ADVANCES IN THE TREATMENT OF SCHIZOPHRENIA

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SUMMARY We review advances in the treatment of schizophrenia. We begin with an overview of antipsychotic drug development, focusing on the in vitro and in vivo binding profiles of clozapine and a new generation of D2:5HT antagonists. We then consider the main barriers to effective treatment: non-compliance (and side-effects) of medication, recurrent relapse, 'treatment resistance', negative symptoms and neurocognitive deficits. Within this framework, we review the mechanisms of action and clinical uses of the 'atypical' antipsychotic drugs. We also show how a variety of psychosocial interventions, particularly those that incorporate cognitive techniques, can be used in combination with pharmacotherapy to overcome the same clinical hurdles. (*Br J Clin Pract* 1996; **50(6):** 315-323.)

Schizophrenia is at once a biological disease, a neuropsychogical disorder and a dysfunction of social interactions. Consequently it presents therapists with a series of clinical hurdles. First, we must control the 'positive' psychotic symptoms — the delusions, hallucinations, and thought-disorder — that cut the schizophrenic patient off from reality and can lead to inappropriate or dangerous behaviour. Second, we must ensure that the patient complies with long-term prophylactic treatment in order to reduce the risk of relapse. Third, we must overcome the amotivation, asociality and other 'negative symptoms', that further alienate the schizophrenic patient from society. Finally, we must tackle the neuropsychological deficits that impair his ability to manipulate his environment. In this review, we begin with an overview of antipsychotic drug development. We then consider each of these clinical problems in turn and, within this framework, review the recent advances in pharmacological and psychosocial treatments, thus showing how even a disorder as pervasive and complex as schizophrenia can now be managed effectively.

Antipsychotic drug development

The modern era for the treatment of schizophrenia began in 1952 with the introduction of chlorpromazine.[1] The discovery that psychotic symptoms could be alleviated pharmacologically revolutionalised the clinical management of schizophrenia. Numerous antipsychotic drugs were subsequently introduced, the most popular including haloperidol, thioridazine and trifluperazine. These ranged widely in their basic chemistry, but had one feature in common — all blocked dopamine (DA) receptors.[2] Furthermore, their clinical potencies were directly proportional to the degree to which they blocked the D2 receptor in vitro.[3] These findings supported the idea that schizophrenia resulted from an overactivity of DA in the mesolimbic system, [4] but this 'dopamine hypothesis' had one glaring defect: clozapine.

Clozapine: beyond the dopamine hypothesis

Clozapine was introduced into clinical trials in the 1970s. Although it is at least as effective as other antipsychotics, in vitro studies show that its binding profile is quite different: notably, its affinity for the D2 site is relatively low.[5] Clozapine was withdrawn because of the high incidence of potentially fatal agranulocytosis with which it was associated.[6-7] However, evidence that it was not only free of neurological side-effects, but could alleviate symptoms in schizophrenics resistant to treatment by other antipsychotics,[8-9] permitted its reintroduction almost two decades later, for a selected group of patients, on the unprecedented condition of a haematological monitoring service. Clozapine's unique clinical profile has stimulated an enormous amount of research into its pharmacological properties, and has led to the development of a new generation of antipsychotic drugs.

This research has been spurred on by two major advances. One is the discovery of the tremendous heterogeneity within the dopamine system: there are two main classes of DA receptor,[14] of which five subtypes have been cloned,[10-13] and there appears to be further heterogeneity within these subtypes.[14] Second, functional neuroimaging technology has allowed us to look directly at the receptor occupancy of drugs in the brain in vivo.[15]

The receptor-binding profile of clozapine differs from conventional antipsychotic drugs both within and outside the DA system. Within the DA system, most antipsychotic drugs at therapeutic doses occupy at least 60% of D2 receptors in the striatum.[16] In contrast, the average occupation of D2 by clozapine is only 20%.[17-19] Furthermore, in vitro, clozapine's affinity for the D4 receptor is approximately 10 times greater than that for the D2 receptor and it has also been shown to bind to the D1, D3 and D5 receptors.[14]

However, the most significant impact of clozapine has been a recognition of its activity at a broad range of

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receptors outside the DA system. Of particular interest is its high affinity to serotonin (5HT) receptors, including the 5HT2,[5] 5HT3,[20] and the recently discovered 5HT6 and 5HT7 receptor subtypes.[21] The possibility that clozapine's novel effects might be explained by the ratio of 5HT2:D2 antagonism[5] has led to the development of a new group of drugs: the 5HT2:D2 antagonists.

