Comparison of systematic and narrative reviews: the example of the atypical antipsychotics

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INTRODUCTION

Making rapid decisions is a key component of everyday clinical practice. Informed decision making requires physicians to combine their own clinical expertise and training with high quality scientific evidence. New scientific knowledge is emerging all the time and all health workers need to update their knowledge continuously. Most busy practising clinicians simply do not have sufficient time to read all the important primary research reports. Over two million articles are published every year in twenty thousand biomedical journals (Mulrow, 1994) and even if a clinician restricts his reading to high yield clinical psychiatry journals, he would need to read over 5000 articles a year (Geddes *et al.*, 1999). The clinician therefore needs a reliable system of *knowledge management*. One essential part of such a system is a method of summarising primary research findings into a form that provides a trustworthy overview of current knowledge. There are two main approaches to reviewing literature: narrative reviews and systematic reviews. In this article, we will outline the main features and limitations of systematic reviews. We will then illustrate the advantages of systematic reviews by comparing the conclusions of narrative and systematic reviews of the atypical antipsychotic drugs. Finally, we will suggest ways in which further syntheses of primary trial data may yield clinically useful information.

Narrative reviews are the traditional approach and usually do not include a section describing the methods used in the review. They are mainly based on the experience and subjectivity of the author, who is often an expert in the area. The absence of a clear and objective method section leads to a number of methodological flaws, which can bias the author's conclusions (Murlow, 1987).

On the contrary, systematic reviews (or overviews) are syntheses of primary research studies that use (and describe) specific, explicit and therefore reproducible methodological strategies to identify, assemble, critical appraise and synthesise all relevant issues on a specific topic (Carney & Geddes, 2002). There is evidence that systematic reviews improve the reliability and accuracy of the conclusions, however the results are rarely unequivocal and require careful appraisal and interpretation (Hopayian, 2001): clinicians therefore need to integrate the results with clinical expertise and the patient's preferences.

There is a further difference between narrative reviews and systematic reviews. New research evidence emerges continuously, and reviews are most useful if they are continuously updated. This tends not to be the case with conventionally published narrative reviews, but the systematic reviews of the *Cochrane Library* are publised electronically and can be periodically updated to take into account the emergence of new evidence.

SYSTEMATIC REVIEWS – KEY ISSUES

The first stage in conducting a systematic review is the formulation of a clear question. The nature of the clinical question determines the optimal primary study design and hence the *a priori* inclusion and exclusion criteria. If the question concerns drug efficacy and safety (which treatment is better? which dose is better tolerated?), the most reliable study design would be a randomised controlled trial: randomisation avoids any systematic tendency to produce an unequal distribution of prognostic

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factors between the experimental and control treatments, influencing the outcome (Altman & Bland, 1999). However, randomised controlled trials are certainly not the most appropriate research design for all questions (Sackett & Wennberg, 1997). For example, for aetiological questions, it would neither be possible or ethical to randomise subjects to many harmful exposures: systematic reviews would therefore need to include cohort and case-control studies. Likewise, a diagnostic question such as "how well can a screening tool identify patients with psychiatric disorder" would be best answered by a cross-sectional study of patients at risk of being ill (Mulrow *et al.*, 1995). Systematic reviews of these other study designs have their own methodological problems: guidelines exist for undertaking reviews (and meta-analyses) of diagnostic tests (Irwig *et al.*, 1994) and the observational epidemiological designs used in aetiological research (Stroup *et al.*, 2000).

For all questions, it is crucially important to avoid common and misleading errors that might materially affect the results and limit the reliability of the results. These errors include both those that occur by chance alone (random errors) or by systematic bias (Oxman, 1994). Systematic reviews and meta-analysis estimate the degree of random error by presenting the quantitative results of individual studies and the "pooled" weighted average result with a confidence interval that provides a good indication of the precision. It shows the extent to which the results are likely to differ from the "true result" because of chance alone; however a confidence interval does not provide any indication of the likelihood of bias (Altman & Gardner, 1992).

