Foreword

Dear colleague,

The past few years have seen exponential growth in the psychopharmacology of schizophrenia. Rapid expansion in the number of therapeutic agents available to the practicing psychiatrist, coupled with developments in technologies such as molecular genetics and brain imaging, have heralded a new era in the etiology and treatment of schizophrenia.

These advances have been accompanied by a huge growth in the amount of related literature — more than 2000 articles have been published over the last 12 months. Clearly, this makes it almost impossible for busy clinicians to keep up-to-date with the literature.

The *Journal of Advances in Schizophrenia and Brain Research* is the answer. The journal provides psychiatrists with an overview of the recent literature, along with in-depth reviews of areas relevant to clinical psychiatry. The journal will endeavor to bring important issues to the attention of psychiatrists while ensuring that the research literature is interpreted in a clinically meaningful way.

We hope that you will find the *Journal of Advances in Schizophrenia and Brain Research* stimulating and informative, and welcome your comments and suggestions.

Tonmoy Sharma
Senior Editor

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LEADING ARTICLE

Community Care for Patients with Schizophrenia — a UK Perspective

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This article gives an overview of current community treatment used in the maintenance phase of schizophrenia. It emphasizes the importance of engagement, maintenance medication and social care as the mainstay of such treatment. It also discusses some more specific interventions, such as compliance therapy, and psychosocial interventions, such as family work, cognitive behavior therapy and social skills training, and considers their importance in the prevention of relapse. The merits of Community Mental Health Teams versus more specialized Assertive Community Treatment Teams are also discussed. Current issues, including cognitive aspects of schizophrenia, early intervention in psychosis, and the current controversies surrounding assertive outreach are described. Finally, the future of community care for schizophrenia is examined.

In the 1960s, most people with severe mental health problems received long-term care in large mental hospitals. Since the introduction of de-institutionalization, more emphasis has been placed on caring for them in the community and few patients now receive long-term inpatient care (Fig. 1).

Early in the 20th century, following the daily observation of chronic inpatients, schizophrenia was thought to have a fixed, progressive, deteriorating course and a principally endogenous genetic cause. Ciompi [1] challenged this general prognostic pessimism with his systematic follow-up studies of the evolution of mental illnesses, initiated in the 1960s. His review suggested a more positive picture with only 14–24% of schizophrenia patients suffering from severe chronicity and 24–29% from intermediate residual symptoms. A total of 53–57% had a favorable outcome, with 24–33% having only minor residual symptoms and 20–29% having a complete recovery. He described an enormous heterogeneity, rather than uniformity, and challenged the correlation between genetic loading and outcome, describing a variety of outcomes for schizophrenia, and great difficulty in accurately predicting the long-term outcome in any particular case. He also described a complex interplay between biological and psychosocial factors, with psychosocial factors playing a major role in determining both course and outcome.

Harding et al. [2] also challenged the earlier pessimism with a review of the long-term outcome of subjects who retrospectively met the diagnostic criteria for schizophrenia. They found an evolution into productivity and competent functioning in one-half to two-thirds of cases, rather than the 'increasing residual impairment between episodes' that had been predicted. Hence, it appeared that not only was the prognosis for schizophrenia more positive than had been previously thought, but that the course of schizophrenia had remained remarkably unchanged over time.

Birchwood et al. [3] described a 'vulnerability–interaction' model for schizophrenia, with a vicious circle of stress, relapse and adverse social effects leading to further stress and relapse. This interaction of biological and psychosocial factors produces a heterogenous disorder with multiple phases and a varied course and outcome. Psychosocial interventions aimed at reducing stress, such as improving coping skills and reducing conflict, alter the course of the illness.

Three distinct phases of illness can be identified and each is best suited by different management:

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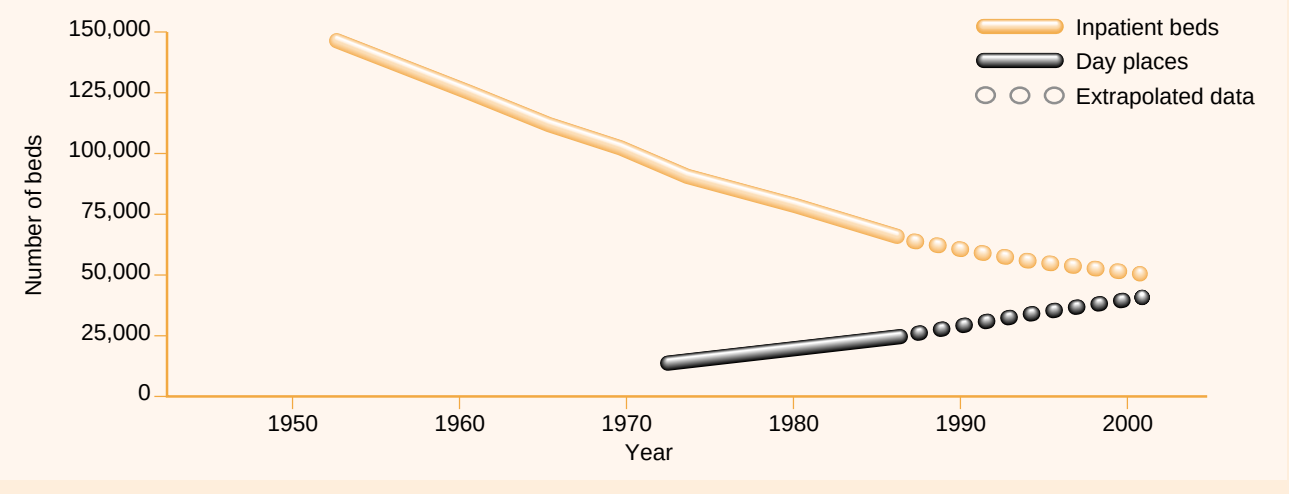
Figure 1. Reduction in psychiatric hospital beds.



- phase 1, the acute phase — characterized by florid positive psychotic symptoms, with hallucinations, delusions and high levels of both agitation and arousal. Inpatient care is often required because of the nature of the symptoms
- phase 2, the maintenance phase — a mixture of positive and negative symptoms are present, but characteristically the level of arousal is reduced. The patient is usually cared for in the community by a mixture of outpatient care and community nursing, with emphasis on the reduction of social stressors and medication
- phase 3, the recovered phase — characterized by a decline in positive symptoms and the presence of some negative symptoms. Patients require only limited maintenance treatment, the majority of which can be, and is, offered in primary care settings by General Practitioners (GPs).

For the purpose of this article, the authors examine the community treatment of schizophrenia concentrating on phase 2, the maintenance phase of care. As indicated, the patient usually resides in the community at this stage, although periods of hospitalization may be required during times of relapse. The main focus of treatment is:

- the supervision and monitoring of mental state
- maintenance medication
- social care, including occupational activities, help with accommodation and finances, and family and carer support.

Specific psychosocial interventions can be added to these specific areas.

Contributions of primary care to community treatment

GPs are the only healthcare professionals involved with many schizophrenia patients [4]. In the 1960s, Murray Parkes et al. [5] followed-up schizophrenia patients who had been returned to their relatives or lodgings after a period of time in a mental hospital. They found that a greater number of patients received more care from their GP than from their psychiatrist within the following year. The main responsibility for day-to-day care of the discharged schizophrenia patient rested with the GP, who initiated treatment when the patient relapsed and was expected to cope with crises at home.

In 1991, Melzer et al. [6] reported that 1 year after hospital discharge of patients with schizophrenia into the community, over half of the patients still had psychotic mental states. Whilst most patients remained in contact with either their GP or psychiatrist, they received little help with any practical issues, such as housing or day care, and were experiencing 'revolving door' patterns of short, but frequent, hospital admissions. Around the same time, Kendrick et al. [7] investigated the number of long-term mentally ill patients on the lists of GPs in the southwest Thames region of the UK and the willingness of GPs to take responsibility for them. They found an uneven distribution of long-term mentally ill patients, with large numbers localized in Greater London and within 3 miles of large mental hospitals. Most GPs were receptive to a care plan shared with psychiatrists.

Importance of maintenance medication

Maintenance medication is the mainstay of treatment for schizophrenia. A working party of the Section for Social and Community Psychiatry from the Royal College of Psychiatrists, London, UK, chaired by Hirsch, produced a report entitled 'Psychiatric beds and resources; factors influencing bed use and service planning' [8]. This emphasized the importance of maintenance medication in the treatment of schizophrenia, claiming it to be associated with a reduction in relapse rate and, therefore, a cost-effective way of utilizing resources for the mentally ill.

Jolley et al. [9] evaluated the benefits of prescribing intermittent medication at the first signs of relapse, as soon as 'prodromal symptoms' had been noticed. They found that the group on intermittent medication suffered more frequent and prolonged relapses than the group on continuous prophylaxis, although lower scores for extrapyramidal side effects were recorded in the intermittent treatment group. Little adverse effect on psychosocial functioning was found in the continuous group, hence confirming the need for continuous medication in the majority of patients.

The typical antipsychotics, such as chlorpromazine, haloperidol and thioridazine, cause drowsiness and have a high incidence of extrapyramidal side effects, although they suppress symptoms without these side effects in many patients. The availability of some typical antipsychotics as depot medication helps improve compliance because of the regular, but infrequent, observed dosage. However, this treatment is often not popular with patients because of the side effects and the necessary injections. It is imperative that the minimum required dosage be prescribed, to reduce side effects, improve tolerance and improve compliance. The study on compliance by Corrigan et al. [10] cited side effects of medication and complex treatment regimes as major barriers to treatment adherence.

The recent introduction of atypical antipsychotics, such as olanzapine, quetiapine and risperidone, associated with fewer side effects, has improved compliance in those previously intolerant to conventional antipsychotics. They have, however, made the monitoring of compliance more difficult since they are only available in oral form. In some cases, where the risks of non-compliance with oral medication outweigh the benefits of the atypical antipsychotics, it may be pertinent to continue depot medication.

Clozapine, the prototype atypical antipsychotic, is now widely used in treatment-resistant schizophrenia. Two prospective, double-blind, randomized, controlled trials have shown clozapine to be superior to the typical antipsychotics in the treatment of schizophrenia [11,12]. However, the risk of neutropenia and agranulocytosis requires blood monitoring, which again affects compliance. Despite the relatively high cost, clozapine may be a cost-effective treatment for resistant schizophrenia; although there are increased demands on community resources, these are outweighed by the large savings associated with reduced hospitalization.

The effect of antipsychotic medication on cognitive dysfunction

Cognitive dysfunction is a recognized symptom of schizophrenia, and has been identified as an important measure of outcome in the treatment of the disorder. In addition, antipsychotic drug treatment of schizophrenia may be complicated by side effects of widespread dopamine antagonism, including exacerbation of negative and cognitive symptoms due to frontal cortical hypodopaminergia. As previously described, antipsychotic medication is effective in reducing the positive symptoms of schizophrenia. However, it typically fails to associate with improvements in cognitive functioning, and this can result in a failure of the patient to fully recover to their previous level of functioning and reintegrate into society. Sharma et al. [13] argue that a shift in practice towards treatments that aim to improve cognitive function, rather than focusing on a reduction of positive symptomatology, is necessary. Clozapine treatment has been shown to provide a significantly greater improvement in several aspects of cognitive function, including attention and verbal fluency, as compared with typical antipsychotics, and risperidone appears to have a beneficial effect on working memory.

Compliance

Since medication only works if it is taken, compliance is a difficult and important issue in community patients. There are many reasons for non-compliance, including denial of illness, apathy and forgetfulness, which can manifest either as refusal to maintain contact with healthcare professionals or refusal to take medication. Corrigan et al. [10] cited side effects, the complexity of medication regimens, poor understanding of the role of medication by patients, the poor relationship between patients and clinicians, and aspects of the service system, such as long waiting times in clinics, as reasons for non-adherence to treatment regimens. The study by Hoge et al. [14] demonstrated that 35% of those who refused medication cited side effects as their reason, while doctors thought side effects were important in only 7% of cases. As mentioned, depot medication has the advantage of improving compliance as it removes the daily risk of non-compliance through ambivalence or forgetfulness. It also removes any debate over compliance because a non-compliant patient has to refuse the injection, and hence inform staff and carers that he/she is not taking medication. This is not the case with oral medication, since a prescription can be accepted but disposed of elsewhere without the knowledge of staff or carers. The observable side effects of the typical antipsychotics make monitoring of compliance possible, but the lower side-effect profile of the atypical antipsychotics makes compliance more difficult to assess. The fact that the superior atypical medications are available only in oral form is a distinct disadvantage in community care. Some teams who work intensively with patients can offer daily medication, but this is time consuming. Relatives and carers can also supervise medication and monitor compliance, but this can increase the burden on them.

Kemp et al. [15] recognized that compliance with antipsychotic medication is an important determinant of outcome in schizophrenia, and that non-compliance is a major preventable cause of psychiatric morbidity. They described compliance as strongly linked to attitudes to treatment, insight, culture, treatment response and side effects. Their study found that a simple brief intervention using compliance therapy lead to improved compliance, as compared with non-specific counseling, and that this was sustainable over time. Compliance therapy is a cognitive–behavioral approach borrowed from motivational interviewing, a technique which is used in a number of medical settings and aims to help people change their behavior while avoiding confrontation and stalemate. In compliance therapy, the approach is brief and pragmatic, providing a more active therapeutic stance, guided problem solving and an increased educational component.

Social care

There are various aspects to social care, which are described in detail below.

Accommodation

Ensuring adequate accommodation is an important element of community care. There are various options, including staffed or unstaffed hostels, group homes, bedsits and flats, depending on the level of support required. Supporting patients through liaison with staff, carers and neighbors plays an important role in preventing eviction followed by transient accommodation, such as bed and breakfast, or homelessness. It is difficult to make contact with patients who are homeless or in unsupported environments and living in transient accommodation. This results in decreased contact, inability to monitor mental state and, frequently, non-compliance with medication followed by subsequent decline and relapse.

Occupation

Ensuring adequate daytime activity is an essential part of community treatment and helps improve skills, quality of life and self-esteem. It also reduces stress in both patients and carers, therefore improving the overall community tenure of patients. Each patient has different needs and requirements for activities, ranging from day hospitals to day centres, sheltered work, voluntary work and paid employment. With support and encouragement, patients can work upwards through the system towards paid employment, something that is frequently reported as important by patients. Lehman et al. [16], in their study on chronically ill patients, cited that unemployment was a significant area of dissatisfaction and reduced the quality of life. Offering support, education and advice to employers can help ensure that employment continues successfully.