A new generation of antipsychotics: the 5HT2:D2 antagonists

The first of these new drugs to be introduced was risperidone, which has a higher affinity for the D2 receptor than clozapine and an even higher affinity for the 5HT2 receptor.[22-23] Like clozapine, it also has high affinity for α_1 and α_2 receptors, although it has little or no D1 or muscarinic activity.[22-23]

Four other 5HT2:D2 antagonists are now in phase III (efficacy) trials and will probably be marketed within the next three years: olanzapine (Lilly)[24] and seroquel (Zeneca)[25] can be thought of as 'clozapine-like', with a low D2 affinity and higher 5HT2 affinity, while sertindole (Lundbeck)[26] and ziprasidone (Pfizer)[27] are 'risperidone-like' with a higher D2 affinity and an even higher 5HT2 affinity.

Olanzapine evolved from a research programme designed specifically to find an analogue of clozapine with comparable pharmacological properties but without its propensity to induce agranluocytoisis. Like clozapine, it shows relatively high muscarinic and histaminergic blockade. It also binds strongly to α_1 receptors, although not to α_2 receptors. It shows a high affinity for 5HT2a receptors, but a relatively low D2 affinity (less than that of haloperidol but greater than that of clozapine).[24] Functional imaging studies confirm its low striatal D2 receptor binding in vivo.[28] In vitro, seroquel has a very low affinity for D2 receptors with greater binding to 5HT2 receptors. It has a low affinity for the α_1 and α_2 sites and virtually no affinity for the muscarinic binding site.[29]

In vitro, sertindole binds strongly to D2, 5HT2a and α_1 adrenergic receptors.[30] However, in vivo animal studies suggest that sertindole's dopamine antagonism is relatively weak and that its action on central 5HT2a receptors is potent and long-lasting.[31] Ziprasidone has the highest 5HT2/D2 ratio.[31] It binds strongly to 5HT2a and several other 5HT receptors (5HT1A, 5HT1D, 5HT2C) and has a high affinity for the dopamine D2, D3, D4 and D1 receptors and α_1 adrenergic receptors.[27] It has moderate affinity for H1 receptors and very little affinity for the α_2 and muscarinic receptors.[27]

Future directions in drug development

The departure from the dopamine hypothesis has widened the doors for very different strategies in the development of antipsychotic drugs. Two other receptors in particular have generated interest. Firstly, the opioid sigma receptor: several antipsychotic drugs, including remoxipride (a selective D2 antagonist[32]), bind strongly to the sigma receptor, and it has been suggested that this interaction partially accounts for their clinical efficacy.[33] The distribution of sigma receptors overlaps the distribution of D2 receptors,[34] and it could be that binding at the sigma site somehow modulates activity at DA receptors. The second receptor of interest is the N-methyl-D-aspartate (NMDA) glutamate receptor. This is a ligand-gated ion channel composed of receptor sites for glutamate, glycine, polyamines and a cation-selective channel in which a phencyclidine (PCP) receptor is located.[35] PCP is known to induce positive and negative symptoms very like those seen in schizophrenia,[36] and it has been suggested that a glutaminergic deficiency may be important in its pathogenesis.[37] Direct stimulation of the NMDA receptor itself is not possible because of the possibility of neuronal damage resulting from excess calcium entry. However, it may eventually be possible to develop partial glutamate agonists without neuronal-damaging effects.

