Institution: Imperial College London

Unit of Assessment: 04 Psychology, Psychiatry and Neuroscience

Title of case study: Improved Outcomes for Schizophrenia Using Evidence Based Treatment

1. Summary of the impact (indicative maximum 100 words)

Studies conducted at Imperial College, over the last 20 years, have improved the rational, evidence-based treatment of schizophrenia. Our research has covered symptomatology, neurocognitive function, medication side effects, and comorbid substance use, and involved clinical trials of pharmacological and psychosocial treatments. We lead national quality improvement programmes supporting the implementation of psychopharmacological practice standards. Our work has impacted upon the understanding, clinical assessment and treatment of this condition in both first-episode patients and established schizophrenia, and has improved prescribing practice and the identification and assessment of side-effects.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Thomas Barnes, Professor of Clinical Psychiatry (1984-present)
Professor Michael Crawford, Professor of Mental Health Research (1999-present)
Professor Eileen Joyce, Professor of Neuropsychiatry (1991-2006), Honorary Professor (2006-present)
Professor Tom Sensky, Professor in Psychological Medicine (1989-2009)

Clinical trials: Our clinical trials include the first UK study (1993) to evaluate clozapine in treatment-resistant schizophrenia (TRS), and the first (1997) to recruit patients with predominant negative symptoms as the treatment target. Pioneering clinical work by Professor Barnes and colleagues combining pharmacotherapy and psychological intervention, specifically cognitive-behavioural therapy (CBT), for treatment-resistant schizophrenia (TRS) stimulated one of the first randomised controlled trials (RCT; 2000) showing that adjunctive CBT improved persistent, refractory symptoms in schizophrenia (1). Later, we conducted (2012) a pragmatic RCT of group art therapy as an adjunctive treatment for people with schizophrenia.

In collaboration with the University of Manchester, we developed and conducted the cost utility of the latest antipsychotic drugs in schizophrenia (CUTLASS) studies 1 and 2 (2006): pragmatic, double-blind RCTs of the use of first- and second-generation antipsychotics (FGAs, SGAs) in clinical practice (2). For these studies, Professor Barnes developed the Antipsychotic non-neurological side-effect rating scale (ANNSERS), a comprehensive measure for rating non-neurological, adverse drug reactions to both FGAs and SGAs.

Antipsychotic medication side effects: Professor Barnes' work was among the first to report an association between high-dose antipsychotic medication and electrocardiogram (ECG) changes such as prolonged QT interval, a period representing depolarisation and repolarisation of the heart ventricles A long QT interval is a marker for risk of ventricular arrhythmias and potentially sudden death.

Professor Barnes also built on his work on akathisia (with studies in 1994 and 2000), a side-effect of antipsychotic medication for which he had provided the first detailed description of the typical subjective experience (a subjective sense of inner restlessness/mental unease) and characteristic patterns of restless movement. Studies of prevalence, incidence, and risk factors were conducted and the reliability, validity and clinical utility of the Barnes Akathisia Rating Scale (BARS) was demonstrated (3). Work continued on the nature and correlates of negative symptoms in schizophrenia, particularly the phenomenological overlap between depressive features and negative symptoms.

Improving prescribing practice in mental health: Professor Barnes was a co-founder of the Prescribing Observatory for Mental Health (POMH-UK) in 2005. POMH-UK promotes and supports the optimal, safest use of existing medications in psychiatric practice via national, audit-based, quality improvement programmes (QIPs), and provides customised change interventions for

clinical services. Thus far, QIPs have tackled topics such as use of high-dose antipsychotic medication, assessment of metabolic side effects of antipsychotics (4), monitoring of lithium treatment, antipsychotic medication for dementia, use of ADHD medication, and prescribing for personality disorder.

Schizophrenia: We were among the first in the UK to identify the relatively high prevalence of comorbid substance use in schizophrenia, in an early, epidemiologically-based survey (1994) in south Westminster, which revealed a high prevalence of alcohol misuse and cannabis use. In collaboration with the Imperial College Toxicology Unit, we conducted pioneering work using hair analysis to identify substance use in such patients, reporting (1998) on the advantages and disadvantages of this new laboratory ability to test for substance use. Professor Barnes also collaborated with Professor Lingford-Hughes (Imperial) on systematic reviews of the relationship between cannabis use and psychotic outcomes (2007-8).

Our prospective, neurobiological study of first-episode schizophrenia in West London, which started in 1994, was the first UK study to investigate the nature and prevalence of cognitive deficits in early schizophrenia and their relationship with functional outcomes, and the nature and clinical correlates of comorbid substance use, including cannabis (5). We also investigated the relationship between the period from onset of psychosis to receiving antipsychotic medication (duration of untreated psychosis: DUP) and clinical outcomes (6). Further Wellcome funding (2002) allowed expansion of the work to first-episode psychosis.

