Clozapine-resistant schizophrenia: a positive approach

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Clozapine is widely regarded as the 'gold standard' treatment for treatment-resistant schizophrenia, after failure of two antipsychotics at adequate doses for an adequate duration of time. However, even after 1 year, a number of patients fail to respond to clozapine alone. We question the term 'treatment-resistant', which implies that little further can be done and generates therapeutic nihilism, and instead suggest the term 'neuroleptic-resistant schizophrenia' as a more positive alternative. In this editorial we suggest a number of treatment options for patients resistant to clozapine monotherapy, and hope to generate a fresh and positive approach.

Confirming neuroleptic-resistant schizophrenia

Before discussing possible treatment options, the importance of a thorough assessment and review of the diagnosis must be emphasised. In addition, the identification of perpetuating factors such as comorbid drug use or non-compliance should be addressed. Clozapine plasma concentration monitoring should be performed to investigate the latter, and should be used frequently as a guide to assessing outcome of interventions where a sub-therapeutic clozapine concentration is recognised.

TREATMENT STRATEGIES: MEDICATION

Antipsychotics

When antipsychotic monotherapy with clozapine fails, combination strategies to enhance the antipsychotic effect of clozapine can be considered. Shiloh *et al* (1997) have conducted the only randomised controlled trial to date. They showed that, compared with placebo, sulpiride augmentation of clozapine produced a reduction in psychotic symptoms at 10 weeks. Other smaller, open studies have shown clinical improvement using pimozide (Friedman *et al*, 1997) or loxapine (Mowerman & Siris, 1996) in conjunction with clozapine.

Atypical antipsychotic drugs also have been used for augmentation, although all the reports to date are case reports or small, open studies. Gupta *et al* (1998) reported two cases of patients who made good progress after olanzapine was added. Further studies have reported good responses when risperidone was added to clozapine (Morera *et al*, 1999; Raskin *et al*, 2000). Although some authors have attempted to use other atypical antipsychotics after clozapine has failed, because of either non-response or intolerance (Weiss *et al*, 1999; Dossenbach *et al*, 2000; Wahlbeck *et al*, 2000), it appears that such approaches may be unjustified (Chakos *et al*, 2001; Tuunainen *et al*, 2001).

Antidepressants

There have been several reports describing the augmentation of clozapine with a selective serotonin reuptake inhibitor (SSRI). Evidence is unconvincing except as a result of the increased clozapine serum level using the SSRI–clozapine interaction. Buchanan *et al* (1996) found no effect on positive or negative symptoms with the addition of fluoxetine to clozapine. Therapeutic use of this interaction should be considered only when compliance is assured, maximal dosing has been achieved and the serum level is below 350 ng/ml. It should be attempted cautiously and with regular monitoring of plasma levels. When adding an SSRI, the dose of clozapine should be reduced in anticipation of the likely rise in plasma concentrations. Five- to tenfold for fluvoxamine (Koponen *et al*, 1996) and approximately twofold for fluoxetine and paroxetine (Centorrino *et al*, 1994). This interaction may be useful clinically, but use of it to reduce drug costs is not advisable (Markowitz *et al*, 1996).

Mood stabilisers

Valproate is suggested as the anticonvulsant of choice for clozapine-induced seizures (Novartis Pharmaceuticals UK Ltd, 1998). Valproate may be effective in managing refractory psychotic or manic symptoms in addition to seizure prophylaxis, although combination with clozapine is not specifically mentioned (Kando *et al*, 1994).

Both carbamazepine and lamotrigine have been used in combination with clozapine but are not recommended because both drugs have the potential to depress bone marrow function. However, despite these risks, Dursan *et al* (1999) describe some benefits following the addition of lamotrigine to clozapine.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) has been used in combination with clozapine and has been found to be safe and clinically beneficial (Bonator *et al*, 1996; Bhatia *et al*, 1998). Combining ECT and clozapine also has been described for achieving rapid control of disturbed behaviour, when time would not allow for dose titration with clozapine as monotherapy (James & Gray, 1999). However, the improvement with this combination may not be sustained after ECT is discontinued (Kales *et al*, 1999).