Family and carer support

The role of family and carers in the community management of patients who suffer from schizophrenia cannot be overestimated. With support and education, carers can offer an alternative to inpatient care. They play an important role in monitoring mental state and alerting professionals to signs of deterioration, as well as supervising and administering medication. Since a significant number of carers suffer stress and depression, it is important that they are supported and not overloaded. The availability of day care and respite care, and professionals to provide advice and back-up when required, all helps to support carers. If the carer-patient relationship is overstretched and breaks down, the patient may spiral into transient accommodation, lack of contact and relapse.

Finances

Patients with schizophrenia often suffer financial hardship due to unemployment, and their inability to comprehend and navigate the benefit system. Ensuring adequate income for patients, by assisting with benefit claims and offering help with budgeting skills, is an important part of community care [17].

Psychosocial interventions

Following the biological–psychosocial model for the evolution of schizophrenia described by Ciompi [1], and the recognized impact of environmental factors and external stressors, psychosocial interventions have been accepted as effective treatments for schizophrenia [17]. Psychosocial interventions can be directed towards difficulties commonly shared with other chronic illnesses, such as compliance therapy [15] and family therapy [18,19], or towards areas specific to schizophrenia, e.g. cognitive therapy for delusions [20].

Family interventions

Brown et al. [18] showed that the relapse rate in young men who had just recovered from a first episode of schizophrenia was much higher if they returned to live with a relative who was prone to make critical comments. The ill effects of this 'expressed emotion' were confirmed by Leff et al. [19] who described that behavioral family management reduced expressed emotion in high expressed emotion families, resulting in a subsequent reduction in relapse rate. Several studies have confirmed the effectiveness of family treatment in reducing relapse rate. Hogarty et al. [21] observed a significant and persistent effect of family intervention on forestalling relapse by using family therapy to control

stimuli from the family environment believed capable of provoking further episodes in vulnerable patients.

Cognitive behavior therapy

Chadwick and Birchwood [21] proposed a cognitive approach for understanding and treating drug-resistant auditory hallucinations. Their study demonstrated that patients hold abnormal beliefs about their voices and that these beliefs are responsible for their emotional and behavioral responses to them. They described the application of the 'cognitive model of depression' devised by Beck et al. [23] to these voices, developing a cognitive behavior therapy strategy of 'collaborative empiricism' [22]. They aimed to reduce the distress caused by hallucinations rather than the frequency of them, disputing treatment-resistant delusional beliefs by 'hypothetical contradiction' and 'verbal challenge', and 'empirically testing' the beliefs. Their study demonstrated an unexpected reduction in hallucinations.

Social skills training

The study by Hogarty et al. [21] compared social skills training with family therapy and drug maintenance therapy. Social skills training aimed to reduce conflict, and hence indirectly control stimuli that were believed capable of provoking a new episode of illness among vulnerable patients. Their model included social perception training within both family and extrafamilial relationships, placing emphasis on strategies to avoid and reduce conflict with problem solving and requests for negotiation. Following this intervention, there was a significant reduction in relapse rate, although the effect was lost towards the end of the second year of follow-up. Social skills training is now losing popularity as a psychosocial intervention.

Other treatment strategies

Nelson et al. [24] described modifying auditory input, for instance with a portable cassette player, earplugs or subvocal counting, as a strategy for decreasing the severity of auditory hallucinations. Chadwick and Lowe [20] described 'belief modification' as a treatment for delusions, encouraging patients to view their beliefs as a reaction to experiences. In therapy, the patient examined a delusional belief and the arguments for and against it, with a view to altering the belief. Problem solving is a general approach used to help patients manage personal issues and improve coping skills by identifying problems and targeting specific problems with identified solutions [25].

Community Mental Health Teams versus Assertive Community Treatment Teams

There is a current debate about whether community patients in the maintenance phase of schizophrenia should be cared for by specialist teams with particular skills in dealing with psychotic relapsing patients or by standard Community Mental Health Teams (CMHTs). An example of a specialist team is the Assertive Community Treatment (ACT) Team which was developed in Madison, WI, USA as an intensive program of community care, providing a full range of services within one team and, hence, reducing the need for other community resources (Table 1) [26]. The team (Fig. 2), which contains essential disciplines such as nursing, social work, occupational therapy and psychiatry, delivers the care at the patient's door utilizing the '*in vivo*' approach and assertive follow-up (reluctance to take no for an answer). This model demonstrated impressive reductions in hospitalization and was subsequently replicated by Hoult [27] in Sydney, Australia. However, Mueser et al. [28] demonstrated that the differences in favor of ACT have steadily declined in the USA, and in Europe few studies have found case management or ACT to make a significant difference to hospitalization [29]. There is debate as to whether this is because ACT is not properly applied in Europe [30] or whether control services in Europe already contain many elements of ACT [28].

One negative aspect of treating sufferers of schizophrenia within specialist teams is that treatment can become depersonalized and more routine. Many patients are adequately cared for by CMHTs, who have the skills and resources to care for all but the most severely ill, unstable 'revolving door' patients. It is therefore pertinent to target ACT at the group of

Table 1. Components of assertive community treatment.

- Assertive follow-up
- *In vivo* approach
- Increased contact frequency
- Emphasis on engagement
- Small caseloads
- Offer psychosocial interventions

Figure 2. The Assertive Community Treatment Team.

patients who may otherwise be unmanageable in the community by virtue of complications such as substance misuse.

An international perspective on community care for patients with schizophrenia

The model of community care described is emulated to a greater or lesser degree in most of Europe. In Italy, for example, the move to community care has paralleled that in UK, with the closure of psychiatric hospitals and the establishment of Community Mental Health Centers (CMHCs) [31]. Significantly, the sites of previous hospitals have been re-utilized as CMHCs and for other public services, e.g. schools, as well as for flats for the previous long-stay population. Similar changes have also been observed in Denmark, with the implementation and expansion of district psychiatric services, a reduction in hospital beds and an expansion of both outpatient services in the immediate environment and social services in terms of housing and care [32]. In the US, there has been a move towards community treatment for schizophrenia since the early 1950s, with a shortening of hospital stay and substitution of day hospital treatment, the use of halfway houses for transitional living and the establishment of Community Psychosocial Rehabilitation Centres [26].

Special problems

Mobility

Schizophrenia patients are a mobile group prone to transient accommodation and are therefore difficult to maintain contact with. Relapse of illness and the behavioral manifestations of psychosis can precipitate difficulties with accommodation, making the patient most difficult to contact when most ill. For this reason, it is important to ensure secure and stable accommodation as a vital part of community treatment.

Dual diagnosis

Many patients with schizophrenia also abuse illicit drugs and alcohol, complicating their illness, treatment and community care, and significantly increasing dangerousness and psychiatric morbidity. Patients with dual diagnosis frequently 'fall between two stools' and do not receive the care that they need. It is important that problems with drugs and alcohol are recognized and treated, either by the CMHT/ACT Team or by referral to a specialist community drug and alcohol team, with an emphasis on joint working, communication and liaison between teams. Teague et al. [33] evaluated a model integrating key features of ACT with substance abuse treatment. They found this to be successful and claimed that, because of the high prevalence of substance abuse and comorbid mental illness criteria for substance abuse, treatment should be considered for more general incorporation into the ACT model.

Current issues

The controversies surrounding Assertive Outreach in the UK

In the 1980s, concerns were expressed about 'Care in the Community' following several high profile cases of homicide by people with mental health problems, e.g. the murder of Jonathon Zito by Christopher Clunis. The government responded by prioritizing mental health, with the advent of the National Service Framework [34], which prioritizes the establishment of Assertive Outreach Teams. Since this time there has been a surge of new Assertive Outreach Teams around the country, working to various models. Many prefer the ACT approach, which prioritizes the team approach as an essential component. However there is much disagreement over which components of the original model are essential, with continuing debate about what constitutes a 'team approach', a 'reduced case load size', or the necessity for 24-h care.

The UK700 group published their randomized control trial of Intensive Case Management (ICM) (one case manager per 10–15 patients) versus Standard case mangement (SCM) (one case manager per 30–35 patients) [35]. This study failed to demonstrate a difference in outcome between the two groups, causing further confusion. Critics of this study argue that it lacked program fidelity to the original ACT model, not using the full team approach or having small enough caseload size. It has also been proposed that the control group (SCM) would qualify as an ACT Team using Teague's measure of program fidelity [36], and that this is why no difference in outcome was found between treatment arms.

Early detection and intervention of schizophrenia

The processes that make schizophrenia a lifelong disorder may be most active and do the most damage early in the course of the disorder [37]. As previously described, all current treatments for schizophrenia improve the course of the disorder, but they do not cure the disorder or alter the persons lifelong vulnerability to developing psychotic symptoms in the face of sufficient stress.

Recent studies of first episode psychosis document that the average time between onset of psychosis and first effective treatment is often one year or more. A current line of theory postulates that active psychosis may be neurobiologically toxic, either accelerating or adding to the primary deficit neurobiological processes that lead initially to onset [38]. Recent studies of first episode schizophrenia have found significant inverse correlations between the duration of untreated

psychosis and better outcome. There is much work to be done into the development of early detection systems for schizophrenia, and evaluating the long-term benefits of reducing the duration of untreated psychosis with early intervention.

Cognitive function and brain pathology

Virtually all aspects of cognitive function have been reported to show impairment in some patients with schizophrenia, although executive functions [39], memory functions [40] and various aspects of attention have been described as especially prone to impairment [41]. Weinberger et al. [42] examined cerebral blood flow in patients at rest and during performance of the Wisconsin Card Sorting Test, a prototypal frontal/executive task. The schizophrenia patients performed more poorly than the controls, and this was mirrored by significantly smaller increases in blood flow to the prefrontal cortex. However, this finding has not been consistently replicated, and McKenna [41] found that over 50% of a sample of acute and chronic schizophrenia patients showed normal executive functioning depending on the task used.

A critical review of the structural and functional cerebral abnormalities found in schizophrenia concluded that any brain pathology is subtle rather than gross [43]. It suggests that schizophrenia is characterized by complex alterations in the normal reciprocal patterns of activation between anatomically related areas of the cerebral cortex, rather than by simple focal reductions in regional brain activity. Easily the most consistently replicated abnormality in schizophrenia is lateral ventricular enlargement, although it does not appear to be associated with any aspect of the clinical picture and emerges more as a trait marker for schizophrenia. Crow et al. [44] found that lateral ventricular enlargement in schizophrenia was largely restricted to the temporal horns, in contrast to that seen in Alzheimer's disease, which was more generalized.

Goldberg et al. [45] studied learning and memory in monozygotic twins discordant for schizophrenia, and demonstrated that the affected group performed significantly worse than the discordant group on various tasks, including story recall, paired association learning and verbal fluency. The fact that the twin paradigm had controlled for genome, family environment and socioeconomic circumstance led them to conclude that the intercession of the disease had produced the cognitive deficits in this sample.

Patients with chronic schizophrenia tend to have more marked cognitive impairments than acute cases [46] and it appears that in the minority of cases there is a progressive decline in cognitive impairment. However, the majority of evidence suggests that there is no progressive deterioration in cognitive function in most patients with schizophrenia over time [47].

Balance of care and liberty

Caring for patients who suffer from schizophrenia in the community requires the maintenance of a constant balance between the human rights and liberty of the patient on one hand and the safety of the patient and the public on the other. The current UK Mental Health Act gives us little opportunity to compulsorily treat patients in the community, other than following a period of enforced inpatient treatment. This has the unfortunate consequence of requiring the admission of patients with the sole purpose of compulsorily reinitiating treatment, without any other reason for the restriction of liberty.

Future of community care in the UK for schizophrenia

The effectiveness of care in the community has been the subject of great debate. Indeed, due to some high-profile murder cases, it has been claimed by the media to have failed despite research findings from the US to the contrary [48]. A recent prospective 5-year follow-up study based in London, UK dispelled some of these myths, providing 'robust evidence that community care has worked well for the former patients of psychiatric hospitals' [49].

The UK government's current modernization fund for mental health services [50] is committed to improving care in the community for schizophrenia patients. It has prioritized the establishment of Assertive Outreach Teams to work more intensively with patients to further reduce risk, categorizing patients with comorbid substance abuse as a high-risk group. A proposed revision of the UK Mental Health Act was sent out for consultation in late 1999 [51]. Controversially, it proposes a community treatment order, and is the source of much current debate. Proponents of the order argue that, if introduced, it would have an enormous effect on community treatment and care, making it more tenable and further reducing risk and the need for hospitalization. Conversely, opponents argue that it would constitute a further erosion to the civil liberties of the mentally ill [52]. Either way, the improvement of community care for people with schizophrenia is set to remain high on the current agenda.

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Prediction and Intervention in the Pre-Psychotic Phase

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The psychotic prodrome is an important illness phase that has until recently only been accessible retrospectively. At the Personal Assessment and Crisis Evaluation (PACE) clinic, our research has suggested that it is possible to identify young people at ultra-high risk of developing psychosis and to monitor them both prior to and during the onset of psychosis. We suggest that 'at risk mental state' is a more appropriate term for the prospective study of this illness phase. Through research at our clinic we have developed clinical criteria for identifying this ultra-high-risk group, with a 'close-in' strategy that reduces the amount of time required for follow-up before the transition to psychosis. In our largest published study to date the transition rate was reported to be 41%. This suggests that our criteria detect those at risk of psychosis, which allows future development of treatment that may delay or prevent psychosis, as well as reducing the duration of untreated psychosis. This could have long-term health benefits for both individuals and the community, and could reduce the overall impact of such illnesses in vulnerable young people. This unique patient group also allows the study of risk factors for illnesses such as schizophrenia, without the confounding effect of medication and acute symptomatology that is a constant problem in chronic and first-episode patient groups.

The mental healthcare focus on prevention and intervention has made the psychotic prodrome increasingly important. The conceptualization of this illness phase has changed with the development of strategies that make its study possible — it has become a prospective rather than a retrospective term. At the Personal Assessment and Crisis Evaluation (PACE) clinic we have been refining methods for identifying individuals who are at ultra-high risk of developing psychosis. Our clinical criteria utilize a 'close-in' strategy, which maximizes the transition rate to psychosis. Clients can be in one of three groups:

- those with attenuated symptoms
- those with transient psychotic symptoms that spontaneously remit
- those with state or trait risk factors such as family history.

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During the 6 years since the clinic was established these criteria have been refined and tested so that we have a transition rate of 41% within a 12-month period. Now we are extending our focus, utilizing our selection criteria to investigate biological and psychological risk factors for psychotic illness. This paper discusses the evolution of the concepts and strategies we have used at PACE for studying young people at ultra-high risk of developing psychosis, and concludes with the application of these methods to investigate risk factors for psychosis.

