Institution: The University of Manchester

Unit of Assessment: 4

Title of case study:
CUtLASS: Changing attitudes and prescribing practice: cost effectiveness of first versus second generation antipsychotic drugs in people with schizophrenia

1. Summary of the impact

Schizophrenia affects 1% of people, usually leading to lifelong disability. Antipsychotic drugs, first developed in the 1950s, are the mainstay of treatment. A new class of second generation antipsychotic (SGA) drugs was introduced in the 1990s. SGA drugs cost 20-30 times more than first generation (FGA) drugs. Research at the University of Manchester (UoM) between 1999 and 2003 demonstrated that, against globally-held expectations, the heavily-promoted SGA drugs (global market value 2008 $18.2bn – Datamonitor) had no advantages in effectiveness, tolerability, or patient preference over more cost-effective FGA drugs. The results have informed clinical guidelines in the UK (NICE), USA, Canada and other countries, with evidence of change in prescribing practice.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

The UoM research team led on the clinical, statistical and economic elements of the trial design, as well as execution, analysis and report writing. Key researchers:

- **Shôn Lewis** (Professor, 1994-date)
- **Graham Dunn** (Professor, 1996-date)
- **Linda Davies** (Reader, 2000-2008; Professor, 2008-date)

The aims of the research were to test the hypothesis that, in people with schizophrenia requiring a change of treatment, the class of SGA drugs other than clozapine would be associated with improved quality of life over one year compared with FGA drugs. We conducted an NIHR HTA non-commercially funded, pragmatic, 14-site randomised controlled trial of FGA versus SGA class of antipsychotic drug, with blind assessments over one year analysed by intention to treat, in people age 18-65 with DSM-4 schizophrenia and related disorders.

The results showed that:

- The primary hypothesis of significant improvement in quality of life (QLS scale – primary outcome) over the year following commencement of SGA compared with FGA drugs was excluded (2); in fact, participants in the FGA arm showed a trend towards greater improvements in QLS and symptom scores.
- Carefully-assessed neurological side effects showed no difference between the groups.
- Participants reported no clear preference for either class of drug.
- Economic analysis showed FGA drugs to be more cost-effective and the dominant choice (4).
- Conclusion: in people with schizophrenia whose medication is changed for clinical reasons, there is no disadvantage over one year in terms of quality of life, symptoms or associated costs of care in using FGA drugs rather than non-clozapine atypical drugs. Neither inadequate power nor patterns of drug discontinuation accounted for the result.

3. References to the research

Our research into the use of typical and atypical antipsychotics is well documented in the top tier of international peer-reviewed journals.

1. **Lewis SW, Davies L**, Jones P, Barnes T, Murray R, Kerwin R, Taylor D, Hayhurst KP,

Markwick A, Lloyd H, **Dunn G**. Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technology Assessment.* 2006;10(17).
DOI: 10.3310/hta10170
This was the 70 page detailed monograph of the trial methodology and results.

2. Jones PB, Barnes TR, **Davies L, Dunn G**, Lloyd H, Hayhurst KP, Murray RM, Markwick A, **Lewis SW**. Randomized controlled trial of the effect on quality of life of second- vs first generation antipsychotic drugs in schizophrenia - CUtLASS 1 *Archives of General Psychiatry*. 2006;63(10):1079-1087.
DOI: 10.1001/archpsyc.63.10.1079

3. **Lewis SW**, Barnes TRE, **Davies L**, Murray RM, **Dunn G**, Kerwin R, Hayhurst K, Jones PJ. Randomized controlled trial of effect of prescription of clozapine versus other second generation antipsychotic drugs in resistant schizophrenia. *Schizophrenia Bulletin*. 2006;32(4):715-723.
DOI: 10.1093/schbul/sbj067

4. **Davies LM**, **Lewis SW**, Jones PB, Barnes TRE, Gaughran F, Hayhurst K, Markwick A, Lloyd H, on behalf of the CUtLASS team. Cost effectiveness of first- v second generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy. *The British Journal of Psychiatry.*2007;191:14-22.
DOI: 10.1192/bjp.bp.106.028654

4. Details of the impact
See section 5 for corroborating sources S1-S8.

Context
Antipsychotics are among the biggest selling and most profitable of all drugs, generating $22 billion in global sales in 2008 (healthcarefinancenews.com, 2009). Atypical or second generation antipsychotic (SGA) drugs were introduced in 1994 and were twenty times more expensive than typical, first generation (FGA) drugs. They were perceived to be and promoted as being more effective, with fewer side effects and preferable to patients. SGAs were also claimed to be cost-effective since the higher acquisition costs would be recouped from savings on inpatient stays. Most evidence had come from industry-sponsored, short-term efficacy trials concentrating on symptoms. Widespread uptake of SGAs caused the expenditure in England on antipsychotic drugs to increase from £19.9m in 1994 to £211.9m in 2004.

Pathways to impact
The research findings were the subject of a range of editorials and reviews. The results went on to influence clinical guidelines for schizophrenia in the UK, USA, Canada and other countries.