There are several forms of systematic bias that need to be considered in reviews. One of the most important is selection bias, in other words, a systematic bias in the selection of primary research studies that are included in the review. For example, a reviewer may only select those studies that support his prior beliefs. Selection bias, however, may also be due to "publication bias" (the tendency of investigators, reviewers and editors to differentially submit or accept manuscripts for publication based on the direction or strength of the study findings) (Gilbody & Song, 2000), "language of publication bias" (studies finding a treatment effect are more likely to be published in English-language journals, whilst opposing studies may be published in non-English-language journals (Egger & Smith, 1998) and biases introduced by an over reliance on electronic databases (electronic databases do not offer comprehensive or unbiased coverage of the relevant primary literature)

META-ANALYSIS

Meta-analysis is the statistical combination of the results of several studies into one pooled value and can be a useful way of reducing random error and increasing precision. Meta-analysis can be misleading unless it is performed in the context of a systematic review of the literature to avoid systematic biases. Whereas a systematic review can be applied to any form of research question, meta-analysis should not be used indiscriminately, especially when the primary data are inadequate. In psychiatry many trials are small (Johnson, 1983; Thornley & Adams, 1998): meta-analysis is a tool that can increase sample size combining studies, but, even if attractive, it may not always be appropriate. First of all, it is necessary to ensure that the individual studies are really looking at the same question: the criteria used to select including studies and to assess the quality of the studies included should be explicit and consistent with the focus of the review. Results from poor quality studies quality can result in misleading conclusions and so inclusion of these studies in a meta-analysis may bias the pooled result towards an overestimate of the effectiveness of the intervention being evaluated. (Detsky *et al.*, 1992). The methodological quality of the included studies is important even if the results or quality of the included studies do not vary: if the evidence is consistent but all the studies are flawed, the conclusions of the review would not be nearly as strong as if consistent results were obtained from a series of high quality studies.

Another important role of meta-analysis is to investigate variations between the results of individual studies (heterogeneity). When such variation exists, it is useful to estimate if there is more heterogeneity than can be reasonably explained by the play of chance alone. Attempts should be made to identify the reasons for such heterogeneity, such as variations in trial quality, patient populations, etc. However, when there is substantial heterogeneity it may then be inappropriate to operate overall pooled estimate (Thompson, 1994).

ATYPICAL ANTIPSYCHOTICS AND SCHIZOPHRENIA: A COMPARISON BETWEEN SYSTEMATIC REVIEWS AND NARRATIVE REVIEWS

As we have outlined above, there are substantial theoretical advantages for systematic reviews compared to narrative reviews. It is important to consider if these advantages lead to material differences in the conclusions

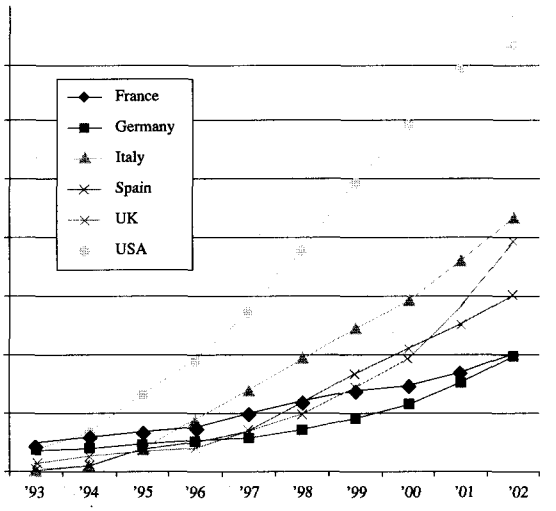
of the two types of review. This has been shown to be the case in general medicine (Antman *et al.*, 1992) and, in this section, we will compare the conclusions of narrative and systematic reviews of the effectiveness of the atypical antipsychotics.