The concept of prodrome versus 'at risk mental state'

The term prodrome has been used in the majority of studies that have focused on the period directly preceding the onset of psychosis where a change in mental state is first recognized. This term is largely retrospective in nature, as it has been traditionally applied only after acute psychosis has developed [1]. As a result, studies that have investigated the prodromal period have also been of a retrospective nature and may have been affected by recall bias and 'effort after meaning' [2]. Prodrome has also been used to refer to

the period immediately preceding relapse of acute psychosis in individuals with an already established illness. Due to the retrospective nature of this concept, and the potential confusion in the use of this term, we suggest the use of 'relapse prodrome' to describe the period before psychotic relapse, and the use of 'at risk mental state' as a more appropriate term for prospective psychosis prediction [2].

There are a number of reasons for the use of 'at risk mental state'. This term takes into account that not all the clients who come to the PACE clinic will make the transition to psychosis. Rather than taking the view that the prodrome is the earliest form of psychosis, and is therefore inevitable, the new term recognizes this mental state as conferring a heightened vulnerability to developing psychosis [2]. The distinction between these views is important because the former takes for granted that transition to psychosis will occur, whereas the latter recognizes that being 'at risk' results from a number of reasons, including family history and stress, and may be avoided through a change in circumstance or via clinical intervention and/or treatment [3,4]. The use of 'at risk mental state' is also conceptually different to the notion of schizotaxia [5]. It is not confined to being an unexpressed genetic predisposition because, in our model, risk factors do not require a family history of psychosis.

The implication of using 'at risk mental state' is that vulnerable individuals can now be studied prospectively, and the changes in psychopathology and biological variables that coincide with the transition to psychosis can be monitored [3,4]. It also enables a 'close-in' strategy to be used [1]. This involves combining risk factors to enhance the number of true positive cases; thereby reducing the follow-up period required to observe transition [2].

A number of ethical issues have been raised in relation to the prospective study of 'at risk' individuals. The first is the perceived danger of including false positives in the PACE clinic and related research program [2]. While some individuals appear to have similar characteristics to clients who go on to develop acute psychosis, they may not make the transition. It was originally thought that these individuals would be unnecessarily exposed to stigma, and the medical labeling of their presenting problems. However, experience with our client group has shown that many are aware of their risk of developing a psychotic illness and would like to discuss it, particularly if another family member is unwell. Provided that information is given in a sensitive manner, discussion of risk can be positive and health promoting [3]. The potential benefits of this strategy outweigh the risks, and may contribute to a reduction in the duration of untreated psychosis, a better outcome and lower relapse rates in people who develop an illness. In others it may delay transition and reduce the disability associated with their presenting symptoms.

Clinical criteria for detecting 'at risk mental states'

In a series of studies, our center has developed and refined criteria that make it possible to identify young people at ultra-high risk of developing psychosis. These criteria have been actively used in the PACE clinic since 1994, and were originally applied to individuals aged between 16 and 30 years — a time that corresponds to the period of maximum risk. More recently we have changed this age range to individuals between 14 and 30 years of age [1]. Our criteria for identifying 'at risk mental states' have evolved with experience. We currently accept people into our clinic if they belong to one of three groups:

- an attenuated symptom group
- a brief limited intermittent psychotic symptom group
- a state or trait risk factor group, i.e. clients that have a decrease in functioning and a first degree family member with a psychotic illness [1].

Inclusion and exclusion criteria for these groups are based on the Brief Psychiatric Rating Scale (BPRS) [6] and the Global Assessment of Functioning (GAF) rating scale [7].

Group 1 consists of people experiencing attenuated symptoms. These symptoms may include ideas of reference and magical thinking (BPRS rating 2–3 on unusual thought content), perceptual disturbances (BPRS rating 1–2 on hallucinations), paranoid ideation (BPRS rating 1–3 for suspiciousness), or odd speech (BPRS rating 1–3 on conceptual disorganization) [1,8]. These symptoms need to be held with a reasonable amount of conviction, and occur several times per week during the past year, but for no longer than 5 years [8,9].

Group 2 consists of people that have experienced Brief Limited Intermittent Psychotic Symptoms (BLIPS). These may include ideas of reference, magical thinking, perceptual disturbance, paranoid ideation and odd speech, but will exceed the rating threshold used in the attenuated group [1,8,9]. Therefore, the severity of symptoms would also exceed the threshold for psychosis. However, the duration of the 'BLIP' has to be less than one week, and the symptoms need to have spontaneously resolved. The BLIP is required to have happened within the 5 years before referral to the PACE clinic [8,9].

Group 3 consists of people with trait and state risk factors. These people have a first degree relative with a psychotic disorder, including diagnoses of schizophrenia, schizoaffective disorder or bipolar

disorder, in a parent or sibling [1,8,9]. In addition, they need to have experienced a marked reduction in functioning of 30 points or more on the GAF from premorbid level, within the last year [8,9].

Subjects are excluded from the PACE clinic if they have an intellectual disability, a known organic disorder, poor English skills, a history of acute psychosis or treatment with neuroleptics [8,9].

Clients are considered to have made the transition to psychosis according to BPRS scores [6]. Clients need to have one of the following:

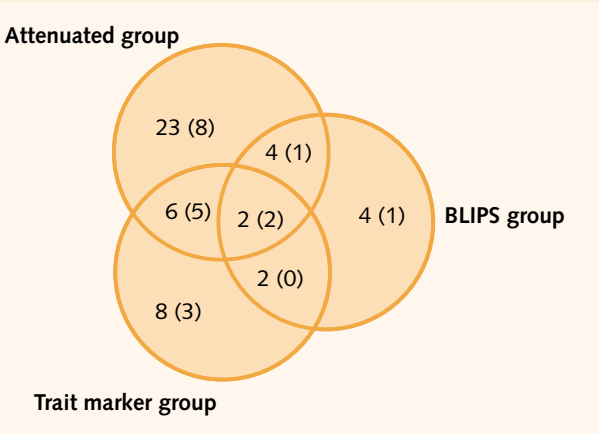
- a BPRS score of 3 or more on the hallucination item
- a score of 4 or more on the unusual thought content item
- a score of 4 or more on the formal thought disorder item.

These symptoms need to occur several times per week, with the change of mental state persisting for more than 1 week [8,9].

In our largest study to date, 49 subjects were followed-up monthly for a 12-month period, 41% of these young people made the transition to psychosis within this time period [8,9]. Many of these clients developed psychosis within the first few months after referral to our service. The people who participated were referred to the clinic over a 16-month period. In total we received 119 referrals from a variety of services including school and university counselors, general practitioners, council youth programs and our own first-episode psychosis triage team [1]. Out of these referrals, 73 were seen for an initial interview, and 49 met our criteria. The remaining referrals were either deemed unsuitable by telephone screening, or failed to attend their appointment. Distribution of these 49 young people with an 'at risk mental state' across the three inclusion groups is shown in Fig. 1. The results of this study suggest that it is possible to identify 'at risk mental states' using our clinical criteria, and highlight the importance of raising community awareness of our service to facilitate referrals.

We have since revised our inclusion and exclusion criteria so that it is no longer reliant on BPRS ratings. Instead, we have implemented new criteria based on the Comprehensive Assessment of At Risk Mental States (CAARMS), an instrument that we have been developing in the clinic over a number of years, with the specific purpose of monitoring 'at risk mental states'. The new symptom threshold for psychosis requires the presence of bizarre (thought broadcasting) or non-bizarre (paranoia) beliefs that are held with delusional conviction, or hallucinations that the subject believes are true and very distressing, or lack of coherence or speech with loose associations. The minimum frequency of these symptoms is either at least three times per week for a minimum of 1 h, or more frequently for a shorter duration. The symptoms need to be present for more than 1 week.

Figure 1. Number of patients in each intake group, according to our criteria. The number of patients who made the transition to psychosis is indicated in brackets.



BLIPS: Brief Limited Intermittent Psychotic Symptoms.

Current and future research directions within PACE

Having established criteria that we know reliably identify young people at ultra-high risk of developing psychosis, with a good transition rate, we have begun to develop a research focus on psychological and biological risk factors for psychosis [3], as well as preventative treatments. In light of the heterogeneity of schizophrenia and other psychoses it is unlikely that one factor alone predisposes a person to develop this illness. Instead, a number of factors combine to increase a person's vulnerability threshold. Much of the research in illnesses such as schizophrenia to date has been confounded by the effect of neuroleptic medication. Therefore, the PACE sample of young people at ultra-high risk of psychosis presents us with a unique opportunity to investigate biological and psychological risk factors without the influence of medication, and without the presence of acute psychosis. In this way we can study the biological changes associated with the transition to psychosis and/or the abnormalities in various systems that may have been present prior to illness onset. We can also investigate whether early use of preventative treatments may delay or prevent the transition to psychosis.

The ultimate goal of establishing a clinic such as PACE is not only to develop reliable ways of identifying at risk young people, but also to use this information to develop preventative strategies to reduce the development of disorders such as schizophrenia. In the period between 1996 and 1999 we conducted a

randomized controlled trial that combined cognitive behavioral therapy and neuroleptic treatment, with supportive therapy. Out of a total of 60 patients that agreed to randomization, 35.7% (10/28) of the supportive case management group made the transition to psychosis within the 6 months of treatment, whereas only 12.5% (4/32) of patients in the cognitive therapy and risperidone group became psychotic [10]. The difference in the transition rate between these two groups was significant. Although not finalized, data from a 12-month follow-up suggests that more of the patients in the cognitive therapy and risperidone group have become psychotic after treatment ceased. This may indicate that a longer treatment period is necessary [11].

We are currently commencing another randomized trial at PACE that is double-blinded. Patients that consent to participate will receive a combination of treatments, both antipsychotic and therapy based. As with the previous study, it is hypothesized that preventative treatment will reduce the rate of transition in young people at ultra-high risk of developing psychosis. In this way we hope to determine treatments that may be suitable for this group, whether they be therapy based or biological through medication [11]. Given the 41% transition rate found in one of our previous studies, we hypothesize that these treatments will decrease the transition rate to psychosis.

Our preliminary findings concerning biological and psychological risk factors for psychosis have suggested that our ultra-high-risk group have significantly larger left hippocampi compared with controls [9]. There was no significant difference on the right side. A Cox regression analysis showed that greater left hippocampal volume in this group was predictive of transition. These findings suggest that hippocampal volume reduction may occur during the transition from high risk to first-episode psychosis because previous magnetic resonance imaging studies have reported hippocampal reduction in chronic and first-episode psychosis patients [9,12]. Other variables that we have studied include neurocognitive testing and developmental risk factors, such as prenatal complications. These were not found to be associated with onset of psychosis. However, maternal age of more than 30 years and cannabis dependence were associated with an increased risk of transition [11]. As a whole, these tests have not shown a high specificity or sensitivity for psychosis (Table 1).

We are currently investigating the role of stress on transition to psychosis. This study measures diurnal hypothalamic-pituitary-adrenal axis function, and employs a more intensive combined dexamethasone and corticotrophin releasing factor test. These measures have been obtained at intake to the clinic, for a period of 12 months, or until the transition to psychosis is made, whereupon the initial tests are repeated. A general psychopathology interview is performed to compliment these measures. MRI scans at intake and then at 12 months, or at transition, complete the study. This gives a comprehensive assessment of how stress may be involved in the onset of psychosis. A pilot version of this study will be complete at the end of 2000, with a larger scale study commencing in 2001 and continuing for 3 years.

Table 1. Predictors of psychosis in the PACE sample.

Duration of symptoms >900 days
GAF score <51
BPRS total score >15
BPRS psychotic subscale score >2
SANS attention score >1
HRSD score >18
Normal left hippocampal volume
Cannabis dependence
Maternal age >30 years

BPRS: Brief Psychiatric Rating Scale; GAF: Global Assessment of Functioning; HRSD: Hamilton Rating Scale for Depression; PACE: Personal Assessment and Crisis Evaluation; SANS: Scale for Assessment of Negative Symptoms.

In addition to the studies reported thus far, we are investigating other indices such as neurological soft signs, neurocognitive tests, and a wider range of hormones. Taken together, our research has the potential to develop effective treatments that can delay or prevent the onset of psychosis in vulnerable individuals and, with the identification of biological risk factors, it could give a valuable insight into the development process of illnesses such as schizophrenia [11].

Summary

Our research at the PACE clinic suggests that it is possible to identify young people at ultra-high risk of developing psychosis. These young people can be monitored prospectively, with a high likelihood that many of them will make the transition to psychosis within a 12-month period, according to our clinical criteria. The transition rate of 41% found in our first study has made it feasible to use this ability to identify 'at risk mental states' to study psychological and biological risk factors for psychosis, as well as allowing a focus on prevention. In the long-term, this mental health strategy may reduce or delay the debilitating effects of illnesses such as schizophrenia, and direct resources to a period of illness that has the potential to return the maximum benefit for the patient and the community [3,11].

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Recent Saccadic Eye Movement Research Uncovers Patterns of Cognitive Dysfunction in Schizophrenia

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The frontal cortex and the subcortical areas of the brain play a major role in the control of thought and action. Eye movements are increasingly used in neuropsychological research to explore the executive and sensorimotor functions of such neural networks. This interface links the control of action, at the fundamental levels of neurophysiological and neurochemical processes, with the high-level cognitive operations that underlie visual orienting. Patients with schizophrenia have neurocognitive impairments that can be readily investigated with novel saccadic eye movement paradigms. Animal, human lesion, and neuroimaging studies have identified the cerebral centers that underlie saccadic eye movements. The areas of the prefrontal cortex include the dorsolateral prefrontal cortex, the frontal eye fields, the supplementary eye fields, and the anterior cingulate gyrus. Pathology of saccadic eye movements therefore provides information on the functional status of the underlying neural circuitry in brain disorders such as schizophrenia.

Information processing and the voluntary control of action are mediated by the precise control of visual attention to specific objects and to events in the environment. The focus of attention is most readily reflected by the line of sight as determined by the oculomotor system [1]. However, neurocognitive research in schizophrenia has largely been restricted to traditional psychological tests of cognition. In recent years, research on eye movement behavior has provided an alternative index of high-level cognitive functions. In schizophrenia research, abnormalities of smooth pursuit eye movements have been a primary focus of research, and are widely proposed as a potential biological marker of this disease [2–6]. Slow eye movements include:

- smooth pursuit: for tracking a visual target that is moving smoothly across the environment
- vestibulo-ocular reflex: for maintaining steady fixation of an image on the retina during a head or body rotation by generating an equal and opposite compensatory eye movement response
- vergence: for tracking a visual target that is moving towards or away from the observer.