TREATMENT STRATEGIES: PSYCHOSOCIAL APPROACHES

There is a growing body of evidence for the effectiveness of psychosocial treatment approaches in psychosis. The majority of studies are not specific to clozapine resistance but may be useful in guiding strategies for such patients. However, Pinto *et al* (1999) have conducted a small randomised controlled trial demonstrating that clozapine plus cognitive–behavioural therapy was superior to clozapine plus supportive psychotherapy.

Working with systems

Knowing that some patients continue to suffer enduring symptoms, in spite of treatments such as clozapine, challenges mental health service providers. Effective treatment relies on a diversity of approaches, delivered by a multi-disciplinary team as a clearly defined care package. The increased awareness of the importance

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of psychosocial approaches in psychosis has been accompanied by the development of staff training courses. The Thorn Nursing Initiative (Gamble, 1995) was the first systematic training course for mental health professionals working in the community. Good outcomes included reductions in positive symptoms and an improvement in social functioning (Lancashire *et al*, 1997). There is still a lack of such training in institutional settings, and recent concerns have been expressed in *The National Visit* regarding the deficiencies of care within in-patient settings (Sainsbury Centre for Mental Health & Mental Health Act Commission, 1997).

As a result of high expressed emotion attitudes found in nurses working with patients with chronic psychosis (Herzog, 1998), training within in-patient settings has been undertaken. Finnema *et al* (1996) found that their programme led to general changes in the ward atmosphere, such as a decrease in 'ward rules'. We have used a combined psychoeducational and therapeutic training approach, which produced positive results on levels of knowledge and stress among staff (further details available from the author upon request).

Working with individuals

General principles

In the past it was thought that psychological therapies were contraindicated in psychosis, but studies such as the London–East Anglia study (Garety *et al*, 1997; Kuipers *et al*, 1997, 1998) have shown that this is not the case, with good outcomes following 9 months of therapy and at 18-month follow-up. In addition, for both positive and negative symptoms of schizophrenia there is good evidence to support psychological approaches, such as manualised cognitive–behavioural therapy (Sensky *et al*, 2000). Usually, a lengthy assessment period is required before a detailed formulation can be developed. This should lead to specific interventions related directly to the formulation. However, those patients who are resistant to clozapine are among the most severely disabled, both socially and emotionally, and any psychosocial strategy undertaken will require a flexible approach.

Engagement

Kingdon & Turkington (1998) describe two components to engagement: coming to an understanding of why the person has developed unusual beliefs; and providing credible alternative explanations. Specific techniques used to promote engagement include using the patient's own words, agreeing to disagree, avoidance of jargon and accepting the unlikely as possible but unlikely, all of which supplement the general techniques of warmth, empathy and unconditional positive regard. Tailoring the therapy to the patient's particular needs may include short, frequent sessions. The use of a normalising rationale, which reframes a person's psychotic experiences into understandable and explainable terms, reduces the anxiety and distress associated with psychotic symptoms.

Positive symptoms

Treatment for positive symptoms is well researched and has been described elsewhere in detail (Chadwick *et al*, 1996; Dickerson, 2000) and therefore will not be covered in depth here. However, because negative symptoms and thought disorder are often more problematic in this patient group, their treatment has been described.

Therapy for thought disorder

Working with patients with thought disorder is challenging, but there are techniques that may be helpful, such as keeping sessions short. Just spending time with the person is important, as he or she may have had many years of not being understood and being avoided by others. Themes emerge in apparently unintelligible speech during regular sessions, and tape-recording can help. Once themes have been identified, the patient is helped to focus on them in a structured way before moving on to problem-solving, reframing or reality-testing where appropriate. If able, the person may get some control over his or her speech by writing the thoughts down.