The term "atypical" was originally used to describe drugs that in animal models predict antipsychotic effects but do not produce catalepsy. Nowadays it is applied to drugs that are potentially more effective (particularly against depressive, negative or cognitive symptoms) or better tolerated (especially causing fewer extrapyramidal side effects) than conventional antipsychotics and have a different pharmacological profile (they are receptor antagonists that *in vitro* have low affinity for dopamine D2 receptor, combined with higher affinity for 5-HT2A receptor). We use the term to refer to clozapine and all the novel antipsychotics introduced in the past decade (olanzapine, risperidone, quetiapine, sertindole[1], amisulpride, ziprasidone and – in USA - aripiprazole). The value of global sales of antipsychotics increased more than ten-fold following the introduction of the new drugs but there are significant variations in their uptake: the rate of uptake has been much higher in the USA than in Europe, where there are also substantial variations between countries in the EC (figure 1).

These variations also exist within countries (i.e. UK) and this has caused concern in the context of a nationalised health service funded through general taxation with the aim of providing equal free access to high quality health care. Variations in clinical practice often reflect uncertainty about optimal practice and so this is precisely the sort of situation in which a clinician may turn to the literature for an up-to-date review of the effects of atypical antipsychotics.

To investigate the difference between a representative sample of systematic and narrative reviews, we searched PubMed for "Olanzapine AND Schizophrenia [MeSH]" and we found 34 articles. To focus the comparison, we selected from this literature 9 different reviews published in 1999, choosing those which included only RCTs, concerned the effectiveness and safety of olanzapine both in young and elderly people and have been edited in worldwide journals with the biggest impact factor

Figure 1. – *Percentage of atypicals of all antipsychotic prescriptions, by country, 1993 to 2002. Source: IMS Health Inc (reproduced with permission).*



(*British Journal of Psychiatry, Journal of Clinical Psychiatry, British Journal of Clinical Pharmacology, Schizophrenia Research, Cochrane Library*). To facilitate the comparison of the conclusions of narrative and systematic reviews, we have summarized the conclusions of these reviews in table I.

It can be seen that the identified narrative reviews did not include a description of the search strategy. This means that it is unclear which of the included articles are primary reports of clinical trials (marked with roman numbers). There seem to be more trials than there actually are (see Stahl's, 1999; Kane's, 1999; or Marder's, 1999 reviews: from 7 to 3 RCT or from 2 to unknown). This multiple counting of trials clearly reduces the reliability of the results. The systematic review by Leucht *et al.* includes the same studies as the narrative reviews by Stephenson & Pilowsky (1999), Campbell *et al.* (1999) and Tollefson & Kuntz (1999): we may assume that Leucht *et al.* (1999) use a search methodology more thorough than in other narrative reviews, but as it is not clearly and explicitly reported, we can be less confident about the reliability of the results. Similar search strategies and included trials do not guarantee similar conclusions: Tollefson & Kuntz (1999) state that "olanzapine has been shown to be effective long-term maintenance option and the first line choice for treatment of schizophrenia", on the other hand, Campbell *et al.* (1999) state that "there is no published evidence for olanzapine efficacy and safety during long term treatment and the use of atypical agents is therefore not straightforward". These

[1]The European Commission has lifted the suspension of the marketing authorisation for sertindole. Changes have been made to the prescribing information and, initially, all patients who receive sertindole are required to be carefully monitored and enrolled in large-scale surveillance studies to assess the safety of the drug.

Table I. – *In this table are summarised methodological characteristics and conclusions of 7 narrative and 2 systematic reviews.*