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Abnormalities of smooth pursuit eye movement in patients with schizophrenia were first reported by Diefendorf and Dodge [7], but emerged as a promising biological marker for the disease in the 1970s [8,9] following the demonstration of abnormalities in family and twin studies. Abnormalities of smooth pursuit eye movements are reliably associated with both adult and childhood forms of schizophrenia [10].

Saccadic eye movements

Two major types of rapid eye movements (saccades) can be distinguished: reflexive (or visually-guided) saccades, and voluntary (or internally-guided) saccades [11]. A reflexive saccade can be defined as an automatic orienting response to a novel event in the peripheral field. This requires the integration of spatial attention, visual encoding, and a precisely targeted motor program, but places few demands on higher-order executive functions. For voluntary paradigms, there is an increased demand on higher order cognitive resources, which results in an increased complexity in the pattern of brain activation. The ability to resist a prepotent stimulus, and to generate an action that is based on a

cognitive analysis of the task, can be evaluated with the memory-guided and the anti-saccade paradigms where an impulsive response will impede performance (Fig. 1). The control of eye movements therefore incorporates the integration of visuospatial information and high-level cognitive operations in a complete behavioral system. By using a battery of paradigms [12,13], it has been possible to dissociate key cognitive operations and thus identify distinctive abnormalities in the behavioral profiles of saccadic eye movements (Table 1).

The programing of a voluntary saccade is the product of a multilevel network of sensorimotor processors and cognitive subsystems. The cerebral centers underlying saccades are known from primate, human lesion, and neuroimaging studies. Several areas of the prefrontal cortex have been identified including the dorsolateral prefrontal cortex, the frontal eye fields, the anterior cingulate gyrus, and the supplementary eye fields [14]. Detailed neurophysiological research in animals [15–17] and neurological eye movement studies in Parkinson's disease [18–20] have elucidated the functions of the nigrostriatal dopaminergic pathways in the control of saccadic eye movements (Fig. 2).

Inhibitory control in schizophrenia

The anti-saccade paradigm [21] is used widely to explore the programing of volitional eye movements and the inhibition of inappropriate action. Correct anti-saccades are directed towards a spatial position in the opposite visual field to that of the stimulus (Fig. 1b). The paradigm requires suppression of the reflexive saccade that would normally be generated in response

Figure 1. Saccadic paradigms. A: A visual stimulus is presented in a random sequence to the left or right of a central fixation point; subjects are instructed to respond with a rapid and accurate eye movement. B: Anti-saccades are directed towards a spatial position in the opposite visual field to that of the stimulus. The paradigm requires suppression of the reflexive saccade that would normally be generated in response to a novel visual target, and the generation of a volitional saccade to the opposite hemifield. C: Subjects are instructed to suppress the normal reflexive eye movement in response to a novel stimulus, and to delay the saccade until the offset of the central light. There is no visual information on the location of the previously presented target at the moment of saccadic initiation. D: A visible target steps between (two) fixed locations in a predictable temporal sequence. In some studies there is an additional phase where a series of visible targets is followed by a sequence in which target visibility is withdrawn [12,13].

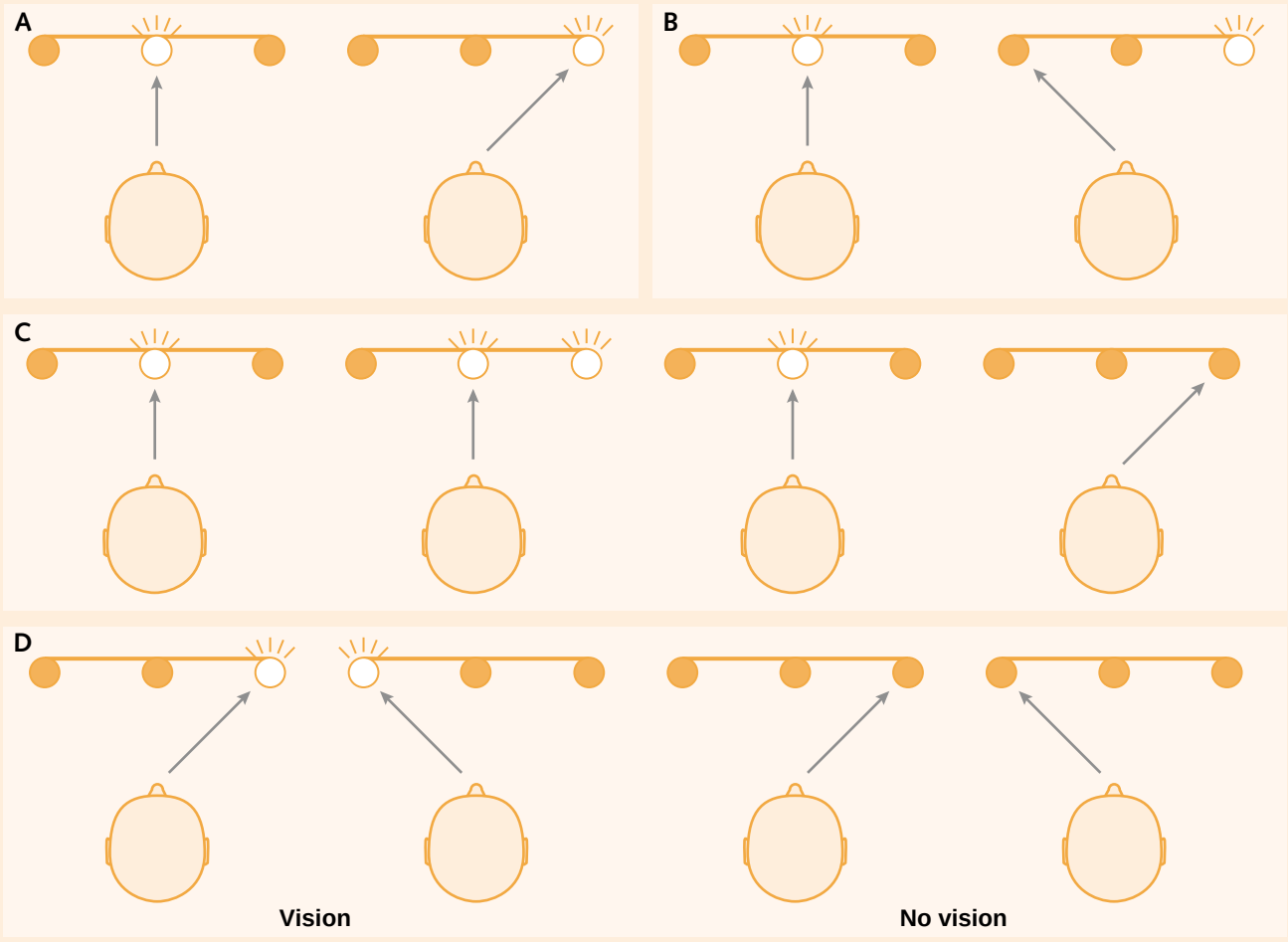
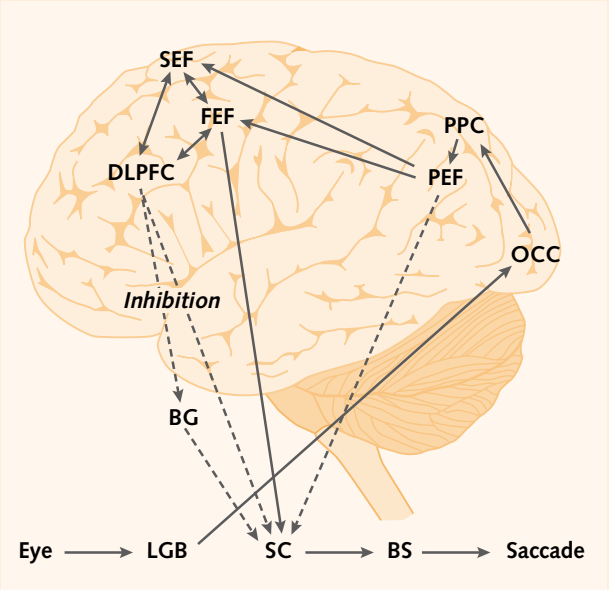


Figure 2. Neural control of anti-saccades.



BG: basal ganglia; BS: brain stem; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; LGB: lateral geniculate body; OCC: occipital cortex; PEF: parietal eye field; PPC: posterior parietal cortex; SC: superior colliculus; SEF: supplementary eye fields.

to a novel visual target, and the generation of a volitional saccade to the opposite side.

There is a general consensus on the increased frequency of inhibition errors in schizophrenic patients; a consensus that is striking in the context of schizophrenia research [13,22–36]. The dramatic impairment of saccadic distractibility in schizophrenia is also evident in other volitional eye movement tasks, such as the memory-guided movements. The abnormality is correlated with errors of perseveration on the Wisconsin Card Sort Test, which is consistent with the view of prefrontal lobe dysfunction in schizophrenia [29]. This is supported by the similar pattern of saccadic impairment with a unilateral lesion of the dorsolateral prefrontal cortex [37]. Chronic [12] and first-episode patients with schizophrenia [38] show a similar severity of disturbance on this task. Functional brain imaging studies with PET [39] and SPET [24] have revealed that the cortical centers underlying the abnormality include the dorsolateral prefrontal cortex, the anterior cingulate, the neostriatum, and the temporal cortex.

Negative symptoms such as anergia, deficit syndrome and formal thought disorder are associated with poor anti-saccade performance, whereas this is not true for positive symptoms [12,25,26,31]. Patients with tardive dyskinesia (TD) generate more inhibition errors than patients without TD [40]. Treatment with conventional antipsychotic medication [12,30,31] appears to have no effect on anti-saccade error rates [12].

Table 1. Dissociation of two key operations in the saccadic paradigms. The ability to inhibit reflexive glances and the ability to perform actions based on spatial working memory can be assessed separately by combining four saccadic paradigms.

	Inhibition of target	Spatial working memory
Visually-guided saccades	–	–
Anti-saccades	+	–
Memory-guided saccades	+	+
Predictive saccades*	–	+

*No-vision target phase (see Fig. 1)
+ : Cognitive operation requires high priority for correct performance
– : Cognitive operation requires low priority for correct performance

Dopaminergic systems and eye movements

The hypothesis that volitional eye movements are a sensitive behavioral marker of dopamine receptor function in nigrostriatal projections is supported by extensive research in animal studies [41–44] and Parkinson's disease [18–20,45]. The pattern of eye-movement changes produced corresponds to those found in schizophrenic and bipolar patients on typical neuroleptics. These abnormalities are most severe in patients with increased extrapyramidal symptoms [12], suggesting an effect that is related to dopamine depletion within the nigrostriatal pathways. Eye-movement measures proved to be the most robust predictor of neuroleptic status, and were superior to conventional psychiatric and extrapyramidal rating scales [12].

Animal studies have supported these findings by showing that the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the neostriatum induces a specific abnormality in memory-guided saccadic eye movements [42,43]. Effects on volitional saccadic eye movements requiring working memory have also been shown to be acutely sensitive to a D_1-antagonist in the prefrontal cortex [44]. A D_1-antagonist impairs performance in a dose-related manner in the delayed oculomotor task (a task analogous to the memory-guided task used in man). The effect in monkeys does not appear with D_2- or D_3-antagonists, which suggests that the effect is specific to frontal lobe D_1-receptors.

The neuroreceptors that mediate the abnormality in schizophrenia are unclear, though some recent clinical data indicate that the 5-HT_2 receptor may play a critical role [46,47]. This distractibility of visual attention and eye movement is not reversed by treatment with conventional neuroleptics. The effects of the 'newer' atypicals are currently under evaluation in a number of laboratories.

Anti-saccade abnormality as a biological marker in genetic research

Measures of oculomotor performance are among the most promising endophenotypes for schizophrenia, and are becoming increasingly applied as biological markers in genetic research [48,49]. The abnormal frequency of inhibition errors in the anti-saccade paradigm rarely occurs in the general population, but is strongly correlated with the presence of schizophrenia (although distinct from active psychotic symptoms). Recent studies with the families of schizophrenic patients have detected the abnormality in non-psychotic biological relatives and have demonstrated a link to the presence of the abnormality in the probands. Probands with high levels of inhibition errors were more likely to have relatives who also displayed the anti-saccade abnormality than probands with normal performance [36,50,51]. Using an analytical model based on anti-saccade inhibition errors, an impressive risk ratio for non-psychotic first degree relatives was achieved and 70% of patients were correctly classified [34]. Anti-saccade inhibition errors were increased in first, but not second-degree relatives [50], which is consistent with the genetic inheritance patterns in schizophrenia [52].

Conclusions

In recent years there has been a growing interest in eye movement abnormalities in schizophrenia, demonstrated by several publications. Saccadic paradigms now supplement the more traditional methods of cognitive research. Research strategies that examine a profile of saccade performance across a range of saccadic eye movement tests can target different neuropsychological operations. The anti-saccade and the memory-guided saccade paradigm, in particular, are increasingly used to probe selective neurocognitive operations. Current developments suggest that research programs incorporating a battery of saccadic paradigms combined with neuroimaging, clinical and psychopathological observations are likely to become more characteristic of future developments, and will provide an important tool in unraveling the pathophysiology of this mysterious disorder.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

BASIC PHARMACOLOGY

Restoration of latent inhibition by olanzapine but not haloperidol in entorhinal cortex-lesioned rats

Coutureau E, Gosselin O, Di Scala G.

Psychopharmacology 2000;**150**:226–32.

Latent inhibition (LI) is the detrimental effect of pre-exposure of a to-be-conditioned stimulus (CS) on its future ability to enter into a conditioned association. It has been intensively studied both in animals and in humans, and is considered a relevant animal model for the study of the biological bases of schizophrenia.

Studies in rats have previously shown that disruption of LI is due to the release of dopamine in the nucleus accumbens [1]. Coutureau et al. [2] recently observed that lesions of the retrohippocampal area, comprising the subiculum and the entorhinal cortex, also disrupt LI. Since disruption of LI following lesioning of the hippocampal formation is thought to depend on the secondary alteration of dopaminergic activity within the nucleus accumbens, it should be sensitive to antipsychotic treatment. Consistent with this idea, haloperidol has been found to restore LI in retrohippocampal-area-lesioned rats.

