Outcomes in the pre- and post-antipsychotic eras

Kraepelin (1913) and Bleuler (1911) were influential in establishing a therapeutic nihilism regarding outcomes in schizophrenia. However, this case-based view was contradicted by early systematic studies (Langfeldt, 1937; Malamud and Render, 1938) which demonstrated that after approximately 10 years of illness in the pre-medication era, a full, or at least ‘social’ recovery was achieved in roughly 20% of all cases.

Similarly, the IOWA 500 follow-up study (Tsuang et al., 1979) used narrow diagnostic criteria in 200 cases of schizophrenia between 1895 and 1925, with institutional care as the only intervention, and of this cohort, 26% were discharged back to the community following index hospitalisation.

Two of the best long-term outcome studies in the post-antipsychotic era are the International Pilot Study of Schizophrenia (Sartorius et al., 1987) and that of Shepherd et al. (1989). Both these studies found that about a fifth of all cases made a complete recovery, and roughly half of all cases had a generally benign outcome at 2 years. These observations belie the earlier ‘Kraepelinian’ therapeutic nihilism.

In a meta-analysis of 320 studies spanning nearly a century, Hegarty et al. (1994) found that the number of patients who were clinically improved over a long-term follow-up approximately doubled in 1970 compared with 1920, with a significant moderating effect being attributed to the introduction of antipsychotic medication in the 1950s. However, other factors changed over this period too, including deinstitutionalisation, urbanisation, social and employment patterns, as well as innovations in rehabilitation and psychological therapies, as noted by Warner (1994). Wyatt (1991) also examined 19 studies, comparing the outcome of those (primarily first-onset) patients who were treated before and those treated after the advent of chlorpromazine. Wyatt also concluded that the use of medication increased the possibility of better long-term outcome. This is echoed by the findings of Robinson et al. (1999), who studied relapse rates in people in the 5 years after their first hospitalisation for a psychotic illness in the New York area. The relapse rate was over 80% after 5 years in their sample, and the two main independent risk factors predicting relapse were the pre-morbid level of functioning and poor adherence to prescribed antipsychotic medication.

Effectiveness versus efficacy of antipsychotic medication

Since the 1940s, randomised controlled trials (RCTs) have been the accepted method of establishing the efficacy of medical treatments due to high reliability and low intrinsic bias. Efficacy can be defined as ‘does an intervention produce a positive effect in the study variables under ideal conditions’. In psychiatry, traditionally RCTs usually have a pre-agreed change in score on a relevant rating instrument such as the Positive and Negative Syndrome Scale (PANSS) (von Knorring and Lindstrom, 1995) as the primary outcome variable. However, many clinicians would have difficulty in equating an arbitrary 20% or 40% change in the PANSS to their everyday practice, or deciding on whether a statistically significant change in mean score is clinically relevant.

Moreover, RCTs are generally undertaken by the pharmaceutical industry in order to meet regulatory requirements for drug
licensing, and positive results are generally associated with the study sponsor (Als-Nielsen et al., 2003) although this is not invariably the case (Fleischhacker et al., 2009), and more recent meta analyses from Leucht et al. (2009) and Davis et al. (2008) did not detect a significant sponsor effect. Lastly, RCT design (Heres et al., 2006) may also affect results, and negative trial drug results may not be put into the public domain.

RCTs measure efficacy, but the controlled environment of a RCT affects the generalisability of the results in the ‘real world’, especially when high drop-out rates, short trial duration, and the selection bias in patient recruitment are considered (Hodgson et al., 2007; Thornley and Adams, 1998). The drop-out rates of even relatively brief RCTs in medication trials in psychiatry can be up to 70% or even 80%, confounding the applicability of the results. In addition, large multicentre RCTs are expensive to conduct, which militates against undertaking long-term or maintenance studies.

Furthermore, in psychiatry the typical exclusion criteria of RCTs means that individuals with co-morbid substance misuse or serious physical illness, or those who are suicidal or only intermittently cooperative will not be enrolled; nor, importantly, will any woman who cannot guarantee that she will not become pregnant. This problem of recruiting representative ‘real-world’ clinical populations is illustrated by the graphic in Figure 1. Clearly this leads to a potentially unrepresentative RCT study population, which casts doubt on the generalisability of the results.

These limitations of RCTs have resulted in renewed interest in observational studies. Observational studies assess effectiveness, namely whether a treatment or intervention works in the ‘real world’ of day-to-day clinical practice. It has been shown (Mallinckrodt et al., 2003) that well-constructed observational studies do not overestimate treatment effects, and statistical methodologies can reduce the impact of non-randomisation. In addition, the lack of exclusion criteria can reduce selection bias (although this remains a concern), enhancing the utility of the results, particularly in large community-based samples. Observational studies are also generally much cheaper than RCTs, so can often be undertaken independent of any vested commercial interest.

