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REVIEW ARTICLE

Treatment resistant schizophrenia – review and a call to action

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Recovery rates in schizophrenia remain suboptimal with up to one-third resistant to standard treatments, a population prevalence of 0.2%. Clozapine is the only evidenced-based treatment for treatment resistant schizophrenia (TRS), yet there are significant delays in its use or it may not be trialled, potentially impacting the chance of recovery. Better outcomes with earlier use of clozapine may be possible. There is emerging evidence that early treatment resistance is not uncommon from the earliest stages of psychosis. In this review, we provide an update on TRS, its epidemiology and its management, with a specific focus on the optimal use and timing of clozapine and augmentation strategies for the one-third of patients who do not respond to clozapine.

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Introduction

Schizophrenia is a chronic disorder, of variable clinical characteristics and outcome, reflected in the heterogeneous response to antipsychotic medication. Approximately 50–70% of patients with their first episode of schizophrenia (FES) will respond to the first antipsychotic medication prescribed, this figure falling to 20% for those who require a trial of a second (Agid *et al*., 2011). Antipsychotic medication (excluding clozapine) has its greatest effect within the first 2 weeks and thereafter the improvements are more marginal (Agid *et al*., 2003). Despite the expansion in our therapeutic armamentarium over the past decades, up to one-third of patients do not respond to non-clozapine antipsychotics (Wimberley *et al*., 2016; Lally *et al*., 2016a) and are described as having treatment resistant schizophrenia (TRS).

Defining treatment resistance

The concept of TRS first appeared in the literature in the mid-1960s (Itil *et al*., 1966), but definitions remained inconsistent, rendering the literature difficult to interpret. A recent systematic review of randomised controlled trials (RCTs) in TRS identified 42 studies; of these half did not define what they meant by treatment resistance and only two of the 42 studies used the same criteria (Howes *et al*., 2017). International consensus guidelines on treatment resistance (and response) in schizophrenia were therefore developed by the Treatment Response and Resistance in Psychosis (TRRIP) group (Howes *et al*., 2017) in an attempt to construct a unified definition of TRS. According to these guidelines, the following defines TRS: the presence of persistent significant symptoms in a person with a diagnosis of schizophrenia, who has not had a response to at least two antipsychotic trials of adequate dose, duration and adherence. In defining adequate treatment, the guidelines follow the recommendation of the National Institute of Clinical Excellence (NICE) and indicate that each antipsychotic treatment last for at least 6 weeks, with each drug administered at an 'adequate' therapeutic dosage (NICE., 2014), equivalent to the minimum effective dose/target dosage (or the midpoint of the target range as specified in the product summary characteristics) – or to a daily dose equivalent to 600 mg of chlorpromazine (Leucht *et al*., 2015b; Leucht *et al*., 2016). In effect, this means a minimum duration of antipsychotic treatment of 12 weeks is required before treatment resistance can be diagnosed.

In recognition of the possibility that unrecognised treatment non-adherence may mimic TRS, the guidelines recommend that at least one treatment episode utilise a long-acting injection antipsychotic formulation (depot) for at least 4 months before diagnosing treatment resistance. Alternatively, the use of plasma antipsychotic concentrations can be informative. Although

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not routinely used in clinical practice, a growing range of second-generation antipsychotics have suggested therapeutic ranges (minimum target threshold: amisulpride 200 µg/l, aripiprazole 150 µg/l, olanzapine 20 µg/l, quetiapine 100 µg/l and risperidone 20 µg/l (total risperidone and 9-hydroxyrisperidone) (McCutcheon *et al*., 2015), though in Ireland, samples need to be processed at UK laboratories. A recent observational study of 99 people referred to a TRS service identified that 35% of antipsychotic plasma concentrations were sub-therapeutic, and of these, a third were undetectable (McCutcheon *et al*., 2018).

Similarly, it is important not to conflate treatment non-adherence due to intolerability with treatment non-response and resistance.

Factors to consider in differentiating TRS from treatment non-response due to other causes are shown in Box 1.