The present authors report the first investigation of the effects of atypical antipsychotics on LI in entorhinal-cortex-lesioned rats. They examined LI using an off-baseline conditioned emotional response paradigm in which a tone is paired with a foot-shock. Lesions were produced by the electrolytic method. After the recovery period, both lesioned and control (non-lesioned) rats were administered haloperidol, olanzapine or vehicle (saline) before both the pre-exposure and conditioning stages of the experiment. It was found that the deficit in LI induced by lesioning was restored by the atypical antipsychotic olanzapine, but not by the classical neuroleptic haloperidol.

These findings are different from those of previous studies showing a restoration of amphetamine-induced disruption of LI by both typical and atypical antipsychotics. Disruption of LI by lesions of the entorhinal cortex may provide a way to differentiate anatomical and/or neuropharmacological targets of typical and atypical antipsychotic drugs.

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NEUROPSYCHOLOGY

Relationship of cognitive functioning, adaptive life skills, and negative symptom severity in poor-outcome geriatric schizophrenia patients

McGurk S, Moriarty PJ, Harvey PD et al.

J Neuropsychiatry Clin Neurosci 2000;**12**:257–64.

Cognitive impairment is a central feature of schizophrenia. Most patients face a poor functional outcome, including deficits in social, occupational and self-care activities, which persist even in periods of remission of positive symptoms of the illness. Functional outcome in schizophrenia has been shown to be predicted by both negative and cognitive symptoms [1].

Interestingly, substantial correlations have been seen between cognitive deficits and negative symptoms, thereby raising the possibility that extreme scorers for negative symptoms, cognitive functioning and adaptive functioning account for the correlation between these variables in large samples of patients. However, it has also been shown that although cognitive deficits and negative symptoms correlate in their severity, there is no longitudinal relationship between them [1].

The present authors thus suggested that although positively correlated, cognitive deficits and negative symptoms may manifest different underlying physiological processes. To test this possibility, they compared the relationship between cognitive functioning and functional skills in poor-outcome geriatric schizophrenia patients who were in the first [n=81; a maximum total score of 18 on the Positive and Negative Syndrome Scale (PANSS)] and the fourth quartiles (n=127; a minimum total score of 26 on the PANSS) of negative-symptom severity based on the normative data.

The results demonstrated that negative symptoms and cognitive functioning were the strongest predictors of functional skills in this population, regardless of the severity of negative symptoms. Positive-symptom severity was found to be strongly related to the severity of impulsive behavior.

The authors suggest that, because cognitive functioning has a significant relationship with functional skills, the most effective way to improve the outcome of schizophrenia is to target cognitive dysfunction. Importantly, there appears to be considerable promise from atypical antipsychotics, such as clozapine, risperidone, olanzapine and quetiapine, for the enhancement of cognitive functioning in schizophrenia.

1. Harvey PD, Howanitz E, Parrella M et al. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: A comparison across treatment sites. *Am J Psychiatry* 1998;**155**:1080–6.

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Procedural learning in schizophrenia: further consideration on the deleterious effect of neuroleptics

Bédard M-A, Schérer H, Stip E et al.
Brain Cogn 2000;**43**:31–9

Procedural learning is a type of rule-based learning in which performance facilitation occurs with practice on task. Impaired procedural learning was reported first in patients with parkinsonism and Huntington's disease. Based on these findings, the striatum was postulated as the main neural structure underlying this type of learning. More recently, the cerebellum and prefrontal cortex have been proposed as important components of the circuit subserving procedural learning, on the basis of observations of impaired performance in patients with cerebeller degeneration and prefrontal damage.

Attempts to investigate procedural learning in patients with schizophrenia have yielded conflicting results. The authors suggest that this may be related to the type of antipsychotic medication administered. Conventional antipsychotics may account for procedural learning deficits in these patients, perhaps via their strong dopamine-blocking actions in the striatum.

To test the above hypothesis, three groups (n=15 per group) of schizophrenic patients treated with three different antipsychotics were compared with normal healthy controls on two procedural-learning tasks. The antipsychotics were chosen on the basis of their high or low dopamine affinity, and comprised:

- haloperidol, a classical neuroleptic drug with high D_2 occupancy
- clozapine, an atypical antipsychotic without significant D_2 occupancy
- risperidone, another atypical antipsychotic that nevertheless shows a significant D_2 occupancy.

The tasks for the procedural learning assessment were:

- the Mirror Drawing Task, a visuomotor learning task
- the Tower of Toronto test, involving learning of a problem-solving algorithm.

Patients treated with haloperidol, but not those treated with clozapine or risperidone, showed many fluctuations during the initial learning of the visuomotor task. In the problem-solving task, learning rates were slower for the haloperidol and risperidone groups than for the control or clozapine groups.

The authors attribute the observed fluctuations in the haloperidol-treated patients either to a direct deleterious effect of haloperidol on frontal lobe functions or to an improvement in frontal lobe functions brought about by clozapine and risperidone, but not by haloperidol. They attribute slower learning on the Tower of Toronto test in the haloperidol and risperidone groups to D_2 receptor blockade in the striatum by these drugs. The doses of the various antipsychotics used in this study, however, are not reported.

The above findings showing differential effects of conventional and atypical antipsychotics on procedural learning deficits in schizophrenia have important implications for rehabilitation and reintegration of patients, as much of the rehabilitation involves either acquiring new skills or relearning skills that have been lost due to the illness. Atypical antipsychotics may help the patients to acquire skills necessary for independent living in the community.

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Neuropsychological functioning in first-episode psychosis — evidence of specific deficits

Riley EM, McGovern D, Mockler D et al.
Schizophr Res 2000;**43**:47–55.

Patients with schizophrenia exhibit profound neuropsychological deficits when compared with normal healthy individuals. However, studies of neuropsychological functioning involving chronic schizophrenic patients do not allow one to examine whether the cognitive impairment frequently seen in schizophrenia reflects the disease process, long-term neuroleptic treatment, long-term institutionalization, or a combination or two or more of these factors.

The authors have examined the neuropsychological profile of a sample of 40 first-episode patients using a

comprehensive battery including tests of executive functions, verbal memory, non-verbal memory, working memory, attention, psychomotor speed and spatial ability, and compared them with a group of 22 healthy individuals.

Patients underperformed the controls on all test variables. Significant differences were found on tasks of executive function, including those requiring the ability to form and initiate a strategy, to inhibit prepotent responses, and to shift cognitive set, and also on tasks of verbal fluency. Significant differences were also found on verbal learning, delayed non-verbal memory, and psychomotor speed. Impairments on these tasks were up to two standards deviations below the performance of controls. There was, however, no relationship between symptomatology and neuropsychological performance.

Thus, it has been shown that, even at the very first presentation of psychotic symptoms, schizophrenic patients exhibit significant neuropsychological abnormalities. This study represents one step forward towards understanding schizophrenia as a 'cognitive disorder'. The next step perhaps should be to search for antipsychotic (or other) treatments which would, at least, help to preserve the current level of cognitive functioning if not reduce the abnormalities already present at the onset of illness in schizophrenic patients.

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Neuropsychological and conditioned blocking performance in patients with schizophrenia: Assessment of the contribution of neuroleptic dose, serum levels and dopamine D_2-receptor occupancy

Oades RD, Rao ML, Bender S et al.
Behav Pharmacol 2000;**11**:317–30.

Conventional drugs used to treat patients with schizophrenia primarily act on dopamine D_2 receptors. Patients with schizophrenia often exhibit deficits in tasks requiring selective attention (e.g. latent inhibition and conditioned blocking) and standard neuropsychological tests of frontal lobe functioning (e.g. verbal fluency and card sorting). Such deficits are also associated with symptoms of the illness — for example, impaired latent inhibition is seen in patients with positive psychotic symptoms. Importantly, performance on some of these tasks is also known to be affected by manipulations of dopamine activity. The extent to which performance deficits in schizophrenic patients are due to antidopaminergic medication is largely unexplored.

The authors examined the putative influence of the dose of antipsychotic medication, the antipsychotic serum concentration of D_2-blocking activity and the approximated central D_2-receptor occupancy on the conditioned blocking effect (CBE) — retardation of learning about the consequences of a stimulus-component (B in AB) when these consequences are already becoming associated with another component (A in AB) — and performance on a range of neuropsychological tasks in 108 patients with schizophrenia. The control group comprised 62 healthy subjects.

The antipsychotic serum concentration of D_2-blocking activity and the approximated central D_2-receptor occupancy were higher in paranoid compared with non-paranoid patients, and in female compared with male patients; this effect was unrelated to symptom severity. Controlling for D_2-receptor occupancy abolished the difference between paranoid (high CBE) and non-paranoid (low CBE) patients. Performance of some other tasks also showed a functional relationship with D_2 activity. High estimates of central D_2 occupancy were associated with impaired verbal fluency but improved recall of stories, especially in paranoid patients.

This is the first study to have examined the putative role of dopamine activity in left frontal (e.g. verbal fluency) and temporal lobe (e.g. story recall) functions in patients with schizophrenia. Although the study was limited by the availability of central D_2-occupancy data for only five of the commonly prescribed antipsychotics (haloperidol, risperidone, flupenthixol, clozapine and olanzapine), and relatively crude estimations of occupancy data, it is valuable in providing working hypotheses for the role of D_2-related activity in attention and recall.

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Is anhedonia a specific dimension in chronic schizophrenia?

Loas G, Noisette C, Legrand A et al.
Schizophr Bull 2000;**26**:495–506.

Anhedonia, the reduced ability to experience pleasure, is a common feature of depression. It is also considered to be an early symptom and a stable trait in schizophrenia. However, it has been shown that depressive-like symptoms in schizophrenia are related to the use of neuroleptics and that a strong link exists between neuroleptic use and anhedonia. Some researchers have suggested that anhedonia is a persistent negative symptom in schizophrenia, while others have found it to be independent of depressive symptoms.The present authors used factor analysis methods to clarify the relationship among anhedonia, depression, and schizophrenic symptoms in chronic schizophrenia.

The study group comprised 150 subjects (86 males and 64 females) who met research diagnostic criteria for definite chronic schizophrenia. They completed two self-rating scales: the French version of the abridged form of the Beck Depression Inventory, and the Fawcett Clark Physical Pleasure Capacity Scale. The choice of the Physical Capacity Scale, as opposed to the Social Anhedonia Scale, was made as it represents a relatively pure form of hedonic capacity and is less influenced by psychological factors, such as anxiety. Schizophrenic symptoms were rated using the Positive and Negative Syndrome Scale.

The authors subjected the data to rigorous statistical techniques and, on the basis of their findings, concluded that anhedonia is not a negative symptom that co-varies with other classical negative symptoms. Their results also supported the view that anhedonia is separate and distinct from depression in schizophrenia. The relationship between antiparkinsonism and anhedonia, however, was not examined

The findings of this study led the authors to propose, firstly, that anhedonia may be the main characteristic of a particular syndrome in chronic schizophrenia, and, secondly, that there may be a subgroup of chronic schizophrenia patients characterized by severe anhedonia.

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BRAIN IMAGING

A positron emission tomography study of quetiapine in schizophrenia: A preliminary finding of an antipsychotic effect with only transiently high dopamine D_2 receptor occupancy

Kapur S, Zipursky R, Jones C et al.

Arch Gen Psychiatry 2000;**57**:553–9.

Quetiapine is an atypical antipsychotic with evidence of efficacy in schizophrenia at doses of ≥300 mg per day. It is associated with an incidence of extrapyramidal side effects and prolactin level elevation similar to that of placebo. This study was designed to investigate its *in vivo* effects on the D_2 and 5-HT_2 receptor systems, using positron emission tomography (PET) with two radioligands, [^{11}C]-raclopride and [^{18}F]-setoperone.

Twelve patients with schizophrenia were randomly assigned to receive one of four doses of quetiapine: 150, 300, 450 or 600 mg per day. After 3 weeks of treatment, they underwent PET imaging 12 h after the last dose. After the PET scan, the patients reverted to flexible dosing (150–600 mg/day) and were evaluated with structured ratings for another 8 weeks. A further two patients were scanned 2–3 h after the last dose to see the acute effects of quetiapine.

At 12 h after the last dose, D_2 occupancy ranged between 0 and 27%. Despite these low levels of D_2 receptor occupancy, treatment with quetiapine was associated with significant improvement on clinical scales, significant effects on positive symptoms, and a trend towards a significant effect on general symptoms. Furthermore, there were low levels of extrapyramidal side effects. There was also a general reduction in prolactin levels (the basal levels probably being increased because of the previous use of typical antipsychotics). Of particular interest were the two patients who received scans 2–3 h after the last dose. In these patients, D_2 occupancy was 58% and 64%, respectively. However, when these patients were rescanned after 9 and 24 h, respectively, occupancy had declined to 20% and 0%, leading the authors to suggest that quetiapine has only a transient effect on D_2 receptors. The effect on 5-HT_2 receptors was more characteristic, with a dose-dependent receptor occupancy averaging 20% at the lowest dose and 78% at the highest dose.

Drawbacks of this study include the lack of any control for non-pharmacological factors in treatment. In addition, only striatal D_2 receptor occupancy was measured, rather than other extrastriatal regions, which are thought to be responsible for the antipsychotic effect. Nevertheless, this study does suggest very low D_2 occupancy 12 h after the last dose of quetiapine and yet clear antipsychotic efficacy. The authors suggest that transient D_2 occupancy may be sufficient to induce an antipsychotic response. This is a very interesting hypothesis, and one that is likely now to be taken forward in further studies.

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Cognitive performance in relation to MRI temporal lobe volume in schizophrenic patients and healthy control subjects

Krabbendam L, Derix MMA, Honig A et al.

J Neuropsychiatry Clin Neurosci 2000;**12**:251–6.

The aim of this study was to see if specific cognitive deficits are present in schizophrenia and if these are related to specific areas of brain atrophy. The study group comprised 27 patients with schizophrenia, diagnosed according to DSM-IV criteria and verified using the Composite International Diagnostic Interview, and 19 healthy control subjects. All patients were medicated at the time. Although well matched in other variables, the schizophrenic patients had a significantly lower IQ than the controls. A neuropsychological test battery was performed, with particular emphasis on tasks involving speed of cognitive processing. Structural magnetic resonance images were acquired, and a region-of-interest analysis was applied, involving

manual outline of the amygdala, hippocampus, parahippocampal gyrus and temporal lobe.

There was no difference in the volume of the brain regions between patients and controls. However, the speed of performance on the Stroop Color-Word Test (SCWT) and the Concept Shifting Test was significantly lower in patients than controls. This difference tended to increase as the tasks became more difficult. In the patient group, the volume of the left parahippocampal gyrus was inversely correlated with performance on the third part of the SCWT. This was present across all patients and not just limited to those with the lowest IQs. Performance on the other tasks did not correlate with the volume of any of the brain regions investigated. In the control group, no significant correlations were found between brain structure volume and cognitive performance.