3. References to the research (indicative maximum of six references)

(1) Sensky, T., Turkington, D., Kingdon, D., Scott, J., Siddle, R., O'Carroll, M., Scott, J.L., Barnes, T.R.E. (2000). A randomised controlled trial of cognitive-behavioural therapy for persistent symptoms in schizophrenia resistant to medication. *Archives of General Psychiatry*, 57, 165-172. DOI. Times cited: 298 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 12.01

(2) Jones, P.B., Barnes, T.R.E., Davies, L., et al. (2006). Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia - Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Archives of General Psychiatry*, 63, 1079-1087. DOI. Times Cited: 482 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 12.01

(3) Barnes, T.R.E. (2003). The Barnes Akathisia Rating Scale - Revisited. *Journal of Psychopharmacology*; 17:365-370. DOI. Times cited: 45 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 3.03

(4) Barnes, T.R.E., Paton, C., Cavanagh, M., et al. (2007). A UK audit of screening for the metabolic side effects of antipsychotics in community patients. *Schizophrenia Bulletin*, 33; 1397-1403. DOI. Times cited: 52 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 8.80

(5) Barnes, T.R.E., Mutsatsa, S.H., Hutton, S.B., et al. (2006). Comorbid substance use and age of onset in schizophrenia. *British Journal of Psychiatry*, 188: 237-242. DOI. Times Cited: 104 (as at 7th Novemebr 2013 on ISI Web of Science). Journal Impact Factor: 6.61

(6) Barnes, T.R.E., Hutton, S.B., Chapman, M.J., et al. (2000). West London first-episode study of schizophrenia: clinical correlates of duration of untreated psychosis. *British Journal of Psychiatry*; 177:207-211.DOI. Times Cited: 123 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 6.61

Key funding:

- Wellcome Trust (1993-1995; £143,000), Co-Principal Investigators (Co-PIs), T. Barnes and T. Sensky, A controlled study of cognitive behaviour therapy in the management of treatment-resistant schizophrenia.
- NHS R&D Health Technology Assessment programme (1999-2002; £1,291,593), Co-PI T. Barnes (collaboration with Manchester), Cost utility of the latest antipsychotics in severe schizophrenia (CUtLASS): a multi-centre, randomised controlled trial.
- Wellcome Trust (1994-1999; £540,804), Co-PIs E. Joyce and T. Barnes, A prospective neurobiological study of first-episode schizophrenia.

- Wellcome Trust (2001-2006; £1,547,518), Co-PIs E. Joyce and T. Barnes, Cognitive and neuroimaging abnormalities in psychosis: The West London longitudinal first episode study.

4. Details of the impact (indicative maximum 750 words)

Impacts include: practitioners and services, health and welfare, commerce, public policy
Main beneficiaries include: practitioners; pharma, patients, NICE, NHS

The BARS is the most frequently used akathisia scale in research and clinical practice world-wide and is translated into Japanese, Spanish and many other languages. Its introduction facilitated the identification and standard assessment of this common and distressing antipsychotic side effect, which was commonly misdiagnosed and untreated, adversely affecting medication adherence and confounded clinical assessment. The BARS is widely used in the clinical management of akathisia; improving diagnosis and treatment, and remains the standard akathisia scale used in major clinical trials of antipsychotic medication [1], and in the vast majority of industry trials of SGAs for licensing, attempting to show their superiority over FGAs or other SGAs in respect of motor side effects [2].

The ANNSERS scale for the comprehensive assessment of non-neurological side effects has been established as a clinically applicable research tool, with good inter-rater reliability. It was used successfully in the CUTLASS studies and has been adopted to aid the processes of research, and has been made available on request to clinicians for clinical assessment.

Our early ECG study reporting an association between high-dose antipsychotic medication and prolonged QT interval raised concerns that led to QTc (QT interval corrected for heart rate) prolongation becoming an important safety criterion in the licensing of new antipsychotics; the risk of QTc prolongation with some older antipsychotics led to their withdrawal [3]. In clinical practice, liability for QTc prolongation can be an issue in choice of antipsychotic for a particular patient, and national clinical practice recommendations now identify indications for ECG monitoring of antipsychotic treatment, such as prescription of high dosage (e.g. Royal College of Psychiatrists' Consensus statement on high-dose antipsychotic medication. CR138, May 2006).

The findings of CUTLASS 2 confirmed the superior clinical effectiveness of clozapine for TRS in a pragmatic study, and the findings of CUTLASS 1, along with similar findings from the US CATIE study, challenged the claims for superiority for SGAs and influenced subsequent treatment recommendations and prescribing practice dramatically. The distinction between FGAs and SGAs was rendered indistinct, and clinical practice opened up to a single class of 'antipsychotics' with varying side-effect profiles, allowing for individualised risk/benefit appraisal to guide treatment, as reflected in the updated NICE schizophrenia guideline (2009). The findings of our CBT study also informed the US Patient Outcomes Research Team (PORT) psychosocial treatment guidelines [4].