Negative symptoms

Careful assessment of negative symptoms is required, because they are likely to co-exist with other problems, such as side-effects of medication, depression or institutionalisation. The pace of the interview needs to be slow, to give the patient time to respond. Clear, simple, open questions will promote the development of the therapeutic relationship, and writing down key points can help the patient to recall the sessions. Modification of the environment has been shown to be very effective for patients with negative symptoms (Wing & Brown, 1970). Other simple techniques include activity-scheduling, rating mastery and pleasure, and social skills training (Hogg, 1996).

Early warning signs

Many individuals can identify their own idiosyncratic, prodromal signs of relapse. It is useful to map the exacerbation of symptoms and correlate these with potential personal and environmental stressors that may precipitate deterioration. Birchwood *et al* (1989) used early warning sign questionnaires with patients and staff. Patients can often link feeling worse, or being more concerned about their psychotic symptoms, with environmental factors.

Dealing with hopelessness

Clozapine-resistant patients generally have long psychiatric histories. They have received many psychotropic drugs and often have lost faith in medication. Clozapine may be described as the last chance of obtaining relief from psychotic symptoms, and the patient may have high expectations. If clozapine fails to 'live up to expectations', a sense of hopelessness may be generated. Therefore, it is particularly important to deal with such feelings in patients, families and carers, as well as with the negative impact on the person's self-esteem.

Compliance therapy

Kemp *et al* (1998) conducted one of the few randomised controlled trials of compliance therapy for patients with mental health problems. Although the intervention was complex, it led to improvements in insight, attitude to medication and compliance. However, there was little effect on functioning. Important components include: conceptualising the problem, focusing on symptoms and side-effects, exploring benefits and drawbacks of treatment, exploring ambivalence, highlighting discrepancies between actions and beliefs, focusing on adaptive behaviours, encouraging self-efficacy, and emphasising the value of staying well and the importance of treatment.

Working with families

Family interventions are effective in reducing the likelihood of relapse in psychosis. Early work examined the association

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between high expressed emotion among caregivers and poor clinical outcome following discharge (Vaughn & Leff, 1976). Manualised approaches to family work are now available (Barrowclough & Tarrier, 1992). Key features of such interventions include education, enhancing problem-solving and coping strategies and an emphasis on communication styles between family members.

Families are likely to have had lengthy contact with services that may not all have been positive. They may have received unclear or conflicting information in the past and may require a period to 'offload' their concerns. Regular family sessions to improve communication between professionals and families may, in itself, prove an effective way of reducing the stress and burden felt by families.

DISCUSSION

One of the biggest problems in managing treatment-resistant patients is therapeutic nihilism, and this is likely to increase after an unsuccessful trial of clozapine monotherapy. Although, by definition, patients must be 'treatment-resistant' to be eligible for clozapine, treatment encompasses many therapeutic strategies that can be successful within this group, and therefore we suggest the term 'neuroleptic-resistant'. Clozapine should not be viewed as a last ditch attempt; it is a stepping stone to further treatments.

The treatments proposed require a staff group with skills, time and appropriate organisational structures to support such complicated care packages. The choice of treatment should be applied on an individual basis. It should be implemented following an in-depth assessment, as part of a multi-disciplinary care plan, and the effects of the interventions should be monitored objectively. Although various treatment strategies exist and may be used in this group, few firm conclusions can be drawn from the current literature. Many of the strategies suggested in the literature take the form of case reports and open studies. Few randomised controlled trials exist, and in the climate of evidence-based practice there is still much research to be done. However, there are encouraging results from the use of psychological therapies with patients with a diagnosis of schizophrenia and there is considerable scope for adapting these therapies in patients who are resistant to clozapine monotherapy, justifying a more positive approach.

DECLARATION OF INTEREST

None.

REFERENCES

Barrowclough, C. & Tarrier, N. (1992) *Families of Schizophrenic Patients: Cognitive Behavioural Interventions.* London: Chapman & Hall.

Bhatia, S. C., Bhatia, S. K. & Gupta, S. (1998) Concurrent administration of clozapine and ECT: a successful therapeutic strategy for a patient with treatment-resistant schizophrenia. *Journal of Electroconvulsive Therapy*, **14**, 280–283.