Epidemiology of TRS

Schizophrenia has a relatively low incidence (approx. 15.2/100 000), and a lifetime prevalence of approximately 7/1000 (McGrath *et al*., 2008; Moreno-Kustner *et al*., 2018). TRS is highly disabling and affects approximately 20–30% of those diagnosed with schizophrenia (Wimberley *et al*., 2016; Lally *et al*., 2016a, Demjaha *et al*., 2017). In Ireland with a population of approximately 5 million, given that the lifetime risk for schizophrenia is 0.7%, there will be approximately 35–40 000 people with schizophrenia. A conservative estimate is that 20% (Bachmann *et al*., 2017) of those (i.e. 7000–8000) will meet the criteria for TRS. However, there is little contemporary epidemiological data on psychotic disorders in Ireland.

Box 1 Assessment of treatment resistance

- Reassess primary diagnosis
- Assess comorbidities [eg substance use, comorbid mood disorders, anxiety, obsessive compulsive disorder (OCD)]
- Consider organic contributors
- Assess and consider potential for management of unresolved chronic or recurrent stressors
- Assess adherence to and tolerance of past treatment plans
- Optimise antipsychotic dosage
- Consider the use of LAI antipsychotic if partial or inadequate adherence to treatment, not due to intolerance
- Manage medication side effects

Recovery and outcome in schizophrenia

Antipsychotic treatment failure and intolerability come with a high clinical and economic cost (Kennedy *et al*., 2014). Our systematic review and meta-analysis of remission (defined as an improvement in symptoms ± a specified duration criteria (e.g. >6 months) for persistence of mild or absent symptoms) and recovery (defined as sustained improvement in both clinical and functioning domains ± a duration of sustained improvement for ≥1 year) in 5000 people with FES, found a recovery rate of 30% (95% CI = 19.7–43.6., $N = 12$ studies) at 5 years follow-up, with 56.0% (95% CI = 47.5–64.1, $N = 25$ studies) meeting criteria for remission at 7.5 years follow-up (Lally *et al*., 2017a). Remission and recovery rates may be overestimated with shorter duration of follow-up, but our average length of follow-up was 5 and 7.5 years, respectively, and we did not identify that recovery rates decreased during periods of follow-up longer than 2 years.

This study highlighted a better long-term prognosis in FES, and a more positive outlook for people diagnosed with schizophrenia than previously suggested, given that a 2013 review of outcomes in FES and multi-episode schizophrenia estimated that only one in seven patients attain a functional recovery (Jaaskelainen *et al*., 2013). Estimates of the prevalence of TRS derived from clinical samples should be interpreted with this in mind; the prevalence of TRS is likely to be overestimated in most studies as patients with early remission and recovery may not be included.

Although waiting until a second antipsychotic trial fails before defining a treatment resistant course of illness may seem arbitrary at first glance, this is supported by evidence indicating that the response rate drops precipitously after successive failed trials of medication. Approximately 70% of FEP patients remit on their first anti-psychotic, (Agid *et al*., 2011) but after the second drug, the response rate drops to less than 5% (Kane *et al*., 1988). With early use of clozapine, a response of 60–70% can be achieved in TRS with improvement observed up to a year after initiation (Meltzer, 1992). Findings from OPTiMiSE ('Optimisation of Treatment and Management of Schizophrenia in Europe'), a large scale FES study investigating the benefits of antipsychotic switching in patients not achieving remission on first-line amisulpride, indicate that clozapine is effective in substantially reducing psychotic symptoms after 12 weeks of use, when introduced as a second- or third-line treatment (Kahn *et al*., 2018).

Clinical management of TRS

Clozapine is the only evidence-based effective treatment for TRS, as reflected in international guidelines

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(Nielsen *et al*., 2016), with reported clinical response in 60–70% of patients (Meltzer, 1992; Agid *et al*., 2011) and meta-analyses identifying an overall response rate of 40–60% (Chakos *et al*., 2001; Siskind *et al*., 2017).

In naturalistic settings compared to no antipsychotic treatment, clozapine is associated with decreased rehospitalisation (Nielsen *et al*., 2012; Stroup *et al*., 2016; Kirwan *et al*., 2017; Taipale *et al*., 2017) and reduced hospitalisation and risk of relapse (Tiihonen *et al*., 2017). Its use is associated with reductions in comorbid substance use (Brunette *et al*., 2006), hostility and aggression (Krakowski *et al*., 2006; Frogley *et al*., 2012).