In their discussion, the authors note that this association between parahippocampal gyrus volume and cognitive performance has been previously reported. They suggest that this finding is consistent with the theory of a disturbance in the circuitry connecting dorsolateral prefrontal, temporal and limbic areas, a network required for the active maintenance of task-relevant information. However, they accept that this was a small sample, and that patients were taking antipsychotic medication, and suggest the need for the finding to be replicated.

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Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia

Szeszko PR, Bilder RM, Lencz T et al.
Schizophr Res 2000;**43**:97–108.

The authors introduce this study by noting that, although there is a large degree of evidence implicating frontal lobe structural and functional abnormalities in schizophrenia, the relationship between them is less clear. They suggest that this may be because previous studies have failed to take into account the heterogeneous nature of the frontal lobe, and have especially failed to take into account subregions within it. Particular attention is drawn to the presence of archicortical and paleocortical regions, which have different developmental origins and possibly different functions. The authors hypothesized that the volumes of two dorsal archicortical subregions, but not a ventral paleocortical subregion, would be significantly and selectively correlated with executive and motor dysfunction in patients with schizophrenia, as previously reported for the anterior hippocampal region.

In order to answer this question, they performed structural MRI on 35 patients (20 males, 15 females) with schizophrenia or schizoaffective disorder. They were all first-episode patients with less than 12 weeks' (lifetime) use of antipsychotics. Frontal subregions were delineated using a manually defined method aided by computer. All patients also completed a comprehensive neuropsychological test battery when clinically stable.

Results suggested that among men, but not among women, reduced anterior cingulate gyrus volume was significantly correlated with worse executive function. No other correlations between frontal lobe subregions and neuropsychological domains were significant. Among men, anterior cingulate gyrus volume was significantly more strongly correlated with executive functioning than with memory, language, attention, visuospatial and general intellectual functioning.

The authors interpret their results as showing a specific association between reduced anterior cingulate gyrus volume and executive functioning in men. They classify the association as specific because there was no association between the anterior cingulate and any other aspect of neuropsychological functioning measured. They suggest that this specific subregion approach may be a more fruitful avenue for the future than trying to correlate the whole frontal lobe with neuropsychological function. Furthermore, they discuss the sex differences, noting that their findings may be indicative of differences in the pattern of frontal lobe structure–function relations in schizophrenia between men and women. Although the weaknesses of this study include the low subject numbers, the strengths include the use of first-episode patients with short-term use of medication and comprehensive assessment procedures.

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Neural correlates of memory organization deficits in schizophrenia: A single photon emission computed tomography study with 99mTc-ethyl-cysteinate dimer during a verbal learning task

Nohara S, Suzuki M, Kurachi M et al.
Schizophr Res 2000;**42**:209–22.

This study set out to investigate frontal lobe function in schizophrenia. The method used was measurement of regional cerebral blood flow (rCBF), using single photon emission computed tomography (SPECT). The study group comprised 10 male patients with schizophrenia and nine healthy male volunteers. All patients were diagnosed using ICD-10 criteria and all were taking antipsychotic medication with or without anticholinergic drugs. Subjects were asked to

undertake a verbal learning task. This involved learning three lists of 20 words, which differed in degree of semantic organization. Verbal repetition was used as a control task. Analysis was performed using a manual Region of Interest comparison based on co-registered magnetic resonance imaging templates.

For the verbal learning task, schizophrenics performed more poorly than controls, regardless of whether the word list was random or given semantic meaning. In the control subjects, rCBF during the verbal learning task was significantly higher than the baseline during the verbal repetition task in the left inferior frontal and left anterior cingulate regions. In the schizophrenic patients, however, there was no significant activation by the verbal learning task in any region. Compared with controls, patients had significantly reduced rCBF during the verbal learning task, with statistical significance in the bilateral inferior frontal regions and a tendency towards significance in the left anterior cingulate, left superior frontal, and bilateral middle frontal regions. In the controls but not in the patients, activation in the left inferior frontal region was significantly positively correlated with the categorical clustering in the task.

The authors suggest that their findings provide evidence that schizophrenic patients have poorer memory function, specifically in the use of semantic organizational strategies, and that this is associated with a failure to activate frontal regions. They note the problems in understanding whether the failure of activation is due to the poorer performance of the task or to a specific dysfunction in this brain area. This point still requires elucidation. Other confounding influences on the study include the use of medicated patients and the fact that all were male. There was also no attempt made to link any of the findings to clinical processes or symptoms.

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A five-year longitudinal study of the regional cerebral metabolic changes of a schizophrenic patient from the first episode using Tc-99m HMPAO SPECT

Chen RYL, Chen E, Ho WY.
Eur Arch Psychiatry Clin Neurosci 2000;**250**:69–72.

An area of continuing interest in schizophrenia research is the application of neuroimaging techniques to elucidate the neural correlates of clinical and cognitive abnormalities. There have been several previous attempts employing between-subjects designs to examine the relationship between symptoms, treatment response and regional brain activity. Longitudinal within-subjects studies are now required to examine whether abnormal patterns of regional cortical activity seen in schizophrenic patients represent transient symptom/treatment-related changes or whether they are persistent features of the illness.

The authors present a naturalistic study of the relationship between cerebral metabolic activity, clinical symptoms and treatment response in a young female schizophrenic patient for 5 years from the onset of her illness (aged 19 at the time of the illness onset). Serial technetium-99m hexamethyl-propyleneamine oxime (HMPAO) brain single-photon emission computerized tomography (SPECT) was used to measure regional cerebral metabolism. Her neurocognitive abilities were assessed with the Cambridge Neurological Inventory, Wisconsin Card Sorting Test, Wechsler Adult Intelligence Scale (WAIS-R) verbal subscales, semantic verbal fluency test, and logical memory in Weschler Memory Scale. SPECT scans were taken on six occasions over the course of her illness.

The first scan was performed 6 months after the onset of her illness (first-episode) and 1 week after she had started on haloperidol but still had psychotic symptoms. She achieved full clinical remission after 2 weeks on haloperidol. The second and third scans were performed 10 and 40 months after the onset, respectively, during remission, while she was on maintenance medication with sulpiride (100 mg/day). The medication had been changed from haloperidol to sulpiride because of the side effects. The fourth scan was performed 44 weeks after the onset, during the second psychotic episode; this episode was attributed to poor drug compliance. She responded well to sulpiride (400 mg/day), but 6 months later relapsed again. The fifth scan was obtained during this (third) episode, 56 weeks after the onset. This time she also had negative symptoms and cognitive impairments, and failed to respond to conventional antipsychotics (trifluoperazine up to 53 mg/day and haloperidol up to 55 mg/day for 8 weeks each). However, she responded well to clozapine (300 mg/day). Her symptoms subsided completely and cognitive functioning normalized 2 months after treatment. The sixth scan was acquired at 56 weeks, during clinical remission.

Left anterior temporal lobe under-activity was seen in the first scan, but this had returned to normal levels in the second scan, i.e. during remission. Left prefrontal under-activity was also noted in both the first and second scans. In the third scan, left anterior temporal lobe under-activity emerged again, despite clinical remission. The fourth scan, during the second psychotic episode, showed under-activity in the left temporal lobe. There was under-activity of both prefrontal lobes and of the left anterior temporal lobe in the fifth scan. However, in the sixth scan, the right prefrontal activity — but not the left — had returned to normal.

Although limited by a single-case design, this study presents valuable data on regional cerebral metabolic changes during remission, relapse and development of treatment resistance in schizophrenia and provides some insight into this illness as a 'brain disease'. Its findings suggest that clozapine treatment may improve metabolic activity in the frontal lobes. It remains to be seen whether such effects will also be observed with clozapine treatment in patients with relatively longer duration of illness.

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ETIOLOGICAL FACTORS

Obstetric complications and schizophrenia: Two case-control studies based on structured obstetric records

Kendell RE, McInneny K, Juszczak E et al.

Br J Psychiatry 2000;**176**:516–22.

Obstetric complications and affective psychoses: Two case-control studies based on structured obstetric records

Bain M, Juszczak E, McInneny K et al.

Br J Psychiatry 2000;**176**:523–6.

Labour and delivery complications and schizophrenia: Case-control study using contemporaneous labour ward records

Byrne M, Browne R, Mulryan N et al.

Br J Psychiatry 2000;**176**:531–6.

The broad principle of both genetic and non-genetic factors contributing to the etiology of schizophrenia is well established. Efforts to identify specific such factors have met with more frustration than success. This is particularly true regarding the role of perinatal and obstetric complications (PBCs) in the development of schizophrenia, where results so far have been either conflicting or inconclusive. The studies on PBCs reviewed here, tried to address three key methodological shortcomings of most previous studies, namely:

- sample selection biases
- validity of PBC data
- specificity of possible findings to schizophrenia compared with other severe psychiatric disorders such as affective psychoses.

All three studies used large population-based registers from either Scotland (first two) or Ireland (third) to identify cases of schizophrenia and control subjects. Clinical diagnoses were provided from centralized registers, and information on PBCs was obtained from the actual obstetric records for all subjects. Controls were tightly matched to cases on age, gender, maternal age at the time of delivery, parity and socioeconomic status. Patients and controls were compared on the total number as well as on individual PBCs. The unanimous finding of all three studies was the lack of difference in the total number of PBCs between controls and patients with schizophrenia or affective psychoses. When individual PBCs were examined, the results were less consistent, with one type of PBC being more common in patients in one cohort but not in another. With the possible exception of the finding of excess emergency caesarian sections reported in two of the studies, other positive findings regarding individual PBCs were probably spurious.

It would appear, based on the above, that the role of PBCs in the pathogenesis of schizophrenia is rather limited. As none of the specific PBCs were prevalent, it would be difficult to formulate any arguments as to any pathophysiological link between PBCs and schizophrenia.

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Prepulse inhibition of the startle response in men with schizophrenia: Effects of age of onset of illness, symptoms, and medication

Kumari V, Soni W, Mathew VM et al.

Arch Gen Psychiatry 2000;**57**:609–14.

Prepulse inhibition (PPI) is defined as a reduction in response to a startling stimulus when preceded by a non-startling subthreshold stimulus. It is used an index of attention and information processing. Previous basic and clinical research has shown PPI to be abnormal in schizophrenia, but this finding is susceptible to the effects of medication and clinical features such as the severity and age of onset of illness.

These authors examined the effects of the age of onset, current positive and negative symptoms, and the type of medication on PPI in a group of 38 male patients (aged 20–59 years) with a diagnosis of schizophrenia or schizoaffective disorder. Twenty healthy males (aged 20–50 years) served as controls. Ten patients had illness onset in adolescence (aged <20 years) and 28 had adult-onset illness. Nine patients were on typical antipsychotics and 29 were on atypical antipsychotics. Female patients were not tested, given the previous findings of gender and hormonal effects on PPI. Acoustic stimuli were presented to subjects binaurally and electromyographic activity was recorded for 250 ms post-stimulus. The PPI response was measured at prepulse-to-pulse intervals of 30, 60 and 120 ms.

A significant positive relationship was found between the age of illness onset and PPI at 60 and 120 ms intervals. PPI was significantly reduced in the early-onset group but not in the adult-onset group, compared with controls. No significant relationships were found between PPI and symptoms, age at testing, psychopathology, duration of illness, number of episodes, and medication dose. There was some indication that treatment with typical antipsychotics reduced PPI compared with controls, but only at short prepulse trials. The overall pattern, however, was of no difference in PPI between patients on typical or atypical antipsychotics and controls.

The authors suggest that their finding of a lack of PPI normalization in males with early-onset schizophrenia, even when treated with atypical antipsychotics, is consistent with the reported poor outcome and treatment response in this group of patients. As PPI is an objective and simple experimental tool that could be used to examine heterogeneity in illness and responsiveness to antipsychotic medication in schizophrenia, this finding is potentially very interesting. However, it is worth noting that there was no evidence of poorer medication response in this group of early-onset cases, as their symptom scores were no different from those of the adult-onset cases. Furthermore, the study included a sample of only 10 early-onset patients, who were treated with a variety of antipsychotics for variable periods. As the authors themselves acknowledge, further longitudinal studies with concurrent structural and functional brain measurements in a larger sample are required to examine closely the relationship between PPI and age of onset.

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Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: A prospective cohort study

Cannon TD, Bearden CE, Hollister JM et al.

Schizophr Bull 2000;**26**:379–93.

Neurodevelopmental disturbances are thought to contribute to the etiology of at least some cases of schizophrenia. However, it is not known what the etiologic correlates of these disturbances are, or what proportion of the schizophrenia population is characterized by them. Prospective study of cognitive functioning in people who develop schizophrenia provides one way to address these issues.

Longitudinal high-risk studies have provided consistent evidence that the children of patients with schizophrenia exhibit poorer neuropsychological functioning than the children of healthy individuals. These findings indicate that early signs of brain dysfunctioning in pre-schizophrenic individuals may at least to some extent be mediated by genetic predisposition to develop the illness. However, limited information is currently available to determine the degree to which

early cognitive dysfunctioning predicts schizophrenia in such populations. It is also unclear whether high-risk findings apply to the total population of schizophrenic subjects, or whether they are relevant to only the subgroup of patients with a parent diagnosed with schizophrenia.The present authors used a prospective cohort design to examine:

- the degree to which cognitive dysfunctioning in childhood is predictive of schizophrenia in later life
- whether unaffected siblings of those later diagnosed with schizophrenia also display similar deficits
- the time course of these abnormalities
- whether there is a relationship between fetal hypoxia/other obstetric complications and cognitive performance.

The study group comprised 72 patients with schizophrenia or schizoaffective disorder, 63 of their siblings not diagnosed with schizophrenia, and 7971 control subjects, all selected from a birth cohort whose members had been cognitively assessed at 4 and 7 years of age.

Both the patients and their unaffected siblings performed significantly worse than the non-psychiatric controls on verbal and non-verbal cognitive tests at 4 and 7 years of age; patients did not differ significantly from siblings. There was no relationship between obstetric complications and cognitive performance. While it is possible that the sibling group contained a certain percentage of people (about 5%) who may be diagnosed with schizophrenia in their lifetime, it is unlikely to explain the deficits observed.

The pre-schizophrenic subjects did not show intra-individual decline in cognitive performance. As suggested by the authors, this may be due to the limited ability to detect such decline in children as compared with adults, since the former group undergoes both qualitative and quantitative changes with age. Given that by early adulthood most schizophrenic patients perform more poorly on cognitive tests than their unaffected siblings, it is likely that pre-schizophrenic subjects increasingly diverge from the functioning levels expected in their own families with age.