The concept of treatment effectiveness can be subdivided into the constituents of efficacy, tolerability, and adherence. Clearly, efficacy is a crucial constituent, but an efficacious treatment only works if it is acceptable and used on a regular basis by the recipient or patient. Treatment acceptability is usually determined by whether the (subjective) beneficial effects are outweighed by the perception of intolerable treatment-related side effects, including any medically dangerous side effects.

The World Health Organisation has recently suggested that lack of adherence or compliance with maintenance treatment is a key obstacle in the management of long-term clinical conditions, leading to, for example, initiatives to pay people to adhere to their anti-tuberculous antibiotic therapy in parts of the USA. In the management of psychotic illness, medication adherence has long been known to be problematic, and the effectiveness of maintenance antipsychotic treatment is often undermined by poor medication adherence. Patel and David (2007) estimated an oral medication non-adherence rate in schizophrenia of between 40–60%, with adherence to long-acting injections of (or depot) antipsychotics being between 25–40%. Another major medication adherence problem that is commonly observed but poorly studied is the issue of partial adherence or compliance, where intentional or inadvertent intermittent or erratic medication dosing occurs. In the management of psychosis, partial adherence may lead to poor symptom control irrespective of an increased risk of relapse. Partial adherence to medication is commonly encountered in clinical practice, but not extensively studied.

Aren’t all antipsychotic medications the same?

Debate over class and intra-class differences in effect between antipsychotic medications was highlighted initially by a controversial meta-analysis from Geddes et al. (2000). This suggested the then newer (and more expensive) antipsychotic medications did not have superior efficacy to low-dose haloperidol. Interestingly, this conclusion was not adopted by the NICE guidelines in 2002 (National Institute for Clinical Excellence, 2002) which suggested second-generation antipsychotics (SGA) should be chosen in cases of first-episode psychosis, after consultation with the patient, although interestingly this recommendation was dropped in the later NICE schizophrenia guideline iteration (Kendall, 2011). This debate moved forward after a further independent meta-analysis of the RCT PANSS outcome data, by Davis et al. (2003). The Davis et al. (2003) study used a larger data set than Geddes et al. (2000) and found small but significant and clinically meaningful effect size differences (in PANSS-rated symptom reduction) between individual antipsychotics compared with haloperidol, as illustrated in Figure 2. Here, clozapine, olanzapine, risperidone and amisulpride were superior to first-generation antipsychotics (FGA) but quetiapine, aripiprazole, ziprasidone and sertindole were not. Davis et al. (2003) also challenged the belief that any apparent SGA superiority over FGA was merely a function of an excessively large haloperidol comparator trial dose.

Leucht et al. (2009) updated the Davis et al. (2003) meta-analysis of antipsychotic efficacy, and also concluded that there were small but important differences between individual antipsychotic medications. In particular, Leucht et al. (2009) found that amisulpride, olanzapine, and risperidone (but not other SGA) were more effective than low-dose haloperidol in terms of global symptoms and negative symptoms. A more recent meta-analysis of FGA
versus SGA in first-episode psychosis by Crossley et al. (2010) added weight to the original conclusions of Geddes et al. (2000) by finding that SGA were no different to FGA for either discontinuation rates (a proxy measure for effectiveness) or symptom efficacy. Crossley et al. (2010) did show that the side-effect profiles of the two groups were different, with FGA being more likely to cause movement disorders, and SGA more often associated with weight gain.

Setting the scene – the early effectiveness studies

The NIMH-funded landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies (Lieberman et al., 2005; Stroup et al., 2006) introduced a paradigm shift in outcome measurement in the treatment of schizophrenia by utilising medication discontinuation rate as a proxy for effectiveness, arguing that if either the clinician or patient discontinued the medication, then either it was not working or it was not being tolerated. After 18 months of randomised controlled study, olanzapine was found by Lieberman et al. (2005) to be the ‘most effective’ oral antipsychotic, despite inducing significant metabolic problems, although this phase of CATIE did not compare clozapine with olanzapine. A re-analysis of the CATIE data (Citrome and Stroup, 2006) produced an impressively low ‘number needed to treat’ (NNT) of between 5.5 and 10 for olanzapine compared with perphenazine, quetiapine, and risperidone. The corresponding ‘number needed to harm’ NNH for olanzapine ranged from -12.4 to -17.7 in terms of discontinuation from adverse metabolic effects. Clozapine (in phase 2 of CATIE) also had low NNT of 3 compared with risperidone and quetiapine, and 6.6 compared with olanzapine. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Studies (CUtLASS – Jones et al., 2006; Lewis et al., 2006) were sponsored by the UK National Health Services in an attempt to compare the effectiveness of the SGA versus FGA medication. Clinicians who entered patients into this study had to determine whether those individuals previously had a treatment-resistant illness or whether a switch of antipsychotic medication was indicated for other clinical reasons. Prescribing clinicians were free to opt for the individual antipsychotic of their choice from within two groups of medications. Quality of life was chosen as the primary outcome measure in the CUtLASS studies, although traditional ratings such as PANSS were also undertaken.