Clozapine use is also associated with lower all-cause mortality (Tiihonen *et al*., 2009; Hayes *et al*., 2015), completed suicide (Meltzer *et al*., 2003; Ringback Weitoft *et al*., 2014) and self-harm (Ringback Weitoft *et al*., 2014; Wimberley *et al*., 2017). An important meta-analysis identified that those continuously treated with clozapine had lower all-cause mortality over a 7-year follow-up compared to those continuously treated with other antipsychotics (Vermeulen *et al*., 2018). This allies to previous work showing that most major side effects with clozapine can be managed without a need for discontinuation (Nielsen *et al*., 2013), and that in certain situations clozapine rechallenge can be successful (Manu *et al*., 2012; Lally *et al*., 2017b, Lally *et al*., 2018), indicates that concerns regarding the detrimental effect of clozapine on longer term mortality compared to other antipsychotics may be overestimated.

When to use clozapine

In a longitudinal study of 246 people with FES, 34% met the criteria for treatment resistance over a 5 year follow-up period (Lally *et al*., 2016a), of whom 70%, 23% of the total study population, were treatment resistant from illness onset. This raises the possibility that TRS may be a distinctive and homogenous schizophrenia subgroup, in line with the biological differences seen between treatment resistant and treatment responsive schizophrenia (Demjaha *et al*., 2014).

The question of staging and early recognition of treatment resistance in people with schizophrenia is of utmost importance. Recent longitudinal data indicate that earlier use of clozapine and fewer pre-clozapine antipsychotic trials are associated with better treatment outcomes for people with TRS (Ucok *et al*., 2015). A retrospective analysis from Japan identified a critical time window of 2.8 years after illness onset, subsequent to which clozapine response was poorer (response rates of 82% *v*. 32%) (Yoshimura *et al*., 2017). Emerging evidence to suggest additional benefits with earlier use of clozapine exists (Agid *et al*., 2011; Lally *et al*., 2016a, Kahn *et al*., 2018), much earlier than the 2.8 years critical time period identified.

We know that people with TRS experience delays of 4–5 years before starting clozapine (Howes *et al*., 2012). Each non-clozapine antipsychotic trial before clozapine is associated with a further 10% reduction in clozapine response rates (Nielsen *et al*., 2012) while in women the functional Improvement achieved with clozapine decreases by 15% (HRR, 0.85; 95% CI, 0.72–1.00) for each year delay to initiation (Kohler-Forsberg *et al*., 2017). Further, high-dose antipsychotic polypharmacy is used in 36.2–65% of patients before receiving clozapine (Taylor *et al*., 2003; Howes *et al*., 2012; Ucok *et al*., 2015), which is not evidence-based practice, and increases the risk of adverse events. In Ireland, a retrospective analysis of 171 FEP cases who presented from 1995 to 1999, identified that 16% ($n = 28$) commenced clozapine in the follow-up period, with a mean delay of 6.7 years and an average of 4.85 antipsychotic trials prior to clozapine use (Doyle *et al*., 2017).

Clozapine underutilisation

Despite its superior and unique effectiveness in TRS, there is marked geographical variation in prescription of clozapine, which in most countries is prescribed to far fewer than the approximately 30% of patients who are likely to benefit from it. Clozapine prescription rates in people with schizophrenia vary from 2% to 5% (Stroup *et al*., 2014) in the United States to 20–30% in the UK, Finland and New Zealand (Downs & Zinkler, 2007; Wheeler, 2008; Tiihonen *et al*., 2011). There are several possible reasons for deciding against starting clozapine. It is likely that the fear of side effects (by clinicians and patients alike) and the inconvenience of blood monitoring limit its uptake. Clinician unfamiliarity with the use of clozapine, complex pathways to qualify for clozapine use, clinician overestimation of the prevalence and severity of side effects and poor communication all contribute (Nielsen *et al*., 2010; Verdoux *et al*., 2018).

Predicting TRS/clozapine responders

Our findings indicate that two distinct patterns of treatment resistance develop in patients, with the majority displaying treatment resistance from the onset, and a smaller subset of patients developing treatment resistance after periods of relapse (Lally *et al*., 2016a). While there is a large literature investigating the predictors of treatment response and remission from illness onset (Carbon & Correll, 2014), treatment resistance has only recently been examined longitudinally as an outcome measure in FEP (Lally *et al*., 2016a, Demjaha *et al*., 2017).