Birchwood, M., Smith, J., MacMillan, F., *et al* (1989) Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers. *Psychological Medicine*, **19**, 649–656.

Bonator, R., Sirota, P. & Megged, S. (1996) Neuroleptic-resistance schizophrenia treated with clozapine and ECT. *Convulsive Therapy*, **12**, 117–121.

Buchanan, R. W., Kirkpatrick, B., Bryant, N., *et al* (1996) Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. *American Journal of Psychiatry*, **153**, 1625–1627.

Centorrino, F., Baldessarini, R. J., Kando, J., *et al* (1994) Serum concentrations of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *American Journal of Psychiatry*, **151**, 123–125.

Chadwick, P., Birchwood, M. & Trower, P. (1996) *Cognitive Therapy for Delusions, Voices and Paranoia*. Chichester: John Wiley & Sons.

Chakos, M., Liberman, J., Hoffman, E., *et al* (2001) Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomised trials. *American Journal of Psychiatry*, **158**, 518–526.

Dickerson, F. B. (2000) Cognitive behavioural psychotherapy for schizophrenia: a review of recent empirical studies. *Schizophrenia Research*, **43**, 71–90.

Dossenbach, M. R. K., Beuzen, J. N., Avnon, M., *et al* (2000) The effectiveness of olanzapine in treatment-refractory schizophrenia when patients are non-responsive to or unable to tolerate clozapine. *Clinical Therapeutics*, **22**, 1021–1034.

Dursan, S. M., McIntosh, D. & Milliken, H. (1999) Clozapine plus lamotrigine in treatment resistant schizophrenia (letter). *Archives of General Psychiatry*, **56**, 950.

Finnema, E. J., Willem, J., Sloof, C. J., *et al* (1996) Expressed emotion on long stay wards. *Journal of Advanced Nursing*, **24**, 473–478.

Friedman, J., Ault, K. & Powchik, P. (1997) Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. *Biological Psychiatry*, **42**, 522–523.

Gamble, C. (1995) The Thorn Nursing Initiative. *Nursing Standard*, **9**, 31–34.

Garety, P., Fowler, D., Kuipers, E., *et al* (1997) London–East Anglia randomised controlled trial of cognitive–behavioural therapy for psychosis. II: Predictors of outcome. *British Journal of Psychiatry*, **171**, 420–426.

Gupta, S., Sonnenberg, S. J. & Frank, B. (1998) Olanzapine augmentation of clozapine. *Annals of Clinical Psychiatry*, **10**, 113–115.

Herzog, T. (1998) Nurses, patients and relatives: a study of family patterns on psychiatric wards. In *Family Intervention in Schizophrenia: Experiences and Orientation in Europe* (eds C. L. Cazzullo & G. Invernizzi). Milan: ARS.

Hogg, L. (1996) Psychological treatments for negative symptoms. In *Cognitive Behavioural Interventions with Psychotic Disorders* (eds G. Haddock & P. D. Slade), pp. 151–167. London: Routledge.

James, D. V. & Gray, N. S. (1999) Elective combined electroconvulsive and clozapine therapy. *International Clinical Psychopharmacology*, **14**, 69–72.

Kales, H. C., Dequardo, J. R. & Tandon, R. (1999) Combined electroconvulsive therapy and clozapine in treatment resistant schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **23**, 547–556.

Kando, J. C., Tohen, M., Castillo, J., *et al* (1994) Concurrent use of clozapine and valproate in affective and psychotic disorders. *Journal of Clinical Psychiatry*, **55**, 255–257.

Kemp, R., Kirov, G., Everitt, B., *et al* (1998) Randomised controlled trial of compliance therapy. 18-month follow-up. *British Journal of Psychiatry*, **172**, 413–419.

Kingdon, D. & Turkington, D. (1998) Cognitive behaviour therapy of schizophrenia. In *Outcome and Innovation in Psychological Treatment of Schizophrenia* (eds T. Wykes, N. Tarrier & S. Lewis), pp. 59–79. New York: John Wiley & Sons.

