalous blood results. It was suspected that one related to inadvertent morning blood sampling, late in treatment, so the logistics of blood taking were revisited but provision was made for

rescue G-CSF. One patient with BEN who had no prior clozapine experience rapidly developed repeated low neutrophil counts of less than $1.0 \times 10^9/L$ with one brief episode at $0.4 \times 10^9/L$. Each episode responded to G-CSF given first intermittently and then regularly. One patient whose initial clozapine had been discontinued after neutropenia at over 800 days of treatment had six episodes of low neutrophils with a nadir of $0.4 \times 10^9/L$; these episodes, within the first two months of clozapine re-challenge, responded to intermittent and then regular G-CSF. Another patient had two amber results followed by a single red result (neutrophil count $1.3 \times 10^9/L$) within the first month of clozapine treatment; clozapine was stopped by the treating team. No patient developed infection or required transfer to general hospital. Of those prescribed G-CSF (rescue or prophylactic), one patient was noted to have splenomegaly on ultrasound imaging; this continues to be monitored by hematology colleagues; no other intervention has been required. No patient has complained of bone pain while on G-CSF. Lithium was discontinued in one case due to sedation.

Discussion

We have described one of the largest series of the use of clozapine following neutropenia from any cause and we believe our length of follow-up exceeds any previously reported. Our high secure forensic patient group presented particular problems, with extreme disturbance, highly uncooperative behavior, lengthy periods of treatment resistant psychosis, the prolonged use of isolation and lengths of stay perhaps more meaningfully measured in years than weeks. Yet even in this group the unique efficacy of clozapine was evident, with life changing effects for many of the men we describe. Some were transformed, from individuals completely incapacitated by psychosis with life threatening harm both to themselves and others and needing the most restrictive interventions imaginable, to men able to participate freely in all aspects of hospital life and who have now been discharged, not only to less secure hospitals but also now to community settings. One man went on to give evidence about Mental Health services at the House of Lords. This response to clozapine is, of course, the usual pattern, even in the most difficult forensic populations (69, 70). As well as transforming patients' lives these interventions have resulted in dramatic reductions in length of stay, expense, and the use of seclusion, segregation, isolation or whatever other argot is used to describe solitary confinement; an issue of both national and international concern (71, 72).

Despite progress, understanding of the aetiology of life-threatening clozapine blood dyscrasias remains insufficient. There are many causes of neutropenia; its definition is not uncontroversial and a low neutrophil count is not necessarily indicative of significant pathology. The existing neutrophil thresholds for the continuation of clozapine are extremely effective at safeguarding patients, but may well be so safe that many who would benefit are not eligible, particularly those of African ancestry. Since at least 1993 the psychiatric literature relating to clozapine has defined agranulocytosis as a neutrophil count of less than $0.5 \times 10^9/L$; (73) this has been convention since. But at the time of the first Finnish cases, agranulocytosis was described as the presence of very few or no granulocytes in the peripheral blood (74) and our haematology colleagues subdivide neutropenia into mild ($1.5-1.0 \times 10^9/L$) moderate ($1.0-$

$0.5 \times 10^9/L$) and severe ($0.5-0.2 \times 10^9/L$) with or without sepsis. Agranulocytosis is strictly the complete absence of neutrophils and it is at counts of less than $0.2 \times 10^9/L$ at which infection is most likely (20). Absolute neutrophil counts have rarely been set out in the reported clozapine rechallenge cases and it is possible that a significant number have included subjects with either benign mild neutropenia coincidental to clozapine use or have taken a broader definition of agranulocytosis than that in the original Finnish cases. In 2015 the US FDA guidelines for interruption of clozapine treatment changed. White blood cell count (WBC) monitoring is no longer required and once clozapine is established the threshold for an absolute neutrophil count requiring treatment interruption was lowered from $1.5 \times 10^9/L$ to $1.0 \times 10^9/L$ and to below $0.5 \times 10^9/L$ in cases of BEN (75-77).

We took an arguably aggressive approach to supporting neutrophil counts using significant amounts of G-CSF. Our decision-making was in the light of the existing UK neutrophil thresholds and with patients for whom cessation of clozapine would result in adverse outcomes: at best a failure to progress; at worst life threatening violence to themselves or others. We were particularly mindful of the difficulties that would be faced by all should we need to care for an acutely psychotic man, experiencing a clozapine rebound psychosis with severe neutropenia or agranulocytosis requiring treatment in reverse barrier isolation on a haematology ward; being sure that this scenario would be unmanageable we took what we considered to be the necessary steps to avoid it. As with other reported series of clozapine rechallenge other less interventional approaches may have been successful. In particular a simple revision of the neutrophil thresholds on an off-license basis. Better still would be wholesale change to align UK and US practice (78).