Non-compliance with medication

Improving compliance by improving the drug: overcoming side-effects

In most studies, intolerance of side-effects emerges as a major reason for non-compliance with medication.[38-42] Many of these (eg the autonomic, cardiovascular and sedative side-effects) result from the blockade of receptors other than DA and have been partially overcome by a class of relatively 'pure' and selective D2 antagonists, the substituted benzamides (for example, sulpiride and amisulpiride). However, the main advance over the past few years has been the development of drugs relatively free from extrapyramidal side-effects (EPS). EPS range from pseudoparkinsonism to potentially irreversible dyskinesias and can be both functionally disabling and socially stigmatising.[43] They are thought to result directly from D2 blockade in the striato-nigral system and have traditionally been considered a necessary concomitant to antipsychotic activity.[44] Indeed, the term 'neuroleptic' (slowing of the nerves) was coined as a synonym for antipsychotic drugs.[45] It was clozapine's position as an 'atypical drug' — an antipsychotic drug that produced no EPS — that forced a re-evaluation of this assumption.

The anatomical and physiological basis for clozapine's atypical profile remains unknown. The evidence from a variety of experimental approaches — biochemical,[46-47] animal behavioural,[48-49] and electrophysiological[50-52] — is mixed. However, it is generally agreed that the end result is a decrease in DA activity in the limbic system, leaving DA activity in the striatum relatively intact. This also appears to be true of some of the new antipsychotic drugs (seroquel,[25] olanzapine,[5f3] and sertindole[54]), which all show selectivity for limbic rather than motor dopaminergic pathways. In principle, there are two ways in which this could arise. The first is through differential binding within the DA system: DA receptor subtypes vary in distribution across different brain regions and, in theory, binding to some subtypes, but not others, could account for such anatomical selectivity.[55] In vivo studies show a clear association between D2-receptor blockade and the incidence of EPS,[56-57] but not clinical response.[19,58-59] It may be that the combination of low D2 activity with higher D1, D3, D4 or D5 binding could in itself lead to an antipsychotic effect without EPS. However, two findings refute this. First, risperidone and remoxipride, which have few EPS, both show high striatal D2 occupancy in vivo.[60] Second, a discriminant function analysis of 10 typical and

seven putative 'atypical' antipsychotic drugs shows that the two classes of drug cannot be distinguished on the basis of in vitro D2 binding alone.[5]

The most direct test of the theory that an atypical profile arises purely from differential binding within the DA system would be the development of highly selective antagonists at DA receptor subtypes. Candidates are the D3 receptor,[61] known to be highly concentrated in the limbic system,[11] the D4 receptor, blocked at precisely the clozapine concentrations found in the spinal fluid of clozapine-treated patients,[13] the D5 receptor,[12] and the D1 receptor,[10] which co-localises with the D2 receptor[62] and could modulate its activity synergistically or antagonistically via post-transductional mechanisms.[63] Many such 'superselective' dopamine antagonists are in the early stages of development, but whether or not this strategy in drug development will prove fruitful remains to be seen.

The second way in which anatomical selectivity might arise is through action at another receptor system interacting with the dopamine system. It has been suggested that the muscarinic cholinergic receptor[64] and α_1 adrenergic receptor[65] might be involved in protecting from EPS. However, most attention has focused on the 5HT system. Serotonergic terminals make direct synaptic contact with DA cells in the substantia nigra and ventral tegmental areas, and 5HT2 neurotransmission can modulate dopamine firing and release.[66] Furthermore, selective 5HT2 antagonists can ameliorate or counteract some of the EPS associated with D2 antagonism[67] and typical and atypical antipsychotic drugs can be distinguished by their D2:5HT2 binding ratio.[5] Of the new 5HT2:D2 antagonists, most is known about risperidone. Several clinical trials show that risperidone leads to fewer EPS than typical neuroleptics, especially at doses of less than 8mg.[68-69] Preclinical animal behavioural studies of olanzapine,[24] seroquel,[25] sertindole,[26] and ziprasidone,[27] all suggested that these drugs would lead to few EPS in patients, and this has been confirmed by the early clinical data: olanzapine leads to few EPS and minimal elevation of prolactin,[70] while seroquel[25] and sertindole[71] have EPS profiles similar to that of placebo.