An early age of onset (<20 years old) and male sex are consistent predictors for TRS (Lally *et al*., 2016a). Severity of psychotic symptoms at first contact for

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psychosis does not predict TRS, though those with TR from onset have more psychotic symptoms at first contact than those with emergent resistance (Lally *et al*., 2016a). Greater impairment on the Global Assessment of Functioning (GAF) scale is associated with an higher risk of TRS within 2 years of first schizophrenia diagnosis (Horsdal *et al*., 2017).

What if, at the early stages of antipsychotic treatment we could identify those patients likely to respond to clozapine – and those likely to have adverse effects? The available neuroimaging and genetic biomarkers cannot yet reliably guide the early use of clozapine (Lally *et al*., 2016b, Samanaite *et al*., 2018). Of 379 investigated gene variants, only three (DRD3 Ser9Gly, HTR2A His452Tyr and C825T GNB3) have independently replicated significant findings in clozapine response prediction. Replicated putative central biomarkers of clozapine response include a lower ratio of the dopamine and serotonin metabolites, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the CSF. Higher prefrontal cortical volumes and increased prefrontal activity on imaging may predict clozapine response (Samanaite *et al*., 2018). Neuroimaging studies have indicated a potential role for glutamate in TRS cases compared to treatment responsive schizophrenia, with higher glutamate levels in the anterior cingulate cortex (Demjaha *et al*., 2014; Mouchlianitis *et al*., 2016), and relatively normal dopamine functioning in TRS (Demjaha *et al*., 2012), with increased levels of glutamatergic metabolites in the ACC in those with TRS compared to controls (Demjaha *et al*., 2014; Iwata *et al*., 2018).

Standardised definitions of TRS and treatment response will allow for the development of comparable, large, homogenous samples to prospectively assess links between genetic and neuroimaging data and clozapine response and tolerability. Such studies will need to account for factors such as concurrent medication use, tobacco smoking, clozapine dose and plasma concentrations. The current best available clinical marker of TR is the careful assessment of antipsychotic non-response with assured adherence and tolerability. Biomarker testing to improve the predictability of response to clozapine is the subject of a number of multicentre/international collaborations but the clinical utility of such an approach will depend on the emergence of an effective alternative to clozapine for people with TRS.

Clozapine non-responders

For the 30% of TRS patients who fail to respond to clozapine (Meltzer, 1992; Lally *et al*., 2016c) and the 25% in whom clozapine is discontinued due to adverse events (Davis *et al*., 2014; Mustafa *et al*., 2015), there is little to guide subsequent pharmacological strategies. If a patient was not to respond to clozapine after 3 months of therapeutic dosing (clozapine plasma concentrations 0.35–0.5 mg/l) (Schulte, 2003; Remington *et al*., 2013), then the following steps would be considered (Box 2).

It is important to assess for and manage comorbid conditions. People with TRS have more comorbid alcohol (51%) and substance abuse (51%), than those with non-TRS (27–35% and 28–35%, respectively). While this can complicate the consistency of adherence to clozapine, an optimised trial of clozapine may give an individual with TRS, the best chance of successfully managing their comorbid substance use. Suicidal ideation is noted in 44% of people with TRS (Kennedy *et al*., 2014) and it is important to be aware of the possibility of a comorbid mood disorder. In clozapine-treated patients, OCD rates of 47% have been identified (Fernandez-Egea *et al*., 2018), 3-fold higher than in non-TRS (Swets *et al*., 2014), with some authors believing OCD to be released by clozapine use (Schirmbeck & Zink, 2012).