We are unclear why the psychiatric literature has used ANC's of below $0.5 \times 10^9/L$ as a single cut off to define agranulocytosis. Similarly there has been no differentiation between the different degrees of neutropenia as used elsewhere. The clozapine literature could be improved by taking that approach, particularly when attempting to improve our understanding of the aetiologies of these difficult adverse events. As described by Legge we hope that a wider understanding of the role of the Duffy-null genotype in BEN in general and in low neutrophil counts in patients taking clozapine in particular (and potentially other psychotropic drugs with a risk of neutropenia) will translate in to an easily obtainable pharmacogenetic test (9). Duffy typing can be performed following a routine laboratory request for a blood group. Prevention is better than cure. Given that a significant proportion of cases of CIN and CIA likely have an immunological mechanism it may well be that slower rates of titration, both on initial use and in the event of rechallenge may result in reductions in adverse events (79). This approach has been effective for rechallenge of lamotrigine and carbamazepine following adverse serious side effects(80-82).

We have described several approaches to allow rechallenge of clozapine despite previous neutropaenia. We are pleased to report that there were no serious adverse events but instead marked improvements in the quality of life for our patients. Careful mitigation of further neutropaenia with a flexible approach is needed to ensure the patient is offered the best opportunity for recovery; it may be necessary to change mitigation strategy at short notice to encourage compliance and minimize risk of life-threatening blood

dyscrasia. We advocate close working with haematology colleagues when prescribing clozapine to patients with previous neutropaenia. Our case series demonstrates that rechallenge with clozapine following neutropenia should not be dismissed without full consideration of the potential benefits.

Tables

Table 1 Clozaril Patient Monitoring Service (CPMS) alert ranges

Traditional (normal blood monitoring)		
Colour alert	WBC x 10 ⁹ /L	Neutrophils x 10 ⁹ /L
Green	> 3.5	> 2.0
Amber	3.0 – 3.5	1.5 – 2.0
Red	< 3.0	< 1.5

Benign Ethnic Neutropaenia		
Colour alert	WBC x 10 ⁹ /L	Neutrophils x 10 ⁹ /L
Green	> 3.0	> 1.5
Amber	2.5 – 3.0	1.0 – 1.5
Red	< 2.5	< 1.0

Table 2 demographics and background information

Patient number	Gender	Diagnosis	Age at diagnosis	Age at admission to HSS	Non clozapine antipsychotics	Polypharmacy	High dose	Previous trial of clozapine
1	M	TRS	16.2	21.3	8	Y	Y	Y
2	M	TRS	26.8	30.0	7	Y	Y	Y
3	M	TRS	18.9	22.7	10	Y	Y	Y
4	M	TRS	21.3	25.6	4	Y	Y	Y
5	M	TRS	20.5	38.8	15	Y	N/K	Y
6	M	TRS	16.0	22.0	3	Y	N	Y
7	M	TRS	22.0	37.6	9	Y	Y	Y
8	M	TRS	20.9	21.0	7	Y	Y	Y
9	M	TRS	18.7	31.1	8	Y	Y	N
10	M	TRS	20.4	39.9	7	Y	Y	N
11	M	TRS	19.4	30.1	7	Y	Y	Y
12	M	TRS	20.4	29.9	6	Y	Y	N
13	M	TRS	18.0	24.6	9	Y	Y	Y
14	M	TRS	19.5	23.0	9	Y	Y	N

Table 3: previous trials of clozapine

Patient number	Length of previous clozapine trial (days)	Mental state improvement	Neutropaenia caused by clozapine (CIN)	Length of CIN (days)	Nadir	Time from onset to nadir (days)	Associated illness or infection
1	893	Y	Y	21	0.7	15	N
2	78	Y	Y	2	1.1	1	N
3	339	Y	Y	3	1.3	0	N
4	1785	Y	Y	4	1	1	N
5	61	Y	Y	N/K	N/K	N/K	N
6	268	Y	N	-	-	-	N
7	287	Y	N	-	-	-	N
8	35	N	N	-	-	-	N
11	150	N	N	-	-	-	N
13	45	N	N	-	-	-	N