Author	Search methodology	Cited RCT	Effective n. RCT	Conclusions
			NARRATIVE REVIEWS	
Kane, 1999	None	2 II III	?	"The atypical drug, olanzapine, with a favourable toxicity profile and proven efficacy, offers a promising alternative to previous treatments"
Stephenson & Pilowsky, 1999	None	4 a b c d	4	"It is efficacious in treating positive symptoms in schizophrenia, and more efficacious for negative and depressive symptoms than traditional antipsychotics. In addition, the side-effect profile is favourable, with low incidence of EPS and little increase in prolactin during acute-phase trials... As a group, the atypical antipsychotics have been recommended for use as first-line therapy, in acute schizophrenic relapse and for those who are responsive but intolerant to classical antipsychotics."
Stahl, 1999	None	7 a b II IV V d VI	3	"Comparable efficacy to haloperidol overall and for positive symptoms, but better than haloperidol for negative and anxious/depressive symptoms. Far more tolerable than haloperidol with occasional akathisia at low doses and much lower EPS ratings than haloperidol at high doses. Only occasional and transient prolactin elevation, much better than haloperidol... More weight gain than other antipsychotics does not mean every patient gains weight... Not necessary to monitor liver function tests except in significant liver disease"
Tandon *et al.*, 1999	None	4 b II d g	3	"In the short-term trials (4-8 weeks), (olanzapine) has been shown to be as effective as conventional agents in treating psychotic symptoms. Some studies suggest a better response with the atypical antipsychotics compared to conventional antipsychotics because of a higher proportion of responding patients, a greater proportion of patients showing a greater degree of response, or a greater mean reduction in symptom scores. However, concluding that there are different rates of efficacy among the conventional and typical antipsychotics based on these studies is premature because of methodological limitations and some inconsistencies in the findings...Clinical trials have revealed atypical antipsychotics to be superior to or at least as effective as conventional agents in reducing negative symptoms...Among the newer agents, symptom relief occurs in the absence of EPS or at doses of medication below those at which EPS become significant...The new atypical antipsychotic medications represent a major step forward in the treatment of schizophrenia and other psychotic disorders. The primary advantage of the new agents is their superior side effect profiles, particularly with regard to EPS...Further refinement of our understanding of the clinical utility of these drugs awaits their widespread use in mainstream clinical settings ..."
Campbell *et al.*, 1999	None	4 a b c d	4	"The published evidence for olanzapine originates from the clinical research department of the manufacturer. Olanzapine is as effective as haloperidol, may be more effective for negative symptoms and the incidence of extrapyramidal effects is significantly lower than with haloperidol...More weight gain than older agents. There is no published evidence of their efficacy and safety during long term treatment...The use of atypical agents is therefore not straightforward. On current evidence, they should be reserved for patient resistant to, or unable to tolerate, optimum doses of conventional antipsychotics."
Marder, 1999	None	2 V VII	?	"These double-blind extension studies provide convincing evidence that olanzapine is effective in preventing relapse in stabilized patients...certainly support the idea that newer antipsychotics may have important advantages for long-term maintenance therapy...The milder side effects of the newer agents may permit clinicians to treat patients at the optimal dose for preventing relapse. In addition, the improved side-effect profile may improve patient compliance with the prescribed medication."
Tollefson & Kuntz, 1999	None	4 a b c d	4	"Statistically significant differences were observed favouring olanzapine over placebo and haloperidol...Olanzapine has been shown to be effective long-term maintenance option in schizophrenia...Olanzapine has demonstrated a broad range of efficacy (for positive, negative, depressive symptoms), improved response and maintenance rates, and a safety profile comparable to placebo and superior to that of standard therapeutic drugs. Taken together, these data provide a strong impetus to consider novel therapeutics, such as olanzapine, as the first line choice for treatment of schizophrenia at any point in the life course of the disease".

