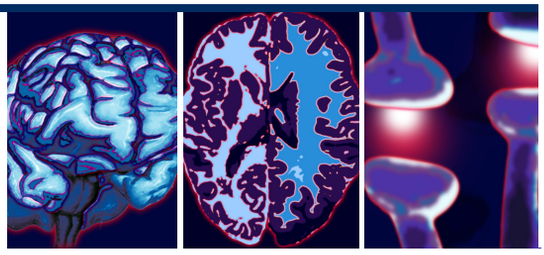

Pursuing the rational pharmacological treatment of schizophrenia

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Q What drew you to the field of schizophrenia & how did it all begin?

I visited the public library to borrow books every week as a teenager, and read anything and everything, including some Jung and Freud and some of the popular antipsychiatry literature, such as RD Laing and, I recall, David Cooper's '*Psychiatry and Anti-Psychiatry*'. This piqued my interest in mental illness, so when I became a medical student, I took the opportunity of an elective period to gain some experience in a busy psychiatric service in inner London. I was immediately fascinated and intrigued by schizophrenia, seeing it as a complex disorder of higher brain function, but also a most disabling illness. I also thought that this would be a good time to enter psychiatry and study schizophrenia, envisaging that during my working life the puzzles of its etiology and the brain mechanisms involved would be solved, and effective treatments developed, although that turned out to be overoptimistic.

Q What do you believe are the most significant achievements & contributions you have made to the field of schizophrenia?

In 1987, I set up one of the first tertiary referral services for treatment-resistant schizophrenia, where we offered a combination of pharmacological, behavioral and psychological interventions. The patients were transferred from long-stay wards in old mental hospitals, and also admitted from acute services. Clozapine was introduced soon after, and our experience with this medication reinforced our view that a response could be maximized with concurrent psychosocial and psychological interventions; it was not merely a case of prescribing the medication, but also realizing the potential for greater social function and engagement over time. That service is still clinically relevant and continues today.

In terms of research, I hope I have contributed positively over the years to clinically relevant questions that were

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of current interest, and therefore also frequently being investigated by other research groups. A series of studies with collaborators such as Peter Liddle, David Curson and Chris Pantelis added, for example, to the literature on the features and assessment of primary and secondary negative symptoms, particularly the phenomenological overlap between depressive features and negative symptoms [1–4]. Furthermore, we conducted one of the first epidemiological studies in inner London on the nature and prevalence of comorbid substance abuse with schizophrenia [5,6]. One early study in the 1980s was a medium-term follow-up study of relapse prevention in schizophrenia, which found that frequent illness relapse was associated with a greater deterioration in social functioning [7]. Although one explanation was that this simply reflected the fact that severe illness was associated with more psychotic episodes and poorer functional outcome, an alternative hypothesis was that relapse had a deleterious impact on prognosis. This study was cited later by Richard Jed Wyatt when mounting the argument that periods of unchecked and untreated psychosis were damaging [8]. This led to notions about the adverse consequences of delay from the onset of psychosis to receiving medication; that is, the initial duration of untreated psychosis (DUP). Later, with Eileen Joyce, I examined the relationship between DUP and outcome in our early, prospective, first-episode study of schizophrenia, finding that longer DUP was associated with worse outcome in the medium term, particularly persistent negative symptoms and poorer social function [9]. In this study, we found that cognitive deficits were already present when patients presented to psychiatric services for the first time, and that they were widespread, causing a lowering of IQ. Our data showed that IQ predicted functional outcome in the first 5 years more strongly than any other clinical or cognitive variable. We also took the opportunity to look at other areas in this cohort of patients, such as the presence of movement disorders in drug-naive patients, and the factors influencing medication adherence, as poor adherence is a common impediment to effective relapse prevention in first-episode patients. One interesting observation was an earlier onset of illness associated with premorbid cannabis use, a piece of evidence that promoted the idea that cannabis is a causal factor in the development of schizophrenia.

I have had a long-standing interest in the extrapyramidal side effects of antipsychotics. My early work on tardive dyskinesia led to a proposal that rather than being a simple side effect, the development of the condition may involve an interaction between exposure to antipsychotic medication, advancing age and age-related cerebral dysfunction, as well as a pathological factor inherent to the illness [10]. Later, Walter Braude and I described in detail for the first time the subjective and objective manifestations of antipsychotic-induced akathisia [11–13]. This was a condition that had been rather ill-defined and commonly overlooked or misdiagnosed in clinical practice. I subsequently generated the Barnes akathisia rating scale, which continues to be widely used internationally in both research and clinical settings.