Table 4: mitigation of neutropenia; clinical outcomes

patient number	Type of neutropaenia	Time in HSS before clozapine trial following neutropenia (years)	Initial Management of neutropaenia	Length of follow up (months) (as at 2 nd census date)	Outcome	Progress
	CIN	5.5	G-CSF if required	54.0	Discharged: 54.0 months after starting clozapine	Mental state improved with clozapine; the frequency of adverse behavioural incidents significantly reduced. The patient had six red results during the first two months of treatment with a neutrophil nadir of $0.4 \times 10^9/L$; these episodes responded to plus rescue G-CSF before the strategy was switched to G-CSF prophylaxis. The patient was prescribed regular filgrastim 15 million units/week. There were no further red results. The patient was discharged to conditions of lesser security 54.0 months after restarting clozapine.
	CIN	3.6	G-CSF prophylaxis	59.1	Death: 59.1 months after starting clozapine	Mental state improved with clozapine; the frequency of adverse behavioural incidents significantly reduced. The patient was prescribed regular filgrastim 30 million units twice weekly. There were no reported side effects associated with G-CSF. The patient died of an unrelated myocardial infarction 59.1 months after restarting clozapine
	CIN	2.5	G-CSF if required	82.8	Clozapine discontinued: 72.6 months	Mental state improved with clozapine; psychotic symptoms were more manageable. Time nursed

					after starting clozapine	in seclusion reduced dramatically; the frequency of adverse behavioural incidents significantly reduced. The patient was transferred to a less restrictive ward environment (from a high dependency ward to a medium dependency ward). Plus rescue G-CSF was available in the event of neutropenia; this was not needed. Clozapine was discontinued after 72.6 months by the treating team due to suspected poor clozapine absorption in relation to an inflammatory bowel condition. At the second census date, the patient remained detained in conditions of high security.
	CIN	3.0	G-CSF prophylaxis	122.9	Clozapine discontinued: 119.6 months after starting clozapine	Mental state improved with clozapine. Time nursed in seclusion reduced significantly; the frequency of adverse behavioural incidents reduced. The patient was initially prescribed regular filgrastim 15 million units three times per week. The patient refused regular G-CSF after approximately five years. Plus rescue G-CSF was subsequently available in the event of neutropenia; this was not needed. Splenomegaly was noted on ultrasound imaging; this continues to be monitored by haematology colleagues; no other intervention has been required. Clozapine was discontinued after 119.6 months due to

						patient refusal. At the second census date, the patient remained detained in conditions of high security.
	CIN	2.5	G-CSF prophylaxis	28.6	Discharged: 28.6 months after starting clozapine	Mental state improved with clozapine. Time nursed in seclusion reduced significantly. Prescribed regular filgrastim 48 million units/week. There were no reported effects associated with G-CSF. The patient was discharged to conditions of lesser security 28.6 months after restarting clozapine.
	Medication induced	0.8	G-CSF if required	117.6	Continues on clozapine in HSS	Mental state improved with clozapine. Time nursed in seclusion reduced significantly; the frequency of adverse behavioural incidents reduced. The patient developed neutropenia after 55 months of clozapine treatment when lamotrigine was introduced. Two doses of filgrastim 30 million units were given over three days; lamotrigine was withdrawn and clozapine continued. G-CSF remains available in the event of a neutrophil count of less than $1.5 \times 10^9/L$; There has been no further neutropaenia. As at the second census date, the patient remained on clozapine in conditions of high security.
	Medication induced	8.2	Watch and wait	0.7	Clozapine discontinued: 119.6 months after starting clozapine	The patient experienced two amber results before a red result (neutrophil count $1.3 \times 10^9/L$) within the first month of

						treatment reaching a maximum dose of 200mg per day before clozapine was withdrawn. He had reportedly shown some clinical improvement with clozapine.
	Medication induced	2.2	Watch and wait	52.6	Discharged: 52.6 months after starting clozapine	Mental state improved with clozapine. Time nursed in seclusion reduced significantly; the frequency of adverse behavioural incidents reduced. There were no episodes of neutropenia following rechallenge with clozapine. The patient was discharged to conditions of lesser security 52.6 months after restarting clozapine.
	Autoimmune	1.8	G-CSF if required	86.1	Continues on clozapine in HSS	Mental state improved with clozapine. Time nursed in seclusion reduced significantly; the frequency of adverse behavioural incidents reduced. Managed using the BEN reference ranges with provision for G-CSF in the event of neutropenia; this was not needed. There have been no episodes of neutropenia since starting clozapine. As at the second census date, the patient remained on clozapine in conditions of high security.
1	BEN	5.6	Lithium	52.7	Discharged: 52.7 months after starting clozapine	Mental state improved with clozapine. Time nursed in seclusion reduced significantly; the frequency of adverse behavioural incidents reduced. The patient was initially prescribed lithium at 400mg/day to increase neutrophil count; this was