SYSTEMATIC REVIEWS

Leucht *et al.*, 1999	- Medline - Current Contents - by cross-referencing - by contacting companies	4 a b c d	4	"This analysis suggests that patients treated with olanzapine and risperidone showed a greater overall improvement than patient treated with haloperidol or other conventional antipsychotics. It is questionable as to whether the superiorities of risperidone and olanzapine are clinically relevant, as the respective effect sizes are modest...All novel antipsychotics were associated with less frequent use of antiparkinson medication compared to haloperidol, ...but many of the trials used relatively high haloperidol doses as a comparison, which certainly favoured the emergence of EPS under this drug"
Duggan *et al.*, 1999	- Biological Abstract - Cochrane Library - Cochrane Schizoph. Group's Register - Embase - Medline - PsycLIT - by contacting companies and authors	20 a b c d e f g h i j k l m n o p q r s t	20	- Olanzapine versus placebo So many people left these studies early (olanzapine 61%, placebo 73%) that all results, except the one of leaving the study early, are so full of assumptions that confident interpretation is impossible...Clinical interpretation of a weighted mean difference of -0.523 is, however, problematic. When analysed by dose, the effect was only seen with the 15mg/day and 10mg/day olanzapine groups. - Olanzapine versus typical antipsychotics There are no clear differences between olanzapine and typical drugs for the outcome of 'no important clinical response at 6-8 weeks'. Using odds ratios do make differences statistically significant but in these heterogeneous data with frequent events random effects relative risk analyses are advisable. The latter render the results not statistically significant. Relapse and CGI data support the suggestion that olanzapine is not conclusively clinically more effective than older typical drugs. - Olanzapine versus typical antipsychotics for those with treatment resistant illness It appears that olanzapine has similar global effects to typical antipsychotics on those with treatment resistant illness but this may reflect a Type II Error and these findings require replication. - Implications for clinical practice The very great losses to follow up make recommendations difficult. Global impression suggests that 10-15mg/day of olanzapine is antipsychotic, being better than placebo, but, for those with severe illness, when compared to typicals and atypicals there is little difference for the same outcome. On one sub-scale score, of one mental state rating scale, olanzapine shows superiority over typical antipsychotics for negative symptoms. This result is difficult to interpret clinically. Such findings need replication in large simple studies and should not form the evidence base of treatment recommendations. Olanzapine may have fewer extrapyramidal effects than chlorpromazine and haloperidol and, perhaps, than risperidone. Despite poor data, olanzapine seems to encourage swift weight gain. Currently not enough data relating to those with treatment-resistant schizophrenia are available to draw definitive conclusions.

Letters indicate the major publication for the study.
Roman numbers indicate further partial publications of previous studies' data.

a) Beasley C.M., Sanger T. & Satterlee W. (1996). Olanzapine versus placebo: results of a double-blind, fixed dose olanzapine trial. *Psychopharmacology* 124,159-167.

I) Tollefson G.D. & Sanger T.M. (1997). Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *American Journal of Psychiatry* 154, 466-474.

II) Tollefson G.D., Beasley C.M. Jr., Tamura R.N., Tran P.V. & Potvin J.H. (1997). Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *American Journal of Psychiatry* 154, 1248-1254.

V) Hamilton S.H., Revicki D.A., Genduso L.A. & Beasley C.M.Jr. (1998). Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology* 18, 41-49.

VII) Dellva M.A., Tran P., Tollefson G.D., Wentley A.L. & Beasley C.M.Jr. (1997). Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. *Psychiatric Services* 48, 1571-1577.

b) Beasley C.M., Tollefson G., Tran P. (1996). Olanzapine versus placebo and haloperidol. *Neuropsychopharmacology* 14, 111-123.

I) Tollefson G.D. & Sanger T.M. (1997). Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *American Journal of Psychiatry* 154, 466-474.

II) Tollefson G.D., Beasley C.M.Jr., Tamura R.N., Tran P.V. & Potvin J.H. (1997). Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *American Journal of Psychiatry* 154, 1248-1254.

III) Tran P.V., Dellva M.A., Tollefson G.D., Wentley A.L. & Beasley C.M.Jr. (1998). Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. *British Journal of Psychiatry* 172, 499-505.

IV) Tollefson G.D., Sanger T.M., Beasley C.M. & Tran P.V. (1998). A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. *Biological Psychiatry* 43, 803-810.

V) Hamilton S.H., Revicki D.A., Genduso L.A. & Beasley C.M.Jr. (1998). Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology* 18, 41-49.

VII) Dellva M.A., Tran P., Tollefson G.D., Wentley A.L. & Beasley C.M.Jr. (1997). Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. *Psychiatric Services* 48, 1571-1577.

c) Beasley C.M., Hamilton S.H. & Crawford A.M. (1997). Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *European Neuropsychopharmacology* 7, 125-137.

VII) Dellva M.A., Tran P., Tollefson G.D., Wentley A.L. & Beasley C.M.Jr. (1997). Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. *Psychiatric Services* 48, 1571-1577.