Clozapine augmentation strategies

The practice of augmentation with a second antipsychotic varies, occurring in 11.7–72% of clozapine-treated patients (Wheeler, 2008; Pai & Vella, 2012; Ucok *et al*., 2015). A recent systematic review and meta-analysis of 46 studies reported improvement in total psychotic symptoms with augmentation with aripiprazole, fluoxetine and sodium valproate, although the quality of included studies was noted to be poor (Siskind *et al*., 2018). Single studies supporting the efficacy of paroxetine, duloxetine and lithium carbonate in reducing total psychotic symptoms compared to placebo were identified (Siskind *et al*., 2018). Leucht *et al.* (2015a) examined the augmentation with lithium in general schizophrenia and noted that the response was

Box 2 Management of clozapine non-response

- Full multidisciplinary team assessment
- Optimise clozapine (plasma clozapine concentrations of 0.35–0.5mg/l (Schulte, 2003))
- Consider trial of supratherapeutic clozapine levels (i.e. > 0.5 mg/l), with seizure prophylaxis
- Manage adverse effects proactively
- Augment in partial responders
- Treat comorbid conditions, such as OCD; depression; hypomania/mania; substance use disorders
- Psychological therapies: CBTp, family work

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limited to those with an identified affective component to their illness (Leucht *et al*., 2015a). Clinical recommendations, including those in the Maudsley Guidelines (Taylor *et al*., 2018), emphasise the importance of recognising and treating co-occurring mood symptomatology. Overall, caution is required and other meta-analyses have identified that clozapine augmentation with a second medication, including a second antipsychotic, an antidepressant, lamotrigine, topiramate or glycine was not superior to placebo in improving psychopathology (Sommer *et al*., 2012; Correll *et al*., 2017), while sodium valproate is highly teratogenic.

An earlier meta-analyses of 14 RCTs of antipsychotic augmentation concluded that clozapine augmentation with a second antipsychotic was modestly superior to placebo and well tolerated (Taylor *et al*., 2012). However, the most recent meta-analysis (Galling *et al*., 2017) focused solely on antipsychotic augmentation after a non-response, rather than concurrent initiation and augmentation trials and provided no evidence for enhanced efficacy of antipsychotic augmentation in high-quality studies. Some evidence for improvement in negative symptoms with aripiprazole augmentation was seen.

Guidelines for clozapine augmentation from 15 years ago would have favoured a trial of amisulpride, based largely on anecdotal evidence and pharmacodynamic properties of the compound, which may synergistically augment clozapine. However, to date there is no trial evidence to support this or indeed alternative antipsychotic augmentation strategies. A recent RCT of clozapine augmentation failed to find an effect of amisulpride compared to placebo in reducing psychotic symptoms, although recruitment was underpowered (Barnes *et al*., 2017) and amisulpride may merit further investigation in larger studies. An earlier single sulpiride trial showed efficacy as an augmentation agent in improving total, positive and negative symptoms (Shiloh *et al*., 1997).

Siskind's recent meta-analysis identified that aripiprazole showed effects in reducing total psychotic symptoms, but the effect was lost when poor-quality studies were removed (Siskind *et al*., 2018). The two high-quality placebo-controlled trials of aripiprazole augmentation show divergent results, with evidence for benefits for negative symptoms in one trial (Chang *et al*., 2008) and positive symptoms in a later trial (Muscatello *et al*., 2011). Aripiprazole has, however, shown efficacy in relation to weight loss when combined with clozapine (mean difference (95% CI) of −1.36 kg (−2.35 to −0.36) ($n = 3$ studies; $p = 0.008$) (Srisurapanont *et al*., 2015) and is used in low doses to improve the tolerance of clozapine.

Various non-antipsychotic agents, such as antiepileptics/mood stabilisers (lamotrigine, topiramate, sodium valproate, lithium carbonate,), antidepressants (citalopram, fluoxetine, fluvoxamine, mirtazapine), glutamatergic agents (CX 516, D-cycloserine, D-serine, glycine, sarcosine), allopurinol, memantine, telmisartan and tetrabenazine have been trialled as clozapine augmentation (Elkis & Buckley, 2016; Siskind *et al*., 2018). Among these, sodium valproate (6 RCTs, $n = 430$) has shown efficacy in reducing total psychopathology and positive symptoms compared to clozapine monotherapy. Prescribing of valproate is, however, a problem in women of childbearing age, given its teratogenicity. Similar findings were reported for topiramate (5 RCTs, $n = 270$), but it is associated with a high rate of discontinuation (Zheng *et al*., 2017). Lamotrigine has shown some evidence of efficacy, but this effect is lost in meta-analyses when outlier studies are removed (Sommer *et al*., 2012; Zheng *et al*., 2017).