						not tolerated by the patient due to increased sedation. G-CSF was subsequently made available in the event of a neutropaenia; this was not required. The patient was discharged to conditions of lesser security 52.7 months after starting clozapine.
	BEN	0.4	G-CSF if required	52.0	Continues on clozapine in HSS	Mental state improved with clozapine. Time nursed in seclusion reduced significantly; the frequency of adverse behavioural incidents reduced. The patient was prescribed lenogastrim 263mcgs if neutrophils fall below $1.0 \times 10^9/L$. The patient required only one dose of G-CSF within one month of restarting clozapine (neutrophil count fell to $0.9 \times 10^9/L$). No side effects were reported due to use of G-CSF. As at the second census date, the patient remained on clozapine in conditions of high security.
	BEN	0.5	Watch and wait	48.8	Discharged: 48.8 months after starting clozapine	Mental state improved with clozapine. Neutropaenia was initially managed by optimizing neutrophil counts with afternoon sampling and exercise. The patient rapidly developed repeated low neutrophil counts of less than $1.0 \times 10^9/L$ with one brief episode at $0.4 \times 10^9/L$. Episodes of neutropenia were initially treated with plus rescue G-CSF, which was later converted to regular G-CSF. Within six

						months of starting clozapine the patient was prescribed regular filgrastim 15 million units on alternate days. There were no reported effects associated with G-CSF. The patient was discharged to conditions of lesser security 48.8 months after starting clozapine.
	BEN	11.5	G-CSF prophylaxis	17.4	Discharged: 17.4 months after starting clozapine	Mental state improved with clozapine. The patient was prescribed regular filgrastim 30 million units twice weekly. There were no reported effects associated with G-CSF. The patient was discharged to conditions of lesser security 17.4 months after starting clozapine.
	BEN	23.8	Lithium	30.5	Discharged: 30.5 months after starting clozapine	Mental state improved with clozapine. The patient was initially prescribed lithium at 800mg/day to increase neutrophil count (this predated clozapine treatment). There were no reported side effects associated with lithium. There were no episodes of neutropenia. The patient was discharged to conditions of lesser security 30.5 months after starting clozapine.

HSS: High secure services

Table 5: clinical outcome; effect of treatment on restrictive practice

Patient number	Time in HSS before clozapine trial with neutropaenia mitigation (days)	Time in HSS on clozapine with neutropaenia mitigation (days)	Time nursed in seclusion before clozapine trial (days)	Seclusion density before clozapine trial	Time nursed in seclusion during clozapine trial (days)	Seclusion density during clozapine trial	Ratio (seclusion density before / seclusion density during clozapine trial)
1	361	1196	0	0%	0	0%	0.00
2	1201	785	0	0%	0	0%	0.00
3	911	1063	803	88%	40	4%	0.04
4	83	2285	38	46%	168	7%	0.16
5	927	870	804	87%	51	6%	0.07
6	274	2122	255	93%	1096	52%	0.55
7	2375	30	2013	85%	30	100%	1.18
8	60	964	60	100%	478	50%	0.50
9	644	1164	294	46%	106	9%	0.20
10	2063	940	2063	100%	318	34%	0.34
11	161	126	141	88%	57	45%	0.52
12	175	1486	1	1%	0	0%	0.00
13	4207	531	102	2%	152	29%	11.81
14	8697	929	236	3%	9	1%	0.36

Table 6: clinical outcome; effect of treatment on clinical (adverse behavioural) incidents

Patient number	Time in HSS before clozapine trial with neutropaenia mitigation (days)	Time in HSS on clozapine with neutropaenia mitigation (days)	Number of clinical incidents before clozapine trial	Clinical incident density before clozapine trial (incidents/100 days)	Number of clinical incidents before clozapine trial	Clinical incident density during clozapine trial (incidents/100 days)	Ratio (Clinical incident density before / Clinical incident seclusion density during clozapine trial)
1	361	1196	59	16.3	41	3.4	0.21
2	1201	785	28	2.3	3	0.4	0.16
3	911	1063	298	32.7	96	9.0	0.28
4	83	2285	8	9.6	4	0.2	0.02
6	274	2122	65	23.7	73	3.4	0.15
8	60	964	51	60.8	339	19.3	0.32
9	644	1164	91	14.1	48	4.1	0.29
10	2063	940	309	15.0	22	2.3	0.16
11	161	126	49	30.4	14	11.1	0.37

Declarations

About the authors

Edward Silva^{1*}, Melanie Higgins¹, Barbara Hammer², Paul Stephenson¹

1*. Consultant Forensic Psychiatrist. Ashworth Hospital, Mersey Care NHS Foundation Trust, Parkbourn, Maghull, Merseyside L31 1HW, UK

2. Consultant Haematologist. Arrowe Park Hospital, Arrowe Park Road, Upton, Wirral, Merseyside, CH49 5PE, UK

*Corresponding Author

email: ed.silva@merseycare.nhs.uk

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