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VI) Tollefson G.D., Sanger T.M., Lu Y. & Thieme M.E. (1998). Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Archives of General Psychiatry* 55, 250-258.

e) Altamura A.C., Velona I., Curreli R. & Bravi D. (1999). Olanzapine in the treatment of Paranoid Schizophrenia. *European Neuropsychopharmacology* 9, 297.

f) Beuzen J.N., Birkett M., Kiesler G. & Wood A. (1998). Olanzapine versus clozapine in resistant schizophrenic patients - results of an international double-blind randomised clinical trial. In *Proceedings of XXIst Collegium Internationale Neuro-psychopharmacologicum*: Glasgow.

g) Conley R.R., Tamminga C.A., Bartko J.J., Richardson C., Peszke M., Lingle J., Hegerty J., Love R., Gounaris C. & Zaremba S. (1998) Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *American Journal of Psychiatry* 155, 914-920.

h) HGBJ (Finland) (*unpublished data only*). Eli Lilly. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

i) HGBL 1997 (*unpublished data only*) Eli Lilly. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

j) Vangala S., Zhang F., Tran P. & Sze S. (1998). Efficacy and safety study comparing olanzapine versus haloperidol in the treatment of Chinese patients with schizophrenia in Hong Kong. In *Proceedings of XXIst Collegium Internationale Neuro-psychopharmacologicum:* Glasgow.

k) Mraz K., Gogus A., Tunca Z., Martenyi F. & Dossenbach M. (2000). Olanzapine versus chlorpromazine in Turkey. In: *Winter Workshop on Schizophrenia. Schizophrenia Research.*

l) Zhang F., Tran P.V., Taylor C., Hwu G.H., Chen Y.S., Chang W.H., Cheng J., Wang A., Chang S., Sze S., Chen R.Y.K., Dunn E. & Lieh Mak F. (1999). Efficacy and safety study comparing olanzapine versus haloperidol in the treatment of Chinese patients with schizophrenia in Taiwan and Hong Kong. In *World Psychiatric Association*: Hamburg.

m) HGDV/Morocco. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

n) HGFH Korea. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

o) Jakovljevic M. & Dossenbach M.R.K. (1999). Olanzapine versus fluphenazine in the acute (six-week) treatment of schizophrenia. *Psychiatric Danubina* 11, 3-10.

p) Jones B. & Tollefson G. (1998). Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. *Schizophrenia Research* 29,150-151

q) Lecrubier Y., Bouhassira M., Olivier V., Lancrenon S. & Crawford A.M.. (1999). Olanzapine versus amisulpride and placebo in the treatment of negative symptoms and deficit states of chronic schizophrenia. *European Neuropsychopharmacology* 9, 288.

r) Loza N., El-Dosoky A.M., Okasha T.A., Khalil A.H., Hasan N.M., Dossenbach M., Kratky P. & Okasha A. (1999). Olanzapine compared to chlorpromazine in acute schizophrenia. *European Neuropsychopharmacology* 9, 291.

s) Thomas A., Grainger D., Andersen S. & Tollefson G. (1998). Olanzapine versus risperidone in the treatment of schizophrenia and related psychotic disorders. *Schizophrenia Research* 29, 147.

t) Tran P.V., Hamilton S.H., Kuntz A.J., Potvin J.H., Andersen S.W., Beasley C.Jr. & Tollefson G.D. (1997). Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *Journal of Clinical Psychopharmacology* 17, 407-418.

discrepancies illustrate the difficulties of appraising and using narrative reviews.

Cochrane systematic reviews use very comprehensive search strategies and include both published and unpublished studies (Cochrane Collaboration, 1995). This approach takes more time, but is likely to result in more reliable and less biased results and conclusions.