The divergent findings from clozapine augmentation trials mean that the evidence base does not allow for assured recommendations, or for the development of treatment algorithms for clozapine non- or suboptimal response. Limitations to studies include the variable definitions of clozapine resistance and the dose and short duration of use of the antipsychotic augmentation agents. Current evidence suggests that augmentation agents may need to be used for longer than the standard 6-week antipsychotic monotherapy trial to enhance effectiveness (Correll *et al*., 2009). It remains the case that augmentation interventions are used as individual patient trials and if no symptomatic improvement is seen then the medication should be stopped, to minimise the risk of adverse effects.

Electroconvulsive therapy

An intriguing finding is the relatively high-response rate in clozapine non-responders to augmentation with electroconvulsive therapy (ECT) in open trials (Petrides *et al*., 2015). A 2005 Cochrane Review of ECT for schizophrenia noted that in treatment resistant psychosis, the recommended number of ECT treatments was 12–20, higher than in affective disorders (Tharyan & Adams, 2005). In our recent meta-analysis, we identified a 66% response to clozapine augmentation with ECT, with an average of 11 treatments used (Lally *et al*., 2016c). To date, it is not possible to identify specific clinical factors that may predict response to ECT augmentation of clozapine. Further, the use of ECT to augment clozapine is far from standard clinical practice in the UK or Ireland, with the usual course of treatment being to augment with other medications, or the addition of psychotherapy.

A note of caution is raised from a recent small single-blind sham-controlled trial that investigated the efficacy of augmenting clozapine with 12 sessions of ECT

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($n = 13$) or Sham ECT ($n = 12$) in clozapine resistant schizophrenia (Melzer-Ribeiro *et al*., 2017). This pilot study did not identify a significant difference in PANSS total, positive and negative scores between the groups, with only one ECT-treated patient having the 40% or more reduction in PANSS scores seen in the Petrides trial, one with a 30% or more reduction and only 2 with a 20% or more reduction, The authors note the small sample size and suggest a marked placebo (Sham ECT) response likely impacted on the pilot study findings (Melzer-Ribeiro *et al*., 2017).

Clozapine augmentation with cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is widely used in patients with schizophrenia, especially in the treatment of positive symptoms such as delusions and hallucinations and in the management of associated emotional distress. A meta-analysis of 12 RCTs of CBT use in medication resistant psychosis showed significant improvement in positive psychotic symptoms compared to controls, supporting the use of CBT as an adjunctive treatment in TRS (Burns *et al*., 2014). Two small unrandomised RCTs assessed the efficacy of CBT in clozapine non-responders, with benefits seen for total psychotic and general psychopathology symptoms compared to a befriending control intervention (total $n = 21$) (Barretto *et al*., 2009) and improvements in positive symptoms compared to supportive therapy (total $n = 37$) (Antonio Pinto *et al*., 1999). The recent Focusing On Clozapine Unresponsive Symptoms (FOCUS) randomised clinical trial is the largest and most rigorous trial of CBT for clozapine resistant psychosis and failed to identify any significant differences in the primary outcome of Positive and Negative Syndrome Scale (PANSS) total score at 21 months (mean difference −0·89, 95% CI −3·32 to 1·55; $p = 0·48$), between those treated with CBT and treatment as usual (Morrison *et al*., 2018). This is an important null study finding and fails to support widespread use of CBT for clozapine augmentation in clozapine resistant schizophrenia and other psychotic disorders. These study findings need to be considered alongside the overall small effect size for total symptom improvement in non-TRS, and lack of significant benefit for positive symptoms identified in meta-analysis of RCTs of CBT use (Jauhar *et al*., 2014).

An important consideration is for carer support and family interventions for those with TRS. Family interventions incorporate psychotherapeutic interventions focused on psychoeducation, facilitating communication and supporting families in developing coping skills and identifying appropriate support services. Family interventions have shown reductions in relapse and rehospitalisation rates, and improved medication adherence in psychotic disorders, along with reduced expressed emotion in families (Pharoah *et al*., 2010). It is important to note that the vast majority of family intervention studies have not focused on TRS, highlighting an unmet need in research of family interventions in this patient population and for practice implementation.