The vast majority of UK mental health Trusts (and private/charitable healthcare organisations) are subscribing members of POMH-UK [5]. POMH-UK has increased the involvement of clinical teams in audit and quality improvement processes, and mental health Trusts routinely include participation in POMH-UK QIPs in their annual Quality Accounts. The benchmarked data provide Trusts with evidence of their quality of clinical care in respect of drug treatment, and support their submissions showing compliance with relevant evidence-based guideline recommendations as part of clinical governance. Detailed POMH-UK information on the quality and variation in national prescribing practice is available on topics such as the use of depot/long-acting injection antipsychotics and services (e.g. learning disability and child and adolescent psychiatry) which lack prescribing guidelines and a robust evidence base for pharmacotherapy. Such data has been provided to NICE development groups generating guidelines and treatment recommendations (e.g. for bipolar disorder and psychosis and schizophrenia in children and young people).

POMH-UK has demonstrated a workable and effective methodology for QIPs in the NHS, with participation recommended by the Care Quality Commission (CQC), Healthcare Quality Improvement Partnership (HQIP) and Royal College of Psychiatrists [6]. Positive changes in clinical prescribing practice in participating services nationally have been seen, for example, reduction in the use of high-dose and combined antipsychotic medication between 2008 to 2012 in both acute inpatient and forensic services [7]; a doubling of the prevalence of screening for

metabolic side effects in community patients with schizophrenia from 2006 to 2012; and improved monitoring of patients on lithium from 2008 to 2012 [7]. POMH-UK change interventions provided to clinical teams have ranged from educational tools such as a 'ready reckoner' for calculating total antipsychotic dose (now commonly employed by clinicians and CQC second-opinion appointed doctors) to more complex interventions such as a side-effect information folder, and a patient-held lithium booklet (developed in collaboration with the National Patient Safety Agency, and widely adopted in mental health Trusts: over 170,000 were ordered from 2010 to 2012) [8]. Such improvements in relation to prescribing for people with schizophrenia were reflected in the 2012 National Audit of Schizophrenia which found high rates of clozapine prescribing and a relatively low proportion of community patients on high-dose antipsychotics.

An early follow-up study by Professor Barnes had found that frequent illness relapse in schizophrenia was associated with a greater deterioration in social functioning. Our first-episode study found an association between longer DUP and more severe positive and negative symptoms after one year of treatment, poorer response to treatment and poorer outcome which informed an international notion that periods of untreated psychosis were damaging, and that this was potentially critical at the onset of illness [9]. This view led to the development of early intervention services for psychosis in the UK. In our first-episode work, one interpretation of our finding that cannabis use brings forward the onset of psychosis in people who otherwise have good prognostic features was that early age at onset may be due to a toxic action of cannabis rather than an intrinsically more severe illness. The systematic reviews in which we collaborated concluded that cannabis increased the risk of psychotic outcomes independently of confounding intoxication effects, and that cannabis use in people with psychotic illness was consistently associated with increased relapse and non-adherence. The notion of cannabis as a risk factor for schizophrenia has prompted advice on cannabis psychosis to service users, psychiatrists and other health workers [10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Rummel-Kluge, C., Komossa, K., Schwarz, S. et al. (2012) Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bulletin*, 38, 167–177. DOI.

[2] Suzuki, T. (2011) Which rating scales are regarded as 'the standard' in clinical trials for schizophrenia? A critical review. *Psychopharmacol Bull*, 44, 18-31.

[3] Chung, A.K., Chua, S.E. (2011). Effects on prolongation of Bazett's corrected QT interval of seven second-generation antipsychotics in the treatment of schizophrenia: a meta-analysis. *Journal of Psychopharmacology*, 25, 646-666. DOI.

[4] Dixon, L.B., Dickerson, F., Bellack, A.S., et al. (2010). The 2009 Schizophrenia PORT Psychosocial Treatment Recommendations and Summary Statements. *Schizophrenia Bulletin*, 36 (1), 48-70. DOI.

[5] POMH-UK website: List of member Trusts (archived on 7th November 2013) and Joint-heads of POMH-UK (archived on 7th November 2013)

[6] National Clinical Audits for Quality Accounts (including POMH-UK). Archived on 7th November 2013.

[7] Prescribing Observatory for Mental Health (2012). Topic 1f & 3c. Prescribing high-dose and combination antipsychotics: acute/PICU, rehabilitation/complex needs, and forensic psychiatric services, CCQI125 (data on file), and Monitoring metabolic side effects of patients on antipsychotics: assertive outreach, adult and forensic psychiatric services (Topic 2f) (2012), CCQI136 (data on file).

[8] Gerrett, D., Lamont, T., Paton, C., Barnes, T.R.E., Shah. A. (2010). Prescribing and monitoring lithium therapy: summary of a safety report from the National Patient Safety Agency. *British Medical Journal*, 341, c6258. DOI.

[9] Boonstra, N., Klaassen, R., Sytema, S., et al. (2012). Duration of untreated psychosis and negative symptoms - A systematic review and meta-analysis of individual patient data. Schizophrenia Research, 142, 12-19. DOI.

[10] Cannabis & psychosis - information for health care workers. Department of Health, Victoria, Australia. Cannabis and mental health, Royal College of Psychiatrists' leaflet, UK.