Psychological methods to increase compliance

Side-effects are not the only reason why patients refuse medication. Treatment compliance is a complex process involving a number of inter-related cultural, symptom-related and psychological factors.[38,72-73] The extent of non-compliance with medication is huge, with rates estimated to be at least 50%.[72] Traditionally, the problem has been tackled by focusing on the drugs themselves (as described above), or by educating[74-75] or manipulating the behaviour[76] of the patient. However, both these approaches are one-sided. They assume that the clinician always knows best and the patient is left with virtually no part in clinical decision-making. Little attempt is made to understand or change the fundamental attitudes of patients towards treatment, and the relationship between doctor and patient is largely ignored. Yet attitudes to treatment[77] and insight into illness[78-79] are among the most powerful predictors of compliance; for many patients, the need for personal autonomy in decision-making about treatment is paramount.[38] In other areas of medicine, compliance is increased when patients are given the opportunity to discuss their expectations, concerns and beliefs.[80] Similarly, there is growing evidence that, by acknowledging the importance of the schizophrenic patient's subjective viewpoint as rational and worthy of consideration,[81] adherence to medication can be increased. It is also possible to change attitudes to drug treatments and insight into illness.[82] Many of these principles are encompassed by the technique of motivational interviewing; this has been applied in a number of medical settings[83] and has recently been adapted and used successfully as a 'compliance therapy' for acutely psychotic inpatients.[82]

Prevention of relapse

Maintenance medication

Compliance with medication is necessary not only to reduce symptoms but also to prevent future relapse. It has long been known that patients who receive antipsychotic treatment experience fewer relapses than non-medicated controls.[84-85] Long-term prophylactic medication is often prescribed in depot form in which the active compound, suspended in an oily base, is injected intramuscularly at intervals of one to four weeks. Compared with oral medication, depots have many advantages,[86-87] including the reduction of covert non-compliance. However, over the last 10 years there has been a gradual realisation that the maintenance doses routinely prescribed are too high.[88-89] Trials have shown that lower doses lead to the same rates of relapse as higher dose regimes, with fewer side-effects and better compliance.[90] Another source of debate has been the optimal prescribing strategy. Some have advocated an intermittent or targeted treatment regime, in which the patient is drug-free most of the time and receives medication only at times of stress or at the first signs of relapse.[91] It seems, however, that continuous regimes are in fact preferable, and lead to fewer relapses.[92-93]

There is no doubt that pharmacological intervention at the first signs of decompensation is more effective than treating the full-blown relapse alone.[93] It may be possible to combine the two approaches by lowering the dose still further and increasing it temporarily at the first warning signs of relapse.[94] This highlights the importance of symptom monitoring and early intervention.[95] There have been several attempts at characterising early prodromal symptoms: a variety of 'neurotic' (eg dysphoria and anxiety) and low-level psychotic features have been described.[96-98] The early recognition of such symptoms, not only by the carer,[98] but by the patient,[99] provides a valuable opportunity to thwart a full-blown relapse.

Family intervention

The psychosocial treatment that has generated the most interest and research in relapse prevention is family intervention. This approach was borne out of the classic papers of the 1970s that showed a relationship between hostility and the over-involvement of relatives or carers (high EE, or 'expressed emotion') and relapse.[100] A large number of prospective outcome studies across different countries and cultures have established that high EE in a relative is associated with a higher risk of relapse in the schizo-

phrenic patient over the 9–12 months after hospital discharge.[101-102]

EE is a way of quantifying aspects of family life, and describes both the content and quality of carers' attitudes towards the patient. It is essentially an empirical measure — little is known about the mechanisms by which it leads to decompensation.[103] In the area of family intervention, this atheoretical position has been an advantage, in that it has allowed the development of diverse, flexible and non-judgmental strategies. We have moved away from the concept that schizophrenia is caused by pathological family interactions[104] and the successful family interventions differ from classic family therapy by taking a more 'here and now', problem-oriented approach. They share a number of components, including communication training, goal-setting and cognitive-behavioural self-management techniques;[105] they can reduce the rate of relapse[105] for up to eight years.[106] Many also have an educational component, although this alone is inadequate.[107]

'Treatment resistance'