Reach and Significance of the impact
Impact on prescribing guidelines nationally and internationally
In the 2009 NICE guidance on core interventions in the treatment and management of schizophrenia (S1), the CUtLASS trials were the only trials not comparing individual drugs which were considered to be sufficiently important to the guidance to be included: '*In particular, evaluations in which two or more antipsychotic drugs were treated as a class, and in which comparisons between specific antipsychotic drugs were not provided, were excluded from further consideration. An exception was made in the case of the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS, Lewis et al., 2006a, 2006b; Jones et al., 2006), two large effectiveness trials conducted in the UK that compared SGAs with FGAs and clozapine with SGAs; it was decided to describe these studies in the systematic economic literature review because their findings and conclusions, although non-informative on the cost effectiveness of specific antipsychotic drugs, were deemed by the GDG to be relevant and useful in decision-making*' (p.

46). Further: '*Lewis and colleagues (2006a) described two effectiveness trials conducted in the UK that aimed at determining the clinical and cost effectiveness of SGAs versus FGAs and clozapine versus SGAs in people with schizophrenia responding inadequately to, or having unacceptable side effects from, their current medication (CUtLASS, Bands 1 and 2). The studies would normally have been excluded from the systematic review of the economic literature because they treated SGAs and FGAs as classes of antipsychotic medications; no data relating to specific antipsychotic drugs were reported. However, these studies were directly relevant to the UK context and their findings could lead to useful conclusions supporting formulation of guideline recommendations. Therefore, their methods and economic findings are discussed in this section*.' (p. 164). The CUtLASS trials are referenced 11 times in the guidance document. A semi-quantitative study comparing the quality of national guidelines for schizophrenia found that the NICE guidance scored the highest (S2).

The results of the CUtLASS trials have influenced clinical guidelines globally, as in: the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia (S3). A 2011 review of the six major schizophrenia treatment guidelines in the US found the CUtLASS trials to be influential (S4).

Impact on global prescribing patterns

Evidence that the CUtLASS trials have influenced global prescribing practices on a large scale comes from audit-based studies such as that of national prescribing patterns in countries with national prescribing databases, for example Canada: '*First-generation antipsychotic (FGA) recommendations for adults with schizophrenia increased by 38% between 2005 and 2009, from 329 380 to 454 960 recommendations. Second-generation antipsychotic (SGA) recommendations increased to a much lesser extent (9%), which was mostly attributable to an increase in recommendations for clozapine...The rate of increase of FGA use is now greater than that of SGAs. This may be due to data from recent comparative trials, which suggest that clinical efficacy, and the rate of neurological side effects is similar between FGAs and SGAs'* (S5).

CUtLASS1 (2) has been incorporated into US residency training programs with documented change in prescribing practice as a result (S6).

Savings resulting from CUtLASS rollout

As part of an NIHR Research for Patient Benefit grant (PI **Lewis**), CUtLASS was implemented in Bury Primary Care Trust in 2010. UoM researchers, supported by commissioners, worked with clinicians in order to encourage the switch from SGAs to FGAs. The resulting drop in SGA dispensing brought about a significant cost saving in Bury: from a peak in Q2 2009/10, the total cost of antipsychotics fell by 20% in Q1 2011/12 and 18% in Q2 2011/12, a real terms decrease in spending of £51k and £46k (S7) in this period. Assuming savings of £200k per annum in Bury (population 100,000), a national roll-out of the policy would save the NHS £100m per annum.

Media impact

The results of the main trial (2) received immediate and global media coverage. For example, *The Washington Post* covered the findings on its front page: '*Schizophrenia patients do as well, or perhaps even better, on older psychiatric drugs compared with newer and far costlier medications, according to a study published yesterday that overturns conventional wisdom about antipsychotic drugs, which cost the United States $10 billion a year. The results are causing consternation. The researchers who conducted the trial were so certain they would find exactly the opposite that they went back to make sure the research data had not been recorded backward... A U.S. government study last year found that one of the older drugs did as well as newer ones, but at the time, many American psychiatrists warned against concluding that all the older drugs were as good. Yesterday, in an editorial accompanying the British study, the lead researcher in the U.S. trial asked how an entire medical field could have been misled into thinking that the expensive drugs, such as Zyprexa, Risperdal and Seroquel, were much better*.' (S8)

5. Sources to corroborate the impact

S1. NICE. Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). CG82. London: NICE; 2009.

S2. Gaebel W, Reisbeck M, Wobrock T. Schizophrenia guidelines across the world: A selective review and comparison. *International Review of Psychiatry.* 2011;23:379-387.

S3. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Thibaut F, Möller H, WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry.* 2012;13:318-378.

S4. Moore T. Schizophrenia Treatment Guidelines in the United States. *Clinical Schizophrenia & Related Psychoses*. 2011;5(1):40-49.

S5. Pringsheim T, Lam D, Lano D, Patten S. The pharmacoepidemiology of antipsychotics for adults with schizophrenia in Canada 2005-2009. *Canadian Journal of Psychiatry.* 2011;56(10):630-634.

S6. Benjamin D, Swartz M, Forman L. The impact of evidence-based education on prescribing in a psychiatry residency. *Journal of Psychiatric Practice*. 2011;17(2):110-117.

S7. Bury antipsychotic expenditure and items prescribed since Q2 2009/2010 (unpublished report).

S8. Vedantam S. In antipsychotics, newer isn't better. *The Washington Post.* October 3 2006. Online version: http://www.washingtonpost.com/wp-dyn/content/article/2006/10/02/AR2006100201378_pf.html