Affective symptoms

Comorbid mood disorders are often missed in treatment resistance but are important to bear in mind, and if comorbid depression is present, whether it is historically in a unipolar or bipolar context. Meta-analytic data exist to support antidepressant augmentation of first generation antipsychotics in non-TRS patients with predominant negative symptoms. The strongest evidence is for augmentation with selective serotonin reuptake inhibitors, although there is low-level evidence for the use of augmentation with mirtazapine with improvements on positive symptom severity (Galling *et al*., 2018).

In a meta-analysis of non-TR schizophrenia cases, a significant risk difference was found in favour of antidepressant treatment, with a number needed to treat of 5 (95% CI 4–9), but the effect did not persist after sensitivity analysis (Gregory *et al*., 2017). It is worth noting that the bulk of the agents showing effectiveness in clozapine augmentation in the Siskind *et al.* (2018) meta-analysis were antidepressants or mood stabilisers, although the presence or absence of affective disorder was not included as a variable in the analysis.

Negative symptoms

To date, no pharmacological strategies have demonstrated consistently replicable effects on primary negative symptoms. However, there is scope for better outcomes, particularly in negative symptoms secondary to depression, positive psychotic symptoms or motor side effects, which may be more amenable to treatment, and for which clozapine treatment may have advantages.

Clozapine refusal

Patients sometimes refuse clozapine due to dislike of phlebotomy or needle phobia. Possible strategies may include the use of the smallest calibre needles, the application of EMLA cream prior to phlebotomy and consideration for the use of psychological interventions based on exposure techniques where appropriate.

An alternative strategy is the use of finger prick capillary blood sampling. This could be considered if all attempts to perform venous sampling fail. A single

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puncture site on the palmar surface of the distal phalanx of the 3rd or 4th digit is used, with the first drop of blood discarded before collecting a volume of approximately 125–250 ul (approximately 4–5 drops of blood). Prior discussion with the local haematology laboratory is essential to ensure that granulocyte counts can be reliably measured from a capillary sample as this is not standard and confirmation with the clozapine regulatory body is needed (e.g. ZTAS or CPMS).

Intramuscular (IM) clozapine is an unlicensed product that has been used as a short-term intervention to potentially enable the initiation of clozapine in those who are refusing oral administration. It is started with a view to establishing regular oral clozapine as soon as possible, and clozapine tablets are offered to the patient as an alternative before each injection. Current formulations of clozapine IM are 25 mg/ml and each ampoule contains 5ml (125 mg). The maximum single IM dose is 100 mg, administered in the gluteal muscle, which restricts the potential for dose escalation.

In an Israeli retrospective analysis of the use of parenteral clozapine in 59 clozapine-treated patients who became noncompliant, 27% ($n = 16$) were switched to oral clozapine within 3 days and a further 71% ($n = 42$) by 7 days. One patient continued with IM clozapine for 8 days. There were no adverse events reported, though patients were already established on clozapine for 'a few weeks' prior to the use of parenteral clozapine (Lokshin *et al*., 1999). Seventeen patients with TRS were identified for treatment with IM clozapine in a Dutch cohort (Schulte *et al*., 2007), of whom 10 started IM injections, while 7 chose oral clozapine in preference. The duration of IM treatment was 1–4 days for four patients (40%), 7–11 days for three patients (30%) and 1–3 months for three patients (30%). The maximum daily dosage of IM clozapine, given in one or two injections, was 12.5–25 mg for four patients, and 50 mg, 150 mg, 200 mg, 225 mg, 300 mg and 500 mg for six patients, respectively (the mg/ml dose used was not provided). Clozapine was discontinued in two patients, one who developed leucopenia and another who developed impaired liver function. A further patient continued IM treatment for 90 days without any evidence that they would switch to oral clozapine, necessitating the ending of the IM regimen (Schulte *et al*., 2007).