Lastly, my interest in the rational pharmacological treatment of schizophrenia led to my involvement in the development of treatment guidelines and statements from the Royal College of Psychiatrists [101], NICE [102] and the British Association for Psychopharmacology [14], and also in a number of clinical trials. For example, I carried out one of the first studies in patients with schizophrenia characterized predominantly by negative symptoms [15], and I was also an investigator on the pragmatic Cost Utility of the Latest Antipsychotics in Severe Schizophrenia (CUtLASS) 1 and 2 trials, which examined the clinical effectiveness of the first- and second-generation antipsychotics in broadly and narrowly defined treatment-resistant schizophrenia [16,17]. I was also on the research team conducting one of the first studies looking into the effectiveness of cognitive–behavioral therapy in treatment-resistant symptoms in schizophrenia [18]. I hope that the findings from these trials have contributed to the evidence base for prescribing practice in psychosis. I am currently leading two further, multicenter, randomized controlled trials testing pharmacological strategies for treatment-resistant schizophrenia.

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Q You head the Prescribing Observatory for Mental Health (POMH-UK): what are the aims & goals of this organization?

POMH-UK was set up in 2005 with a tapering grant from the Health Foundation, and since 2008 has been funded solely through subscriptions from member healthcare organizations; the vast majority of UK mental health trusts, as well as several private healthcare organizations, have joined. The aim is to improve the quality of prescribing practice in mental health; in other words, to promote and support the optimal use of existing medications in psychiatric practice. Carol Paton and I are the joint heads, and our chosen method was a series of focused, audit-based quality improvement programs (QIPs).

Thus far, 11 QIPs have been initiated. The first addressed the use of high-dose and combined antipsychotics in acute adult in-patient settings [19] and the second tackled screening for the metabolic side effects of antipsychotic drugs in patients cared for by assertive outreach teams [20,21]. Subsequent QIPs have focused on the use of high-dose and combined antipsychotics in forensic settings, the use of antidementia drugs, the quality of assessment of side effects in patients treated with depot antipsychotics, the quality of lithium monitoring [22], medicine reconciliation at the point of hospital admission and the use of antipsychotics in people with a learning disability, in children and adolescents and in people with dementia.

For each QIP, an expert group including clinicians, academics and service users/carers is convened to agree the audit standards, usually derived from established evidence-based clinical guidelines, guided by the principle that they should be accepted by clinicians as undeniable criteria of good practice and realistic to achieve in routine clinical practice. The group then develops a bespoke data collection/audit tool. Baseline audit data are collected by clinicians/clinical audit staff in each participating mental health trust and submitted online. After analysis at POMH-UK, each trust receives a customized audit report showing its performance on the audit standards, benchmarked (anonymously) against the other participating trusts. The report also indicates how the individual clinical teams in that trust compared with each other, the trust as a whole and the total national sample. Subsequent reflection by clinical teams on their benchmarked performance is perhaps the most potent element of a QIP. In addition to performance against standards, the audit data include demographic, diagnostic and other relevant clinical information that provide a context for interpretation of their practice, and can inform local strategies and systems to achieve improvement.

Between baseline and reaudit, usually at 18 months, change interventions are developed, informed by qualitative work and the baseline data, and made available to the participating services. The aim of these interventions is to help clinical teams close the gap between evidence and clinical practice. A customized, benchmarked report on performance is again provided after reaudit, showing any change from baseline. To allow continued involvement in individual QIPs, supplementary audits have been conducted over subsequent years, and examples of good practice in individual healthcare organizations have been shared. Several of the QIPs have had a demonstrable impact over time, improving aspects of safe and effective prescribing in clinical practice nationally [23]. We are currently pursuing ways for the POMH-UK audit findings, particularly at the level of individual clinical teams, to more effectively contribute to the clinical quality and effectiveness implementation work in trusts.

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Q Your work focuses on the pharmacological treatment of schizophrenia. How far has the field developed over the last 20 years?

The major development has been the introduction of clozapine. It still has the most robust evidence for efficacy in treatment-resistant schizophrenia. Clozapine aside, the introduction of second-generation antipsychotics was heralded with several claims, such as efficacy for negative symptoms, better tolerability and a lower liability for extrapyramidal symptoms (EPS) than the first-generation drugs. While some reduced risk of EPS

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with second-generation antipsychotics, at least in comparison with haloperidol, may be established, the other claims may partly reflect this lower liability for EPS and are not supported by strong evidence. The two groups of drugs are heterogeneous in their side-effect profiles, and modest differences in therapeutic efficacy between the second-generation drugs have been reported. In essence, a distinction between the two groups of antipsychotics has become increasingly irrelevant. Choice of antipsychotic treatment for an individual patient may be more a question of the correct dose and formulation than of drug group. What the introduction of second-generation antipsychotics has achieved is the availability of a greater number of antipsychotics with a broad range of side-effect profiles, so there is greater choice for clinicians attempting to optimize treatment for individual patients.