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The relationship of prenatal and perinatal complications to cognitive functioning at age 7 in the New England cohorts of the National Collaborative Perinatal Project

Seidman LJ, Buka SL, Goldstein JM et al.
Schizophr Bull 2000;**26**:309–21.

Elevated rates of prenatal and perinatal complications (PPCs) have been associated with the development of schizophrenia. A variety of other factors — such as a positive family history for schizophrenia, poor school/childhood adjustment, cognitive dysfunctioning, and poor motor coordination — have also been found to be related to development of this illness. However, not much is currently known about the relationship of these risk factors to each other and whether they reflect common or different pathways.

The present authors examined the relationship between PPCs and cognitive functioning in a large epidemiological study of pregnancy, birth, and development: the National Collaborative Perinatal Project (NCPP). Thirteen standardized measures of cognitive abilities were obtained on 11 889 children at approximately age 7. The authors performed principal component analysis using the 13 cognitive variables to create three neuropsychological measures: academic achievement skills, verbal-conceptual abilities, and perceptual motor abilities. They then measured the relationship between these factors and three measures of PPCs: low birth weight, presumed hypoxic insults, and conditions reflecting possible chronic hypoxia.

All three measures of PPCs were significantly associated with lower cognitive performance for each of the three factors, after controlling for possible confounding variables, such as socioeconomic status, race, mother's age at birth, age of child at assessment, and NCPP site. Low birth weight had the strongest association with cognitive performance, followed by presumed hypoxic insults. Co-occurrence of the three indicators of PPCs was relatively low.

Although the findings suggest that PPCs are associated with a relatively generalized deficit, it is possible — as noted by the authors themselves — that patterns of association between these PPCs and cognitive functioning may change with development. Such a model has previously been proposed by Weinberger [1], to account for frontal lobe deficits in people with schizophrenia who previously were relatively symptom-free.

The authors intend to investigate in future studies whether the association observed between PPCs and poor cognitive functioning is also true in offspring of subjects with schizophrenia or affective psychoses, to test the specificity of certain PPCs on cognitive functioning in schizophrenia. It is important to note that a previous report from the NCCP [2] described different effects of PPCs on intellectual functioning in children of schizophrenic patients and unselected controls.

1. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;**44**:660–9.
2. Reider RO, Broman SH, Rosenthal D. The offspring of schizophrenics: II. Perinatal factors and IQ. Arch Gen Psychiatry 1977;**34**:789–99.

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EPIDEMIOLOGY

Service use and costs of people with dual diagnosis in South London

McCrone P, Menezes PR, Johnson S et al.
Acta Psychiatr Scand 2000;**101**:464–72.

The significant level of comorbidity between psychosis and substance abuse — so-called dual diagnosis — has led to the setting up of special services to deal with the problem. There is a general feeling that some psychiatric services may be more heavily used by such dual-diagnosis patients, whereas others may be underused. The authors prospectively studied a group of dual-diagnosis patients and a comparison group of patients with psychosis but no substance abuse over 6 months to measure service usage and associated costs.

The study was carried out at the Maudsley Hospital in South London. Overall, 101 patients with psychosis were interviewed, 27 (29%) of whom were considered to be dual diagnosis. Of these, eight (9%) had an alcohol problem, 11 (12%) had a drug-related problem and eight (9%) had both. Significantly higher proportions of the dual-diagnosis patients used inpatient care, the emergency clinic and community psychiatric nurses. Furthermore, the intensity with which dual-diagnosis patients used inpatient care was also significantly higher. The overall costs of service use were calculated using a model that included not just direct health service costs but also more indirect social service costs. The mean cost per patient was just over UK£1000 (US$1600) higher in the dual-diagnosis group.

In discussing the implications of these results, the authors note that the patients with dual diagnosis were on average younger and functioning at a lower level than those in the comparison group. This needs to be taken into account when targeting services towards this group. The authors suggest that it is important to see whether specific training of staff and development of dual-diagnosis teams can reduce costs and improve the outcome in dual diagnosis. They suggest that

prospective studies, including an economic component, should be undertaken to evaluate this.

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Maternal recall of pregnancy history: Accuracy and bias in schizophrenia research

Buka SL, Goldstein JM, Seidman LJ et al.
Schizophr Bull 2000;**26**:335–50.

Perinatal and obstetric complications (referred to as pregnancy and birth complications in the paper (PBCs)) have attracted research interest because of their putative contribution to the causation of schizophrenia. One methodological problem complicating the interpretation of findings in this field is that most studies are based mainly on retrospective maternal recall, which may not be entirely accurate. In this paper, the authors examined whether there is indeed recall biases in reporting PBCs by mothers of psychotic patients compared with mothers of healthy controls.

The subjects were selected from the Providence and Boston cohorts of the National Collaborative Perinatal Project. Members with psychotic illness were identified through interviews and/or record search, and were screened to confirm their diagnoses. Thirty-nine of these subjects were then randomly selected and matched for sociodemographic variables and history of obstetric complications to a control sample of equal size. The mothers of these subjects were interviewed over the phone using the Pregnancy History Instrument, a composite of PBC scales identified in the literature. This information was then compared with the actual obstetric records held on the subjects.

Although the total number of errors was highly comparable for the patient and control groups, the types of errors committed differed. Mothers of controls were equally likely to report PBCs not mentioned in their obstetric records (error of commission) as to miss out PBCs (error of omission). However, in general, the mean number of complications based on maternal report in controls was not different to that based on obstetric records. In contrast, mothers of offspring with psychosis reported on average one less PBC than indicated in the charts. In addition, they committed more than twice as many errors of omission than errors of commission, a difference statistically significant for pregnancy complications (p=0.01) but not for total complications (p=0.12).

These findings are at odds with those of the other two published studies on the accuracy of maternal recall of PBCs in schizophrenia. The first study, from O'Callaghan et al [1], suggested that maternal recall was very accurate, while the more recent study, by Cantor-Graae et al [2], found a significantly higher rate of errors of commission in mothers of schizophrenic patients, particularly those without a family history of the disorder. This would suggest that studies on the accuracy of maternal recall of PBCs in schizophrenia are themselves methodologically complex and therefore unlikely to contribute to our understanding of the role of PBCs in schizophrenia. Given that large cohort studies using information from contemporaneous records (see below) found a rather limited role for PBCs in schizophrenia, one wonders whether it is worth exploring this field further.

1. O'Callaghan E, Larkin C, Waddington JL. Obstetric complications in schizophrenia and the validity of maternal recall. *Psychol Med* 1990;**20**:89–94.
2. Cantor-Graae E, Cardenal S, Ismail B et al. Recall of obstetric events by mothers of schizophrenic patients. *Psychol Med* 1998;**28**:1239–43.

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Objective and subjective extrapyramidal side effects in schizophrenia: Their relationships with negative and depressive symptoms

Dollfus S, Ribeyre JM, Petit M.
Psychopathology 2000;**33**:125–30.

The interrelationship between drug-induced extrapyramidal symptoms (EPS), negative symptoms and depressive symptoms of schizophrenia has long been the subject of debate. Some authors have attempted to isolate depressive and negative symptoms with the least overlap of EPS. In contrast, no study has tried to isolate EPS independent of depressive and negative symptoms. Therefore, the aim of this study was to identify EPS unrelated to depression and negative symptoms. The authors hypothesized that subjective EPS are less interrelated to negative and depressive symptoms than objective EPS. This was based on the theory that objective EPS are more subject to observer bias and to misclassification because of coexisting depressive and negative features.

The study group comprised 91 patients with schizophrenia as diagnosed by at least one of four diagnostic criteria. Fifty-three patients were in an acute phase and 38 were stable. All patients were on antipsychotics. Patients were evaluated using the Scale for the Assessment of Negative Symptoms (SANS), the Montgomery and Asberg Depression Rating Scale and the Extrapyramidal Symptom Rating Scale.

Objective EPS scores were significantly correlated to SANS scores ($r=0.51$; $p<0.001$) and to depressive scores ($r=0.26$; $p<0.01$). In contrast, no significant correlations were observed between subjective EPS

scores and depressive or negative scores. The correlation between objective EPS scores and depressive scores disappeared when the negative-symptom correlation was taken into account. These results held across all subgroups of patients (i.e. the acute vs. stable subgroups, the deficit vs. non-deficit subgroups, and the diagnostic subgroups).

On the basis of their findings, the authors suggest that clinicians should pay more attention to subjective complaints of EPS since these are less likely to be confounded by features of the disease, in particular negative symptoms.

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Finnish adoptive family study: Sample selection and adoptee DSM-III-R diagnoses

Tienari P, Wynne LC, Moring J et al.

Acta Psychiatr Scand 2000;**101**:433–43.

This is the first article in a series from the Finnish Adoptive Family Study of Schizophrenia reporting the application of DSM-III-R diagnostic criteria to both adopting-away mothers and adoptees followed-up into adulthood. This approach, first introduced in schizophrenia research by Heston [1] and known as the adoptees' study method, is useful in evaluating the roles of both genetic and environmental factors in illness and its development. It involves the study of biological and rearing parents separately and thus allows one to disengage genetic and environmental factors contributing to schizophrenia. The authors compared:

- Finnish hospital diagnoses of schizophrenic/paranoid psychosis in a nationwide survey of adopting-away women with DSM-III-R diagnoses for these mothers (index mothers)
- DSM-III-R diagnoses of their offspring (index adoptees) with adopted-away offspring of epidemiologically unscreened control mothers (of which 3.5 % had diagnoses of schizophrenia spectrum disorders and 1% had affective psychoses).

The primary sampling diagnoses of index mothers were confirmed using DSM-III-R criteria. The lifetime prevalence of typical schizophrenia in 164 index adoptees was significantly greater (6.7%; age-corrected morbid risk 8.1%) than that observed for 197 control adoptees (2%; age-corrected morbid risk 2.3%). This difference further increased when the diagnoses of schizoaffective disorder, schizopheniform disorder, schizotypal disorder and affective psychoses were added. There was no evidence for an increased prevalence of other diagnoses, including alcoholism, non-psychotic depression or anxiety disorders, in index adoptees.

Thus, the findings confirmed the genetic liability both for 'typical', narrowly defined DSM-III-R schizophrenia and for a schizophrenia spectrum that includes non-affective psychoses and schizotypal personality disorder. No evidence was found for a link between mental disorders in general and the genetic liability to schizophrenia.

The authors, to their credit, have considered the possibility that schizophrenic illness of women who become mothers may be less genetically 'loaded' than for non-mother schizophrenic women, as indicated by previous findings showing relatively later onset of illness in mothers than non-mothers.

The data addressing the issue of environmental protective and predisposing factors with the adoptive rearing families in this sample are to appear in forthcoming reports from this research group.

1. Heston L. Psychiatric disorders in foster home reared children of schizophrenic mothers. *Br J Psychiatry* 1966;**112**:819–25.

Address for reprints: Dr Pekka Tieneri, Professor of Psychiatry (Emeritus), The University of Oulu, Department of Psychiatry, Peltoantie 5, 90210 Oulu, Finland.

TREATMENT

Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia

Wassef AA, Dott SG, Harris A et al.

J Clin Psychopharmacol 2000;**20**:357–61.

One of the neurochemical theories of schizophrenia involves the γ-aminobutyric acid (GABA) system. It is generally thought that GABAergic drugs downregulate dopamine systems. Consequently, GABA agonists may have a potential role in the treatment of schizophrenia. The authors present a brief report of a prospective, double-blind, placebo-controlled pilot study using divalproex as an adjunctive treatment in acute schizophrenia.

The study group comprised 12 patients hospitalized for acute exacerbations of chronic schizophrenia, as diagnosed by the Research Diagnostic Criteria. Antipsychotic treatment was commenced with a fixed-dose regimen of haloperidol 10 mg per day for 3 days and then 15 mg per day for 18 days. Patients were randomized to receive either divalproex (dose adjusted to achieve a target serum concentration between 75 and 100 μg/ml) or placebo, on days 1–14. Between days 15 and 21, patients who had been assigned to receive divalproex crossed over to placebo, whereas those receiving placebo continued on placebo. The usual outcome variables were used, including the

Clinical Global Impression Scale (CGI), the Brief Psychiatric Rating Scale (BPRS) and the Schedule for Assessment of negative Symptoms (SANS).

At baseline, there were no statistically significant differences on the CGI, BPRS and SANS scores between the two treatment groups. On day 21, however, the divalproex-augmented group had significantly better CGI and SANS scores than the placebo group, with a trend in the same direction on the BPRS.

The authors conclude that the addition of divalproex to standard antipsychotic treatment may prove effective in relieving both the positive and negative symptoms of acute schizophrenia. However, this is a small study, which is still highly preliminary. Clearly, a properly powered and controlled trial is needed to confirm whether this is a constructive strategy. It is also useful to consider whether an augmentation effect may occur with atypical antidepressants rather than with haloperidol. The authors review the results of eight previous studies, involving a total of 130 subjects, in which the efficacy of valproate was evaluated in the treatment of schizophrenia. However, only one of these, involving six patients, used specific diagnostic entry criteria and had a double-blind design. The authors suggest that it is a $GABA_A$ agonism that is the vital component, since other $GABA_A$ agonists, such as benzodiazepines, have been shown to relieve schizophrenic symptoms in a dose-dependent manner, whereas $GABA_B$ agonists have not. The authors did not measure haloperidol levels to see whether there was any pharmacokinetic explanation for their findings – not least because of the effect of valproate on liver enzymes; this should be added to future study design.

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Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life

Voruganti L, Cortese L, Oyewumi L et al.

Schizophr Res 2000;**43**:135–45.

One of the selling points of the new atypical antipsychotic drugs is that patients are supposed to prefer them. However, outside of clinical trials, there is little actual assessment of whether this is in fact the case. Hence, this study was designed to compare the effectiveness of conventional and novel antipsychotic drugs, primarily from a patient's perspective. The authors recruited 230 patients with schizophrenia who had been stabilized on an antipsychotic drug for at least 6 months (the drug being at the convenience of the treating physician). Based on the type of antipsychotic drug therapy received at the time of the survey, patients were grouped into five categories: typical antipsychotics (n=44), risperidone (n=50), olanzapine (n=48), quetiapine (n=42) and clozapine (n=46). Patients filled in a number of questionnaires, and clinician ratings were also made. Thus, the investigators obtained measures of clinical symptom profiles, subjective responses and attitudes towards drugs, and the prevalence of dysphoria, akathisia, abnormal involuntary movements, Parkinsonian symptoms, and quality of life.