The pharmacological approach

Even when patients do comply with long-term neuroleptic treatment, large numbers continue to experience delusions or intractable auditory hallucinations.[108] Several adjuvant treatments have been tried,[109] particularly mood stabilisers (lithium[110] and carbemazapine[111]), which may be particularly beneficial in patients with affective symptoms, and benzodiazepines,[112-114] which may be useful in patients with anxiety or agitation. However, clozapine is the only single antipsychotic that has been shown to be more effective than any other. Its position was established in a multicentre double-blind trial by Kane et al,[8-9] in which the criteria for 'treatment resistance' were rigourously defined: subjects were only eligible if they had failed to respond to at least two other antipsychotic drugs, had had no period of good functioning within the previous five years and were experiencing at least two positive psychotic symptoms at the start of the trial. Improvement on clozapine was demonstrated in one-third of these patients.[8-9]

As noted earlier, clozapine's superior efficacy may be due to differential binding at specific DA receptor subtypes, or it could result from its direct action at 5HT receptors. It is hoped that drugs which share clozapine's receptor-binding profile will also share its superior efficacy. Double-blind trials comparing risperidone with clozapine have shown no significant clinical differences between the two drugs.[115-116] Early clinical trials of olanzapine,[117] seroquel,[25,118] and sertindole[71,117] suggest that these drugs all improve positive symptoms. However, their role in patients who are resistant to conventional antipsychotic drugs has still to be evaluated. In the meantime, can we offer this group of patients an alternative?

Cognitive therapy for positive symptoms

Other than offering a supportive role, the psychologist has traditionally taken a back seat in the management of schizophrenic symptoms. Psychoanalytic approaches are thought to be no more effective than supportive psychotherapy[119] and, apart from a trickle of case studies and small group studies, the behavioural approach has been largely ignored. A major advance over the past few years has been the introduction of cognitive behavioural techniques into the treatment of patients with positive symptoms.[120]

Cognitive therapy seeks to modify patients' beliefs and attitudes. It has been widely applied in the treatment of non-psychotic disorders such as depression and anxiety.[121] In the past few years, it has become increasingly apparent that similar strategies can been used in the treatment of delusions.[122-125] Over a series of sessions, the therapist works with the patient to pinpoint underlying beliefs, identify their nature, question the evidence for and against them and design experiments to test out the reality of this evidence.[124-125] Some of these methods have been incorporated into comprehensive and systematic treatment 'packages' which capitalise on the coping strategies already used by most patients.[126]

Several authors have described specific symptoms in terms of distinct cognitive processes.[127] For example, auditory hallucinations can be conceptualised in terms of an 'inner voice' which is misattributed to an external focus.[128-129] These theoretical models have recently been applied to devising therapies for patients. Thus, hallucinators can be educated about the nature of their experiences and trained to reattribute their voices from external to internal sources.[130] In addition, recent findings suggest that patients feel threatened not only as a result of experiencing auditory hallucinations, but because of the beliefs they hold about their voices' identity, ominipotence and purpose.[131] Cognitive methods can be used to challenge such beliefs and in this way treat hallucinations as well as delusions.[131]

The results of these early studies are very encouraging. There are now several controlled trials in progress in the UK and it is likely that the next few years will see the adoption of such techniques, particularly in the management of those patients who are 'resistant' to treatment with medication.[123]

Towards True Recovery

So far we have used the term 'treatment resistance' to describe both the small subgroup of patients selected to enter Kane's pivotal clozapine trial[8-9] and, even more specifically, to refer to patients who continue to have positive symptoms despite vigorous treatment with antipsychotic medication. Suppose, however, we could keep the schizophrenic patient out of hospital, ameliorate all positive symptoms without disabling side-effects, and prevent relapses. How would he function in the community? Would he get a job, make friends and cope with everyday living skills? Probably not. There remain two interrelated barriers to overall effective functioning: negative symptoms and neuropsychological deficits.