By addressing the methods of the identified primary studies, systematic reviews and meta-analyses can identify common methodological weaknesses and errors that might materially affect the results – these may be missed using a less systematic approach. For instance, Leucht *et al.* (1999) found that "all novel antipsychotics were associated with less frequent use of antiparkinson medication compared to haloperidol, ... but many of the trials used relatively high haloperidol doses as a comparison, which certainly favoured the emergence of EPS under this drug". This issue was investigated more formally in a meta-regression analysis that considered if the heterogeneity observed in the results of trials comparing atypicals with haloperidol might be related to the dose of haloperidol used (Geddes *et al.*, 2000). The key finding that higher doses of haloperidol comparator tend to overestimate the relative efficacy of the atypical has subsequently been replicated for risperidone in a further meta-regression (Davis & Chen, 2002). Furthermore, a systematic review of the limited direct randomised comparisons between lower and higher doses of haloperidol (Waraich *et al.*, 2002), found no difference in efficacy at that higher doses caused more extrapyramidal side-effects.

By weighting the trials and producing a pooled overall

estimate, which is a quantitative, rather than a qualitative assessment of the apparent strength of the results, systematic reviews may often conclude that the effect of a treatment is less impressive than a traditional narrative review would conclude.

If the randomised evidence remains inadequate to make valid and fully evidence-based policy statements, further large randomised trials are required; however, these require patients and clinicians to be in equipoise, or substantially uncertain, about alternative therapies. Premature clinical practice guidelines or expert opinion can lead to changes in clinical practice that make it difficult or impossible to conduct the required trials.

In the case of the atypical drugs, systematic reviews suggest that there are several key residual areas of uncertainty.

- How do the newer drugs compare to conventional antipsychotics in patients with no prior exposure to antipsychotic medication?
- Are the new drugs as effective as clozapine in patients who have not responded satisfactorily to conventional antipsychotic drugs?
- What are the long-term benefits and risks of the new agents?
- Are any advantages of the new drugs worth the increased cost? (Available for decades, conventional antipsychotics are inexpensive and therefore widely available even in countries with very limited resources).

MAKING FULL USE OF THE AVAILABLE DATA – INDIVIDUAL PATIENT DATA META-ANALYSES

The main effect of a trial gives an indication of the average response for an average patient meeting the inclusion criteria, but individual patients in real-life clinical practice deviate from the average to greater or lesser degrees. As we have said before, many trials in schizophrenia are small (Johnson, 1983; Thornley & Adams, 1998) and attempting to do a subanalysis of a subgroup trial participants with a specific characteristics will inevitably reduce the sample size and the statistical power of the results. Estimates of the treatment in subgroups of patients are always more susceptible to random error than the estimate of the average effect for all patients overall effect (Freemantle, 2001). Pooling the results from several trials in a meta-analysis can reduce random error and improve precision, but it is often impossible to do subgroup analyses because only the overall results of trials are reported. A potentially useful approach would be to conduct a meta-analysis of the raw data of the trials, to make an "individual patient data – meta-analysis" (Stewart & Clarke, 1995). In an IPD analysis it is possible to investigate potentially important baseline characteristics that might affect treatment response or prognosis, e.g. gender, age, race, family history, drug doses, dropping out, age of onset, number of previous episodes. Few individual patient data meta-analyses of the atypical antipsychotics have been attempted. Davis and Chen attempted a limited combined analysis of just 2 of 18 identified trials of risperidone – but this would obviously be highly susceptible to bias (Davis & Chen, 2002).

CONCLUSIONS

Systematic reviews seem more likely then narrative reviews to draw attention to the methodological limitations of the primary studies and the possibility of publication bias. In general, they may therefore produce more conservative conclusions that narrative reviews. Indeed, the main conclusion of a systematic review may often be that there is little good quality information in literature. Even this conclusion may be useful in that it highlights areas in need of further primary research.

When substantial data of adequate quality are available, meta-analyses in the context of a systematic review can make far better use of the available data than can a qualitative narrative review. Not only can meta-analysis formally investigate the reasons for variations in the results of individual studies, but it can also produce sufficient power to allow investigation of clinically important subgroups. Efficient analyses of subgroup effects require individual patient data , but such studies require considerable resource and collaboration between the primary triallists.

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