CATIE's Absolution, CUtLASS' Cutting Edge

Clive E. Adams[1]
Mahesh Jayaram[1]

Abstract

Introduction: Recent large independent studies show no clear difference between the thoughtful use of older generation drugs and the new atypicals for people with schizophrenia. *Objective:* Along with well-conducted systematic reviews of all available evidence, these studies assist clinicians to make informed treatment choices. *Results and conclusions:* These choices should be less directed by guilt generated by the pecuniary interest of industry, and more based on the judicious use of the best evidence.

Key words: Schizophrenia, physician's role, antipsychotic agents.

Título: La absolución de CATIE y el filo de CUtLASS.

Resumen

Introducción: Los más recientes estudios independientes y de gran tamaño, hasta el momento, no han mostrado una clara diferencia entre el meditado uso de un medicamento de primera generación y los nuevos atípicos en personas con esquizofrenia. *Objetivo:* Evidenciar que de la mano de revisiones sistemáticas bien conducidas de todos los hallazgos disponibles, estos estudios asisten a los clínicos para hacer elecciones informadas en los tratamientos. *Resultados y conclusiones:* Las escogencias de medicamentos deben ser menos dirigidas por la culpa generada por los intereses económicos de la industria y más basados en el prudente uso de las mejores pruebas disponibles.

Palabras clave: esquizofrenia, rol del médico, agentes antipsicóticos.

[1] Cochrane Schizophrenia Group, Academic Unit of Psychiatry and Behavioural Sciences, Institute of Health Sciences and Public Health Research, University of Leeds, United Kingdom.

Clinicians, policy makers and increasingly recipients of care are bombarded with information on the effectiveness of drug treatments (1). For schizophrenia, largely this information comes from the pharmaceutical industry. The specialty of psychiatry depends on industry for innovation, discovery of new drugs and their testing within trials. Over the last decades, however, the results of this type of trial have been almost entirely predictable (2-3). Most drugs compare favourably with older drugs such as haloperidol, and if compared with similar second generation drugs, the funding source of the trial accurately predicts findings. Further compounding these biases is the potent marketing machine of industry. People with an interest in the care of people with schizophrenia are assailed with claims and images. These are, by no means, entirely false, but often exaggerate or are impossible to substantiate (4-6).

Clinicians are left feeling guilty if not using the second-generation drugs for people with schizophrenia. Somehow to use a first generation drug begins to feel as if you are giving a second-class service and by doing so the patient is deprived of best care. The rich (both countries and people) can afford the newer drugs whereas the poor (both countries and people) cannot. Well-funded health care systems now have drug budgets for antipsychotics hundreds of times greater than had previously been the case 10-15 years ago (7). In poor countries trade agreements are openly flouted, limited deals with drug companies help acquire medication at least temporarily, local drug budgets are stretched to the limit, or people simply do not get newer drugs. A conservative estimate is that 80% of the world's population lives in low/middle income countries. The vast majority of people with schizophrenia also live in less wealthy countries. We do not know what proportion of these people have access to second-generation drugs, but we think it is probably small. The WHO essential drug list lists three essential antipsychotics, chlorpromazine, fluphenazine and haloperidol (8).

Cutting though the confusion of evidence from industry come rare, more independent, studies. Larger trials such as CATIE (9) and CUtLASS (10) have essentially the same message to give us. First, clearly, treating people with schizophrenia within trials is problematic even in these well-funded studies and systems of care. The norm seems to be that people seem to continue medication only for a matter of weeks (attrition rate from these and other studies is enormous). Expecting many people with schizophrenia to regularly take any medication of any sort for any protracted period of time seems over-optimistic. Both industry's evidence and that from more independent studies suggest

that people interested in treating schizophrenia should get used to the idea of skilfully managing intermittent drug treatment.

Second, these studies repeatedly underline findings already evident from systematic reviews (11-17) —that thoughtful and gentle use of first generation drugs is every bit as good as giving new antipsychotics. This applies to the results of these drugs on positive and negative symptoms and the potential for causing troublesome adverse effects. It is well known that potent drugs such as haloperidol are genuinely helpful in managing psychosis but are accompanied by disabling adverse effects (18).