Negative symptoms, such as affective flattening, avolition, apathy and anhedonia, isolate the schizophrenic patient from the rest of society. Although some of these features may be secondary to EPS, depression or positive symptoms,[132] there remain primary negative symptoms, the so-called 'deficit syndrome',[133] which have long been considered the core of schizophrenia.[134-135] Neuropsychological deficits also impede the schizophrenic patient's

ability to interact with his environment.[136] Again, some of these deficits are considered central to schizophrenia, manifesting well before the onset of symptoms[137] and persisting between relapses.[138]

Overcoming negative symptoms

There has been considerable interest in the development of drugs which target negative symptoms.[139] Several antipsychotics are claimed to be particularly effective in this respect, including amisulpiride,[140-141] clozapine,[142-144] risperidone,[144-145] olanzapine,[117] seroquel[25] and sertindole.[71,117] The mechanisms by which they improve negative symptoms are unknown. Nevertheless, there has been much speculation that, while positive symptoms arise from too much dopaminergic activity in the mesolimbic system, the deficit syndrome results from too little dopaminergic activity in the mesocortical system.[146] It has been proposed that amisulpiride, which in animals potentiates DA activity at low doses and blocks transmission at higher doses,[147] improves negative symptoms by enhancing dopamine release.[140] Similarly, clozapine, risperidone and other 5HT2:D2 blockers may ameliorate negative symptoms by enhancing the release of DA in the mesocortical system, either through selective binding to DA receptor subtypes, or through antagonism at 5HT2 receptors.[148] Indeed, the administration of 5HT2 antagonists has been shown to reduce negative symptoms in some patients.[149]

Despite these clinical findings and plausible theoretical explanations, there has been some scepticism. It could be that these drugs have no effect on 'core' negative symptoms but rather lead to the amelioration of 'secondary' negative symptoms by controlling positive symptoms and depression without causing EPS.[132] Such an argument has recently been put forward in the case of clozapine,[150] and there is clearly a need for more carefully controlled clinical trials designed specifically to address the issue.[151]

In the meantime, training programmes designed to tackle the lack of social skills, central to the deficit syndrome, are becoming increasingly popular. A number of early studies showed that interpersonal communication and self-care could be improved through a variety of behavioural psychological methods including role play, modelling and positive reinforcement.[152, 166] Skills acquired during social skills training can be maintained for long periods[153] and there is some evidence that these skills can generalise to improving every-day social interactions.[154] More recently, such training programmes have emphasised cognitive strategies for evaluating and coping with difficult social situations ('social problem solving'[155-156]) — patients are trained to follow through a series of steps including problem identification, goal definition, generation and evaluation of alternative solutions, and selection of the most effective solution.[157]

Overcoming neurocognitive deficits

While pharmacotherapy and social skills training may help overcome negative symptoms, some argue that the schizophrenic patient cannot be truly integrated into the community until his neuropsychological deficits are remedied. Schizophrenics perform poorly on various neuropsychological tasks ranging from the elementary perceptual[158] to complex planning and 'set-changing' tasks of executive function.[159] These are thought to underlie the development of positive and negative symptoms as well as the impairment in psychosocial functioning. Some improvement in cognitive function can be achieved pharmacologically: several groups have shown that clozapine can improve performance on a variety of neuropsychological tasks.[160-162] However, it may be possible to achieve a more selective effect by targeting specific cognitive deficits and remedying them using cognitive-behavioural techniques.[163] There is some precedent for such an approach in the rehabilitation of brain-damaged patients with strokes and head injuries.[164] One of the most effective techniques here has been 'substitution transfer'. This provides the patient with an alternative strategy of achieving the same goal, so that the intact part of the brain takes over the functions of the damaged region.[165] For example, complex problems can be broken down into manageable steps, as in the 'social problem solving' described above.[155,157] Alternatively, the schizophrenic patient's external environment can be altered to compensate for cognitive deficits, eg placing needed objects and prompt cards within visual reach, increasing the salience of cues such as labels and colours, and using checklists.[167]

These techniques may be particularly relevant to schizophrenia where there are significant impairments in overall planning and complex behavioural sequencing.[159] Several psychological tasks which tap into these deficits of 'executive function' have been described but there have been relatively few studies which seek to improve performance on such tasks. One exception is the Wisconsin Card Sorting Test (WCST), a test of problem solving and abstract reasoning performed poorly by schizophrenic patients.[168] It has been shown that it is possible to improve patients' performance on this task.[169-170]