Another advance is the identification of more specific clinical treatment targets for schizophrenia, such as relapse prevention, negative symptoms and cognitive defects, and testing of augmentation strategies for treatment-resistant illness. We have also seen the emergence of large-scale clinical trials in psychiatry, which can provide a stronger evidence base for pharmacological intervention. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and CUtLASS studies, for example, have had a significant influence on clinical practice [16,17,24].

Q There have been some recent studies looking into the side effects of pharmacological agents in schizophrenia. How important are these when considering treatment options?

As I have already commented, the side-effect profile is key in the choice of antipsychotic, as the differences in therapeutic efficacy between the drugs are modest and there is little or no suggestion of particular drugs preferentially benefiting specific symptoms or domains. Side effects are important because of their associated morbidity and adverse effects on functioning, depending on their nature. Monitoring antipsychotic tolerability can be a complex clinical task, and side-effect severity can be assessed on several variables, such as intensity, frequency and associated distress, as well as any impact on social, occupational or interpersonal functioning. The findings of one of our own studies in patients established on clozapine comparing open enquiry about side effects with the administration of a checklist reinforced for me that the full extent of side-effect burden can only be ascertained by systematic inquiry [25]. Many patients may not attribute certain side effects to the medication, or they may be embarrassed about mentioning problems, such as sexual side effects or menstrual irregularities, which are therefore only likely to be elicited by sensitive but direct questioning. A structured approach is required, combining physical health screening, investigation and examination with careful questioning, informed by the recognized side-effect profile of the particular antipsychotic prescribed. Furthermore, some side effects overlap in presentation with psychiatric symptoms, potentially confounding clinical assessment and making it difficult for prescribers to adjust medication regimens appropriately. For example, akathisia may be misdiagnosed as anxiety or an exacerbation of psychotic symptoms. Side effects are also a common reason for nonadherence. This may apply particularly to the aversive subjective experiences such as lethargy and dysphoria; if a patient misses their medication for a few days, they may feel more alert with an improved mood and perhaps relief of mental unease, and this can be a disincentive to restart the treatment.

Q The environmental factors behind schizophrenia remains an area of contention. What is your take on the topic?

It seems likely that the development of schizophrenia in an individual reflects their degree of inherited, genetic liability and an interaction with environmental factors. There are probably multiple genetic variables, and social psychiatry research over the past decades has identified many potential environmental risk factors, such as stressful events, childhood adversity, migration,

inner-city living and substance abuse. One aspect that these environmental factors may share is some kind of effect on brain dopamine systems and dopamine regulation leading to an increase in vulnerability to psychotic experiences.

Q How do you envisage the treatment of schizophrenia changing over the next 10 years?

In terms of pharmaceutical treatments, there do not appear to be a significant number of novel or innovative interventions on the horizon. It is too early to know whether the attempts to develop adjunctive treatments targeted at particular domains, such as negative symptoms and cognitive deficits, will be successful.

One potentially positive development is the use of optimal pharmacological treatment plus evidence-based psychological and psychosocial interventions, such as cognitive–behavioral therapy, mindfulness, family therapy and psychoeducation, among others, in the early stages of the illness. When I was working in the specialist service for treatment-resistant schizophrenia with a range of such interventions, I would have the sense that this was often too little and too late. But I would be more optimistic for such a strategy in early intervention services when people first present to services. There is already preliminary evidence that combining pharmacological and psychosocial treatments can improve the medium-term prognosis in this context.

Financial & competing interests disclosure

TRE Barnes has, in the past, acted as a consultant or advisory board member for pharmaceutical companies in relation to antipsychotic medication. TRE Barnes has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Bibliography

1 Barnes TRE, Curson DA, Liddle PF, Patel M. The nature and prevalence of depression in chronic schizophrenic in-patients. *Br. J. Psychiatry* 154, 486–491 (1989).

2 Liddle PF, Barnes TRE. The symptoms of chronic schizophrenia. *Br. J. Psychiatry* 157, 558–561 (1990).

3 Liddle PF, Barnes TRE, Curson DA, Patel M. Depression and the experience of psychological deficits in schizophrenia. *Acta Psychiatr. Scand.* 88, 243–247 (1993).

4 Barnes TRE, McPhillips MA. How to distinguish between the neuroleptic-induced deficit syndrome, depression and disease-related negative symptoms in schizophrenia. *Int. Clin. Psychopharmacol.* 10(Suppl. 3), 115–121 (1995).