Patients receiving novel antipsychotics experienced fewer side effects, reported positive subjective responses and favourable attitudes towards their treatment, and revealed a lower prevalence of neuroleptic dysphoria. The differences were statistically significant ($p<0.05$) in the risperidone, olanzepine and quetiapine groups, but failed to reach significance in the clozapine group, however, this probably reflects selection bias. Patients receiving novel antipsychotics also had significantly greater self-rated improvements in quality of life. Clinician-rated measures of psychosocial functioning and quality of life, however, did not reveal any significant differences between the conventional and novel antipsychotic drug groups. There were no statistically significant differences identified between groups of patients receiving different new antipsychotics, on any of the variables measured.

This study is constructive in that it uses a naturalistic design of 'normal' patients outside a clinical trial. It also suggests that clinician-rated measures of quality of life may be under-reporting the subjective improvement patients feel when taking atypical antipsychotics. These findings may be valuable when designing future studies of the effects of new drugs on quality of life in schizophrenia.

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Ritanserin as add-on medication to neuroleptic therapy for patients with chronic or subchronic schizophrenia

Den Boer JA, Vahlne J-O, Post P et al.

Hum Psychopharmacol Clin Exp 2000;**15**:179–89.

Several theories have been proposed as to what, if any, are the common neurochemical effects of the atypical antipsychotics. One prominent shared characteristic of the atypicals is $5\text{-}HT_2$ receptor antagonism. Since there is also some evidence of increased $5\text{-}HT_2$ receptor sensitivity in schizophrenic patients, attention has been directed towards this $5\text{-}HT_2$ receptor antagonism. A further theory is that it is a combination of D_2

antagonism and 5-HT_2 antagonism that is important. Thus, a logical step from this is to see whether the addition of a 5-HT_2 antagonist to typical antipsychotics with D_2 antagonism will lead to a similarly improved efficacy as seen with some atypical neuroleptics.

In this international, double-blind, parallel-group study, the effect of ritanserin, a selective 5-$HT_{2A/2C}$ receptor antagonist, as add-on medication to an established neuroleptic therapy in patients with schizophrenia was compared with that of placebo. Included patients needed to have chronic or subchronic schizophrenia according to DSM-IIIR and to have been treated for at least 3 months with typical antipsychotics. From a total recruitment of 160 patients, 82 were randomly assigned to treatment with ritanserin (10 mg once daily) and 78 to placebo for 8 weeks. Efficacy was evaluated using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). The Clinical Global Impression (CGI) scale was also completed, for assessment of the overall severity of illness and for the overall improvement since baseline. Parkinsonian symptoms were evaluated by means of the Extrapyramidal Symptom Rating Scale.

There were no significant differences between the two treatment groups with respect to demography and baseline disease characteristics. After 8 weeks' treatment, the numbers of patients with clinical improvement on the PANSS negative subtotal and the total PANSS were higher under placebo than under ritanserin, but the differences were not statistically significant. The CGIs of overall severity of schizophrenia were better under placebo than under ritanserin (p=0.15 at endpoint). Adverse experiences, the effects on extrapyramidal symptoms and the use of antiparkinson medication, were comparable in the two treatment groups.

The authors accept that the study is resoundingly negative and discuss reasons why this could be. They note that many of the patients included in this trial were severely ill and perhaps treatment-resistant. They detail possible pharmacokinetic explanations for the trend towards placebo being more effective. They also note the possibility that 10 mg is the incorrect dose, given previous studies showing benefit from 20–30 mg, and draw attention to the heterogeneous nature of the group and the wide range of neuroleptics that were being prescribed. Nevertheless, within the confines of the naturalistic study design, this study gives a clear answer to the question asked and suggests ritanserin is not useful in chronic schizophrenia.

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Longitudinal comparative study of risperidone and conventional neuroleptics for treating patients with schizophrenia

Bouchard R-H, Mérette C, Pourcher E et al.
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These authors used a naturalistic setting to try and further delineate what happens with antipsychotics in real life. They conducted a 12-month multicenter study comparing the effectiveness of risperidone with that of conventional neuroleptics in patients with chronic, severe, stabilized schizophrenia who had shown a suboptimal response to conventional neuroleptics.

A total of 184 patients meeting DSM-IV criteria for schizophrenia were randomized to either a conventional neuroleptic (decided according to the preference of the clinician) or to risperidone. Dosing was flexible according to clinical judgement. The assessments were carried out in an open fashion without blinding by the investigators. Subjects randomized to risperidone were switched back to a conventional neuroleptic if they could not tolerate risperidone.

Nine subjects dropped out before the 3-month assessment and were consequently not considered in any analyses. A further 10 subjects included in the analysis dropped out before the end of the study. Three designs were used when analyzing the results: an intention-to-treat (ITT) design (in which those initially randomized to risperidone but switched back to conventional neuroleptics were included in the risperidone group), a last-observation-carried-forward design (which added to the ITT design the dropouts from both groups) and a No ITT design (which excluded switches and dropouts from both groups). However the analysis was done, risperidone showed a greater effect than conventional neuroleptics on total symptoms and both positive and negative subscales. At 12 months, the proportion of good responders in the risperidone group was significantly greater than that among patients receiving conventional neuroleptics (30% vs. 15%; p=0.03). Interestingly, the decrease in baseline psychopathology was highest in the lower dosage range for both risperidone and conventional neuroleptics, of course, this may well be reverse causality, in that for those who were poor responders the dose was increased. Furthermore, the data suggested that negative symptoms and general psychopathology improved early in response to risperidone, whereas the maximal superiority of risperidone for treating positive symptoms did not appear until 6 to 12 months after commencement of dosing. Thus, within the confines of a naturalistic study, it may be that lower doses over longer periods are needed. The authors also discuss the careful method with which they crossed patients over from

conventional neuroleptics to risperidone, which they believe facilitated a high compliance rate.

One caveat of the study is the lack of blinded assessments. The addition of such — although involving extra complexity and expense — would strengthen the validity of findings in future naturalistic studies.

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Recent patterns and predictors of antipsychotic medication regimens used to treat schizophrenia and other psychotic disorders

Wang PS, West JC, Tanielian T et al.
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The authors used data from the 1997 American Psychiatric Association (APA) Practice Research Network (PRN) Study to identify the prescribing patterns of antipsychotics, as well as the factors associated with the use of particular regimens.

Psychiatrists participating in the PRN Study consisted of 224 randomly recruited individuals and 307 self-identified volunteers, generally representative of APA members. Information for this study was provided by the 417 (78%) PRN psychiatrists who provided patient-level data on 1245 patients. All were asked to complete a detailed diagnostic and treatment form for three patients who had been randomly preselected on a patient log. All analyses of psychopharmacologic treatment in this study were conducted among the 154 patients diagnosed as having schizophrenia or schizophreniform, schizoaffective, shared psychotic, or psychotic disorders not otherwise specified.

Nearly all patients (95%) were being treated with at least one antipsychotic at the time of the survey, 15% were receiving two antipsychotics concurrently, and 2% were receiving three or more. Possible reasons for this polypharmacy include a perceived greater effectiveness by the prescriber or a difficulty in completing titration. Overall, 24% of patients were receiving risperidone, 23% olanzapine, and 7% clozapine. Multiple logistic regression analysis showed that factors associated with being prescribed newer antipsychotics included being elderly, having psychiatric comorbidity, making fewer visits to the psychiatrist in the prior month, having more education, and being white.

Several hypotheses were suggested to explain the above associations. It is possible that atypicals are prescribed to the elderly because of concerns regarding their vulnerability to side effects. Prescribers may also consider atypicals safer in patients with comorbidity but not in patients in acute relapse, hence the association between fewer psychiatric consultations and being on an atypical. The findings regarding race and education may reflect prescriber bias, or the patients' ability to advocate successfully for atypicals the better their education and socioeconomic status. Other factors such as differences in illness severity or vulnerability to side effects cannot be excluded. Finally, the associations between patients' features and use of newer antipsychotics might have arisen by chance because of the multiple comparisons employed in the study. Other methodological limitations include the study's cross-sectional nature, the relatively small sample size, and the issue of whether PRN Study psychiatrists and patients are indeed nationally representative. However, the development of data sources such as this one, containing empirical data on patterns, predictors and outcomes of treatment, are important for clinical and policy decision making in the treatment of patients with schizophrenia.

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10th Congress of the Association of European Psychiatrists

Prague, Czech Republic, October 28–November 1, 2000

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This conference brought together approximately 2500 academics and clinicians from across Europe. Prague provided an ideal backdrop, sheltered from the adverse weather conditions in Western Europe and the sweltering political climate in the USA. An unusual group of attendees were the protesters barracking outside the meeting, holding banners asking for psychiatrists to view patients as individuals rather than syndromes. The meeting covered a diverse range of topics organized by the various sections of the Association of European Psychiatry, with some cross-disciplinary symposia. However, the symposia relevant to this readership were predominantly based on the conceptualization and treatment of schizophrenia.

The (dys)connectivity hypothesis of schizophrenia

One of the challenges for schizophrenia research is to link the research findings from the broad range of neurochemical, neuroanatomical and neuropsychological studies and the clinical symptoms encountered in daily clinical practice. One traditional approach has been to compare regional brain changes in schizophrenic patients and controls. E Ceskova (Brno, Czech Republic) presented data on first-episode inpatients with schizophrenia, and used structural MRI to compare the temporal lobes of patients and controls. Significant decreases were reported in the linear measurement of hippocampal complex, and were greater on the right side. However, the decrease in hippocampal cortex was not significantly correlated with the treatment outcome. K Vogeley (Bonne, Germany) reviewed some wider methodological considerations examining how contemporary schizophrenia research is using the following two approaches:

- examining psychopathological syndromes as secondary to core neuropsychological deficits
- examining localized organic brain changes, as in the above study, within certain candidate regions.

Dr Vogely highlighted the fact that, whilst research had identified pathology within several regions, including the frontal, temporal and limbic cortex, it had failed to identify a single site of brain pathology underlying schizophrenia. This suggested the disturbance of a wider network involving different brain structures. He reviewed the data from the most likely candidates, the fronto-temporal and fronto-parietal connections, using functional MRI and post-mortem data to demonstrate the disruption of the normal relationships between these regions. KJ Friston (London, UK) offered a theory from a theoretical neurobiology perspective, with the intention of bridging the gap between clinical symptoms and the neuronal and neurochemical systems. He put forward a hypothesis that schizophrenia arose as a result of dysfunctional integration amongst different neuronal systems within the brain. The pathophysiology of schizophrenia was expressed at the level of modulation of associative changes in synaptic efficacy; specifically the modulation of plasticity in those brain systems responsible for emotional learning in memory. He went on to suggest that this modulation is mediated by neurotransmitters that are implicated in schizophrenia and are known to be involved in consolidating synaptic connections during learning. Failure of this synaptic connectivity would result in disruption and failure of the reinforcement of adaptive behavior, which would give results consistent with the neuropsychological findings evident in schizophrenia, consisting of subtle memory and executive functioning deficits. These neuropsychological deficits would impair the normal processes involved with self-awareness and language processing to culminate in the clinical symptoms seen in schizophrenia, such as hallucinations and delusions. The studies presented at the symposia suggested that the emphasis on future schizophrenia research should be placed on examining the connectivity or relationship between different brain regions rather than concentrating on more of the 'lesion-based' models of the disorder.

Treatment

The usefulness of the atypical antipsychotic drugs is no longer in any doubt; the next challenge appears to lie in the selection of the optimal medication for the patient's symptom profile. P Mohr (Prague, Czech Republic) presented data on a prospective, double-blind, randomized, 14-week trial in which 157 treatment-resistant inpatients diagnosed with chronic schizophrenia or schizoaffective disorder were assigned to treatment with either clozapine, olanzapine, risperidone or haloperidol. The 14 weeks of the trial were divided into an initial 8-week escalation up to a fixed-dose period, and a later 6-week period where the dose could be adjusted. In the initial phase, the doses were escalated to 500 mg clozapine, 20 mg olanzapine, 8 mg risperidone and 20 mg haloperidol per day. The data demonstrated that clozapine, olanzapine and risperidone resulted in statistically significant improvements on the total Positive and Negative Syndrome Scale (PANSS) score during the first period. Clozapine and olanzapine were more effective against negative symptoms than haloperidol, and these differences were not mediated by extrapyramidal side effects. A more clinically based study was presented by L Conlan (Galway, Ireland), who performed a clinical audit of patients prescribed depot neuroleptics (143 patients on depot medication in a service area of approximately 100 000 population). Thirty-three patients were identified who consented to changing their medication to oral risperidone (out of a total of 69 who were eligible). Twenty-three of these completed 6 months of treatment with risperidone, and all were reported as having a good outcome. Nineteen of these patients were still taking risperidone after 12 months. Of the patients who dropped out in the first 6 months, only one showed insufficient response, the others were related to non-compliance (n=4) and adverse advents (n=3). They suggested that approximately half of the patients with chronic schizophrenia receiving depot neuroleptics would do well when switched to oral risperidone.

M Yu Popov (St Petersburgh, Russia) presented a study of 30 first-admission inpatients with a diagnosis of DSMIV schizophrenia who were randomly assigned to 3 weeks of double-blind treatment with clozapine (n=20) or haloperidol (n=10). Dr Yu Popov demonstrated that clozapine produced significantly greater improvements on both the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Improvement scale (CGI). Eighty-five percent of the patients responded to clozapine, whereas only 50% demonstrated a response to haloperidol (clinical response defined as a decrease of 30% in the total BPRS). They also showed that, whilst the total number of reports and adverse events did not differ between the groups, the severity was graded as lower in the clozapine group. There were no cases of agranulocytosis during their study. This is an unusual study in that clozapine is only available for treatment-resistant schizophrenia in most other countries. A study that examined patients' satisfaction with their medication was presented by G Bartko (Budapest, Hungary), with data from 74 chronic patients with DSMIV schizophrenia who had been switched to an atypical antipsychotic (either risperidone, olanzapine or quetiapine) after having either failed to respond to conventional antipsychotics or suffered adverse side effects. They completed a patient satisfaction questionnaire after 3 months of being treated with the atypical antipsychotic and reported that 60% of patients evaluated the new treatment as better than the previous treatment, 83% wished to continue this treatment and over half the patients were fully or very satisfied with the new medication. There was no relationship between satisfaction with treatment and clinical improvement. This supports a conceptual model for patient satisfaction, where satisfaction is influenced by factors other than clinical improvement. This study also provides some support for improved compliance with the atypical antipsychotic drugs.