Our next question is whether any of these new treatments, pharmacological or psychological, lead to an improvement in psychosocial outcome? Several studies show that clozapine can lead to an improvement in a variety of psychosocial outcome measures.[171-173] However, whether an improved performance in neuropsychological tests will generalise to improving social and occupational functioning is not yet known.[174]

Community care

We have described a number of new pharmacological and psychosocial innovations which, in order to be put into practice, require an efficient and co-ordinated care system. There have been several attempts to describe the components of such an ideal system. It is generally agreed that unless it incorporates structured planning, adequate information systems, day activities, residential services and access to care during crises,[175-176] the most vulnerable patients (the chronically ill and most socially deprived) will fall through the cracks. This seems to have been the case for many patients who, after discharge from hospital, are left on the streets,[177] lost to the system only to be readmitted to an acute psychiatric bed through the 'revolving door'. Mental health services in Great Britain are further fragmented by the distinction between health care, which is an NHS responsibility, and social care, which falls under the domain of social services.[178-179]

In an effort to overcome these problems, the Government has advocated a 'case management' (subsequently renamed 'care management' for cosmetic reasons) approach. Here a single individual, the case manager, plays a central position in the patient's care in the community.[180-181] The most vulnerable patients — those at risk of suicide, violence or severe self-neglect — are targeted and registered on a special supervision register.[182] The case manager's role is seen in various ways: some models emphasise the co-ordination and organisation of services,[183] while others focus on his personal relationship with the client.[184]

More recently, it has been recognised that the case manager should be supported by a specialised multidisciplinary 'continuing care team' which would not only have a clear system for co-ordinating care, but would interact clinically with the client.[185-186] Several studies show that case management in this context can have some impact on patients' use, satisfaction and engagement with services.[187]

Conclusion

How can we bring together this information and summarise the advances in the management of schizophrenia? Are there any unifying principles or lessons to be learnt for the future? Recent developments have taught us that we cannot accept dogma: we are continually forced to re-evaluate traditional models. This applies both to the development of new drugs as well as to new psychosocial interventions. While it was once taught that schizophrenia resulted from hyperdopaminergic activity in the mesolimbic system and that all antipsychotic drugs acted by blocking D2 receptors, we can no longer accept this as the whole story. Inspired by the unique clinical and pharmacological profile of clozapine, the development of new antipsychotic drugs proceeds along many fronts, both within and outside the dopaminergic system.

A second assumption has been that the schizophrenic patients' fundamental beliefs, attitudes and neurocognitive deficits can only be shifted through pharmacological means. However, we are beginning to use cognitive methods to treat delusions, which by definition are 'unshakeable and not amenable to logic'. Indeed, the last few years have seen the incorporation of cognitive techniques into almost every psychosocial intervention, including social skills training, compliance therapy, family interventions and rehabilitation programs, perhaps reflecting our growing understanding of schizophrenia from a neurocognitive perspective. Although the particular methods and techniques differ from therapy to therapy, they share the same basic principle: to bridge the gap between the pathophysiology of the disease and its clinical manifestations.

Psychosocial treatments are not alternatives to medication: the two are intimately related. So far we have considered them separately, but theoretically, their effects may be additive or even synergistic.[188] A number of groups have looked into the combined effects of medication in association with family intervention, behaviour therapy and social skills training on relapse[153,189-190] and confirmed that the interactions are complex, depending both on the exact dose of medication and the psychosocial intervention employed.

We believe that the introduction of a new generation of antipsychotic drugs will bring tangible improvements in the quality of life of our patients. We also hope that the psychosocial interventions described will move out of the research setting and into the wider community. These steps are not easy to put into practice. It is difficult to change prescribing habits and there is as yet no atypical antipsychotic drug available in depot form. Psychosocial interventions may be successful when carried out by highly skilled and dedicated researchers, but not in a busy, under-resourced community service setting. The widespread application of these new innovations requires two further steps: an ongoing education and training structure for the therapist and, more importantly, a care system which is strong enough to ensure continuity of care, yet flexible enough to incorporate new innovations as they emerge.

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