CUtLASS was a 1-year open label randomised study, and 227 people with schizophrenia were included. After 1 year in this study 54% of patients were still on FGA and 63% were still taking a SGA, although this difference was not statistically significant. Sulpiride was the FGA medication most frequently chosen (49%) by the participating clinicians.

There were no other significant differences in other relevant outcomes, including the primary outcome of quality of life. Owens (2008) has observed that sulpiride was originally regarded as an ‘atypical’ antipsychotic when it was first marketed in the 1970s, and indeed Owens comments that the term ‘atypical’ is no longer helpful in terms of understanding or dichotomising antipsychotic medication – a view now widely espoused (Kendall, 2011). It is also worth observing that CUtLASS failed to meet its predefined recruitment target – this might have been due to clinician preference for SGA over FGA (i.e. a lack of clinical equipoise). Lastly, as entrance to the CUtLASS study required the need for change in medication, a selection bias of patients who were either non- or partial responders or intolerant to the previous medication may have been introduced.

The effectiveness of antipsychotics in first-episode psychosis

Here, the important data concerning the effectiveness of antipsychotic medication in the context of treating the first episode of psychosis are reviewed. Tiihonen et al. (2006) studied people with first-episode schizophrenia in Finland using a National Hospital Discharge Register which identifies all individuals treated in hospital since 1967 and has good diagnostic validity (Isohanni et al., 1997; Suvisaari et al., 1999). Data on mortality and cause of death are also recorded by Statistics Finland, and all reimbursed drug prescriptions are registered by the nationwide Social Insurance Institution of Finland. These databases (which cover the entire population) were linked by Tiihonen et al. (2006) and the relative effectiveness of the most frequently used antipsychotic drugs among patients in the community after their first admission to hospital for schizophrenia or schizoaffective disorder was assessed using medication rate and rehospitalisation rate.

Tiihonen et al. showed that initial use of clozapine (adjusted relative risk 0.17, [95% confidence interval 0.10–0.29]), perphenazine depot (0.24, [0.13–0.47]), and olanzapine (0.35, [0.18–0.71]) were associated with the lowest rates of discontinuation for any reason when compared with oral haloperidol. Also, during an average follow-up of 3.6 years, current use of perphenazine depot (0.32, [0.22–0.49]), olanzapine (0.54, [0.41–0.71]), and clozapine (0.64, [0.48–0.85]) were associated with the lowest risk of rehospitalisation. Importantly, mortality was markedly raised in patients not taking antipsychotics (12.3, [6.0–24.1]) and the risk of suicide was even higher (37.4, [5.1–276]). These results suggest that there is a differential effectiveness between individual antipsychotic medications.

The CAFÉ study (McEvoy et al., 2007) was a comparison of SGA in first-episode psychosis funded by Astra Zeneca, the
manufacturers of quetiapine. CAFÉ was a double-blind comparison of quetiapine (100–800 mg per day), risperidone (0.5–4 mg per day), and olanzapine (2.5–20 mg per day). CAFÉ was coordinated in the USA, and all-cause discontinuation was the primary outcome measure.

The discontinuation rate over 50 weeks was high, around 70% for all the study medications. No significant advantage was identified for one antipsychotic medication over the other in terms of discontinuation rate. Furthermore, no significant differences were seen between the antipsychotic medications in changes on PANSS. Olanzapine did, however, have a higher rate of significant weight gain.

The European First Episode Study in Schizophrenia (EUFEST) trial (Kahn et al., 2008) was a 1-year multicentre pragmatic open label randomised comparison of four SGA, namely amisulpride, olanzapine, quetiapine and ziprasidone with low-dose haloperidol (mean dose 3 mg). Although sponsored by three pharmaceutical firms (Astra Zeneca, Pfizer, and Sanofi) the trial was described as independent as these companies were not involved in the study design or data analysis. The primary outcome was all-cause discontinuation, and the study population was 489 individuals with first-episode schizophrenia (defined as having no more than 2 years of prior psychotic symptoms).