5 Duke PJ, Pantelis C, Barnes TRE. South Westminster Schizophrenia Survey. Alcohol use and its relationship to symptoms, tardive dyskinesia and illness onset. *Br. J. Psychiatry* 164, 630–636 (1994).

6 Duke PJ, Pantelis C, McPhillips MA, Barnes TRE. Comorbid substance misuse among people with schizophrenia in the community: an epidemiological study in central London. *Br. J. Psychiatry* 179, 501–513 (2001).

7 Curson DA, Barnes TRE, Bamber RW, Platt SD, Hirsch SR, Duffy JC. Long-term depot maintenance of chronic schizophrenic out-patients: the seven-year follow-up of the Medical Research Council fluphenazine/placebo trial. *Br. J. Psychiatry* 146, 464-480 (1985).

8 Wyatt RJ. Research in schizophrenia and the discontinuation of antipsychotic medications. *Schizophr. Bull.* 23, 3–9 (1997).

9 Barnes TRE, Leeson VC, Mutsatsa SH, Watt HC, Hutton SB, Joyce EM. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br. J. Psychiatry* 193, 203–209 (2008).

10 Barnes TRE. The present status of tardive dyskinesia and akathisia in the treatment of schizophrenia. *Psychiatr. Dev.* 5, 301–319 (1987).

11 Braude WM, Barnes TRE, Gore SM. Clinical characteristics of akathisia: a systematic investigation of acute psychiatric inpatient admissions. *Br. J. Psychiatry* 143, 139–150 (1983).

12 Barnes TR, Braude WM. Akathisia variants and tardive dyskinesia. *Arch. Gen. Psychiatry* 42, 874–878 (1985).

13 Barnes TRE. A rating scale for drug-induced akathisia. *Br. J. Psychiatry* 154, 672–676 (1989).

14 Barnes TR; Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J. Psychopharmacol.* 25, 567–620 (2011).

15 Speller JC, Barnes TRE, Curson DA, Pantelis C, Alberts JL. A one-year, low-dose neuroleptic study in chronic schizophrenic inpatients characterised by persistent negative symptoms: amisulpride versus haloperidol. *Br. J. Psychiatry* 171, 564–568 (1997).

16 Lewis SW, Barnes TRE, Davies L *et al.* Randomised controlled trial of effect of prescription of clozapine versus other second generation antipsychotic drugs in resistant schizophrenia. *Schizophr. Bull.* 32, 715–723 (2006).

17 Jones PB, Barnes TRE, Davies L *et al.* A randomized controlled trial of effect on quality of life of second generation versus first generation antipsychotic drugs in schizophrenia. *Arch. Gen. Psychiatry* 63, 1079–1087 (2006).

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

19 Paton C, Barnes TRE, Cavanagh MR, Taylor D; on behalf of the POMH-UK project team. High-dose and combination antipsychotic prescribing in acute adult wards in the UK; the challenges posed by PRN. *Br. J. Psychiatry* 192, 435–439 (2008).

20 Barnes TRE, Paton C, Cavanagh MR, Hancock E, Taylor DM; on behalf of the UK Prescribing Observatory for Mental Health. A UK audit of screening for the metabolic side effects of antipsychotics in community patients. *Schizophr. Bull.* 33, 1397–1401 (2007).

21 Barnes TRE, Paton C, Hancock E, Cavanagh MR, Taylor D, Lelliott P; on behalf of the UK Prescribing Observatory for Mental Health. Screening for the metabolic syndrome in community psychiatric patients prescribed antipsychotics: a quality improvement programme. *Acta Psychiatr. Scand.* 118, 26–33 (2008).

22 Paton C, Barnes TR, Shingleton-Smith A *et al.*; POMH-UK project team. Lithium in bipolar and other affective disorders: prescribing practice in the UK. *J. Psychopharmacol.* 24, 1739–1746 (2010).

23 Barnes TRE, Paton C. Improving prescribing practice in psychiatry: the experience of the Prescribing Observatory for Mental Health (POMH-UK). *Int. Rev. Psychiatry* doi: 10.3109/09540261.2011.606541 (2011) (Epub ahead of print).

24 Lieberman JA, Stroup TS, McEvoy JP *et al.*; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* 353, 1209–1223 (2005).

25 Yusufi BZ, Mukherjee S, Flanagan RJ *et al.* Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int. Clin. Psychopharmacol.* 22(4), 238–243 (2007).

■ Websites

101 Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. Council Report CR138 (2006) www.rcpsych.ac.uk/files/pdfversion/CR138.pdf

102 National Institute for Health and Clinical Excellence. Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. Clinical Guideline 82 (2009) www.nccmh.org.uk/downloads/Schizophrenia_update/CG82NICEGuideline.pdf