CATIE and CUtLASS, however, highlight that other older generation drugs, if thoughtfully chosen and employed, are equally clinically effective but with a different adverse effect profile to that of haloperidol. There are many inexpensive, effective and accessible first-generation drugs with less problematic adverse effects than haloperidol or even second-generation drugs. Recently, with more experience and data available, we begin to see the true, less fully positive, picture of the newer drugs. For example, systematic appraisal of studies comparing risperidone with olanzapine shows that about 10% of people allocated to these drugs have adverse effects so severe that the drug has to be stopped. In total, both drugs cause some serious unwanted effect for about one third of people to whom they are given. This proportion is no different to older drugs and, although the adverse effects may be different, they are nevertheless, highly problematic. Third, these independent studies also tell us that clozapine remains an intriguing drug with something additional to offer, especially for people with an illness that has proved resistant to treatment.

CATIE has absolved clinicians of guilt previously associated with use of older generation antipsychotics. CUtLASS also has sliced through myths about second generation medications really having much of an advantage over the first for people with relatively uncomplicated illness.

References

1. Adams CE, Bartsch S, Fenton MK. Publishing patterns of the four drugs most commonly reported in schizophrenia trials. Schizophr Res. 2004;67:140.
2. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry. 2006;163:185-94.
3. Montgomery JH, Byerly M, Carmody T, Li B, Miller DR, Varghese F, et al. An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia. Control Clin Trials. 2004;25:598-612.
4. Gutknecht DR. Evidence-based advertising?: a survey of four major journals. J Am Board Fam Pract. 2001;14:197-200.

5. Smart S, Williams C. Evidence based advertising? Half of drug advertisements in BMJ over six months cited no supporting evidence. BMJ. 1997;315:1622-3.
6. Villanueva P, Peiro S, Librero J, Pereiro I. Accuracy of pharmaceutical advertisements in medical journals. Lancet. 2003;361:27-32.
7. IMS Health. Schizophrenia: atypical antipsychotics-generating evidence to inform policy and practice [homepage on the Internet]. UK: IMS [cited 2006]. Available from: http://research.imshealth.com/research/research_schizophrenia.htm.
8. WHO Expert Committee. The use of essential drugs [monograph on the Internet]. 6th report. World Health Organization: Geneva; 1995 [cited 2006]. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf.
9. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-23.
10. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. 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). Arch Gen Psychiatry. 2006;63:1079-87.
11. Duggan L, Fenton M, Rathbone J, Dardennes R, El-Dosoky A, Indran S. Olanzapine for schizophrenia. Cochrane Database Syst Rev. 2005;CD001359.
12. El-Sayeh HG,.Morganti C. Aripiprazole for schizophrenia. Cochrane Database Syst Rev 2006;CD004578.
13. Jayaram MB, Hosalli P, Stroup S. Risperidone versus olanzapine for schizophrenia. Cochrane Database Syst Rev. 2006;CD005237.
14. Mota NE, Lima MS, Soares BG. Amisulpride for schizophrenia. Cochrane Database Syst Rev. 2002;CD001357.
15. Soares BG, Fenton M, Chue P. Sulpiride for schizophrenia. Cochrane Database Syst Rev. 2000;CD001162.
16. Srisurapanont M, Maneeton B, Maneeton N. Quetiapine for schizophrenia. Cochrane Database Syst Rev. 2004;CD000967.
17. Wahlbeck K, Cheine M, Essali MA. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev. 2000;CD000059.
18. Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev. 2006;CD003082.

Recibido para evaluación: 25 de agosto de 2006
Aceptado para publicación: 18 de octubre de 2006

Correspondencia
Clive E. Adams
Institute of Health Sciences and Public Health Research
University of Leeds
15 Hyde Terrace, Leeds LS2 9LT, UK
ceadams@cochrane-sz.org