Koponen, H. J., Leinonen, E. & Lepola, U. (1996) Fluvoxamine increases the clozapine serum levels significantly. *European Neuropsychopharmacology*, **6**, 69–71.

Kuipers, E., Garety, P., Fowler, D., *et al* (1997) London–East Anglia randomised controlled trial of cognitive–behavioural therapy for psychosis. I: Effects of the treatment phase. *British Journal of Psychiatry*, **171**, 319–327.

—, Fowler, D., Garety, P., *et al* (1998) London–East Anglia randomised controlled trial of cognitive–behavioural therapy for psychosis. III: Follow-up of economic evaluation at 18 months. *British Journal of Psychiatry*, **173**, 61–68.

Lancashire, S., Haddock, G., Tarnier, V., *et al* (1997) Effects of training in psychosocial interventions for community psychiatric nurses. *Psychiatric Services*, **48**, 39–41.

Markowitz, J. S., Gill, H. S., Lavia, M., *et al* (1996) Fluvoxamine–clozapine dose-dependent interaction. *Canadian Journal of Psychiatry*, **160** (suppl. 17), 22–29.

Morera, A. L., Barreiro, P. & Cano-Munoz, J. L. (1999) Risperidone and clozapine combination for the treatment of refractory schizophrenia. *Acta Psychiatrica Scandinavica*, **99**, 305–307.

Mowerman, S. & Siris, S. G. (1996) Adjunctive loxapine in a clozapine-resistant cohort of schizophrenic patients. *Annals of Clinical Psychiatry*, **8**, 193–197.

Novartis Pharmaceuticals UK Ltd (1998) *Clozaril™ (clozapine) Summary of Product Characteristics.* Camberley: Novartis Pharmaceuticals UK.

Pinto, A., La Pia, S., Mennella, R., *et al* (1999) Cognitive–behavioural therapy and clozapine for clients

https://doi.org/10.1192/bjp.181.3.184 Published online by Cambridge University Press

with treatment-refractory schizophrenia. *Psychiatric Services*, **50**, 901–904.

Raskin, S., Katz, G., Zislin, Z., *et al* (2000) Clozapine and risperidone combination/augmentation treatment of refractory schizophrenia: a preliminary observation. *Acta Psychiatrica Scandinavica*, **101**, 334–336.

Sainsbury Centre for Mental Health & Mental Health Act Commission (1997) *The National Visit*. London: Sainsbury Centre.

Sensky, T., Turkington, D., Kingdon, D., *et al* (2000) A randomised controlled trial of cognitive–behavioural therapy for persistent symptoms in schizophrenia resistant to medication. *Archives of General Psychiatry*, **57**, 165–172.

Shiloh, R., Zemishlany, Z., Aizenberg, D., *et al* (1997) Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *British Journal of Psychiatry*, **171**, 569–573.

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Tuunainen, A., Wahlbeck, K. & Gilbody, S. M. (2001) Newer atypical antipsychotic medication versus clozapine for schizophrenia. *Cochrane Library*, issue 3. Oxford: Update Software.

Vaughn, C. E. & Leff, J. P. (1976) The influence of family and social factors on the course of psychiatric illness. A comparison of schizophrenic and depressed neurotic patients. *British Journal of Psychiatry*, **129**, 125–137.

Wahlbeck, K., Cheine, M., Tuisku, K., *et al* (2000) Risperidone versus clozapine in treatment-resistant schizophrenia: a randomised pilot study. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **24**, 911–922.

Weiss, E. L., Longhurst, J. G., Bowers, M. B., Jr., *et al* (1999) Olanzapine for treatment-refractory psychosis in patients responsive to, but intolerant of, clozapine. *Journal of Clinical Psychopharmacology*, **19**, 378–380.

Wing, J. K. & Brown, G. W. (1970) *Institutionalism and Schizophrenia*. Cambridge: Cambridge University Press.

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