Alternatives to clozapine in TRS

As clozapine may not be suitable for some patients, for example due to intolerability, adverse events or if they are deemed to be non-rechallengeable, alternative treatments for TRS have been tried. The best evidence is for the use of high-dose olanzapine with some trial data (olanzapine mean dose 35 mg (Meltzer *et al*., 2008); mean olanzapine dose of 20.5 mg and 67% treated with 25 mg/day) (Tollefson *et al*., 2001) providing support for equivalent reductions in psychotic symptoms and relapses in comparison to clozapine. Of note, while Meltzer *et al.* (2008) found an equivalent reduction in PANSS score on high-dose olanzapine, those randomised to clozapine had better function and fewer emergent cardiometabolic risk factors. Other trials found high-dose olanzapine to be inferior to clozapine in adults (mean olanzapine dose 50 mg/day) (Conley *et al*., 2003) and adolescents (mean olanzapine dose 26.2 mg/day) (Kumra *et al*., 2008).

Meta-analysis of antipsychotic augmentation with the selective oestrogen receptor modulator (SERM) raloxifene in non-TR schizophrenia suggests that it is useful in improving symptoms compared to placebo (de Boer *et al*., 2018). In a RCT of 56 post-menopausal women with TRS, raloxifene at 120 mg/day was associated with a greater reduction in PANSS total score relative to placebo ($\beta = -6.37$; 95% CI, −11.64 to −1.10; $p = 0.02$) and an increased probability of clinical response (hazard ratio, 5.79; 95% CI, 1.46–22.97; $p = 0.01$) (Kulkarni *et al*., 2016). Raloxifene was well tolerated and offers potential for its use in this difficult to treat patient cohort and follows on previous trials from the same centre showing an effect of adjunctive oestradiol 200 mcg in symptom improvement, particularly positive symptoms (Kulkarni *et al*., 2015). However, other studies have failed to find a benefit for adjunctive raloxifene in improving cognitive symptoms in non-TR schizophrenia (Kulkarni *et al*., 2016; Weiser *et al*., 2017), or in improving symptom severity (Weiser *et al*., 2017).

Key areas for clinical and academic focus to optimise the management of TRS are outlined in Box 3.

Conclusion

The evidence highlights clozapine as the cornerstone of the pharmacological management of TRS. Clozapine is a uniquely effective medication with over half of those treated responding and with additional benefits in reducing suicide, aggression, violence, alcohol and substance abuse, psychiatric rehospitalisation and all-cause mortality. Despite there being no comparable alternatives, clozapine remains underutilised and initiation is delayed. Increasing evidence suggests that it should be used earlier in the course of illness, with better longer term outcomes associated with earlier use.

Despite being available for over 25 years, the incorporation of clozapine initiation into routine practice needs more work. Although non-clozapine antipsychotics confer little or no benefit for a third of all people with schizophrenia, TRS remains a poor relation in the academic community, with a comparative

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Box 3 The management of TRS, clinical and research priorities

Clinical/service
- Audit and feedback of variability in clozapine prescription rates
- Links with primary care practices-management of side effects
- Educational opportunities for service user and family groups
- Community clozapine-initiation services
- Multidisciplinary continuing professional development (CPD) education programs on TRS
- Regional mentorship for complex queries

Research
- Identification of obstacles to clozapine use
- Evaluation/implementation of innovative TRS practice and service models, e.g.:
  - Strategies to minimise cardiometabolic risk
  - Point-of-care testing
- Collaboration/leadership of multinational studies of factors predicting response and adverse effects

paucity of studies on its epidemiology, genetic, molecular and neuroimaging characteristics, and the response to pharmacotherapeutic/psychotherapeutic interventions.

With no current credible therapeutic alternatives, it is worth considerable investment in clinical services and academic structures to optimise our use and understanding of clozapine and of strategies, which may help when clozapine fails or is not, tolerated. It is important to maintain an awareness of the high rates of comorbidity in TRS, acknowledging that addressing these may considerably improve function or quality of life in someone for whom antipsychotics are having little effect. Novel psychotherapeutic approaches, such as Avatar Therapy may also hold potential. As TRS research is now moving more into the personalised sphere, this opens the possibility of identifying effective interventions for subgroups of people with TRS. In the meantime, collaborations between clinicians, academics, service users, families, service-planners and industry are needed to scan the horizon for future developments in the prevention and management of TRS.

Conflict of interest

FG declares a potential conflict of interest, although not in relation to this work.

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Ethical Standards

The authors (JL and FG) assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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