Overall the combined discontinuation rate was 47% over 1 year. The all-cause discontinuation rate varied between 33% for olanzapine and 72% for haloperidol. In fact, all four SGA performed better than haloperidol on this primary outcome measure. One of the secondary outcome measures, the PANSS total score, did not differentiate between medication groups, but the clinical global impression scale and the global assessment of functioning scale did, in favour of SGA. Low-dose haloperidol produced more extrapyramidal side effects than the SGA, and hyperprolactinaemia was common with amisulpride.

Gau et al. (2008) undertook an independent economic comparison of SGA and haloperidol in a sample of over 3000 patients from a national Taiwanese data base. Study subjects were selected if they were discharged after a first episode of psychosis, and if their prescribed medication was antipsychotic monotherapy which was unchanged for at least 1 year. Individuals treated with SGA (clozapine, olanzapine, quetiapine risperidone, and zotepine) had a lower number and shorter duration of subsequent in-patient hospital episodes than those treated with haloperidol, except, surprisingly, for the clozapine group. Olanzapine was associated with the lowest hospitalisation rate, and economic analysis revealed that individuals prescribed haloperidol were the most expensive due to total hospitalisation costs.

As can be seen above, there is some discrepancy between the limited effectiveness data available in first-episode psychosis populations, even though the studies from Tiihonen et al., EUFEST and Gau et al. have some overlap in results consistent with the effectiveness data seen in more chronic populations. These discrepant data reflect the lack of differential effectiveness noted by Crossley et al. (2010) in their meta-analytic review.

Conclusions

Antipsychotic medication is known to improve outcome and reduce relapse rates in schizophrenia and related psychoses. Studies of the effectiveness of antipsychotic medications complement the RCT data as they arguably offer better external validity and generalisability. The debate concerning studies of efficacy versus effectiveness raises a number of important points about design and bias. It would appear that a hybrid methodology which combines large clinically representative populations with a design that also retains the essential ingredient of randomisation (even in an un-blinded method) may be an adequate compromise. This would offer a balance between scientific rigour on the one hand and generalisability to real-world clinical practice on the other. Building clear a priori hypotheses, a robust adverse event reporting system and some degree of statistical control into the pragmatic effectiveness studies would also aid credibility.

When considering the various antipsychotic trials in first-episode psychosis populations, despite their methodological differences, the EUFEST, Tiihonen et al. and Gau et al. studies appear to have some broadly similar results, with some but not all of the SGA (particularly olanzapine) being found to be more effective than FGA (particularly low-dose haloperidol). The CAFÉ study did not find a similar pattern of differential effectiveness. This lack of difference in terms of effectiveness, and indeed efficacy, has been echoed in the findings of a meta-analysis of 15 RCTs of antipsychotic medication in first-episode psychosis populations (Crossley et al., 2010) which did not find any statistically significant difference in efficacy or effectiveness between FGA and SGA. Equally important has been the observation that not using any antipsychotic medication after a first episode of psychosis significantly increases the risk of both all-cause death and suicide in these already pernicious illnesses (Tiihonen et al., 2006).

In view of these conflicting studies, the British Association of Psychopharmacology (Barnes, 2011) guideline on the treatment of schizophrenia focuses on side effects rather than differential efficacy, and recommends low starting doses in first-episode psychosis with careful side effect monitoring.

However, with regard to antipsychotic studies in chronic or ‘non’ first-episode populations, there does appear to be some consensus around the differential effectiveness of individual antipsychotics. Clozapine consistently comes out as highly effective (Farooq and Taylor, 2011) and, interestingly, a large study linking cause of death and antipsychotic use (Tiihonen et al., 2009) suggested that clozapine had the best record of any antipsychotic in terms of promoting longevity for people with schizophrenia. This superiority of clozapine is in agreement with other observational data from the UK (Hodgson et al., 2005; Taylor et al., 2008) but is at odds with a first-episode study from China which found no superiority for clozapine compared with chlorpromazine (Lieberman et al., 2003). It should be observed that in most countries, clozapine cannot be used in first-episode psychosis populations, so the findings noted above will not apply.

Clinicians will continue to base prescribing decisions on a variety of rational and non-rational factors, regardless of the debate over the ‘false dichotomy’ of FGA versus SGA. The factors influencing prescribing will include the scientific evidence base, patient choice, marketing influence, and the prescriber’s prior experience. Our review here of the effectiveness of antipsychotics also reinforces the notion of a ‘false dichotomy’, with some SGA (and presumably some FGA, although data are lacking) being more effective than others, perhaps even in first-episode psychosis populations. It is also recognised that predicting the response to a particular treatment for a specific individual can be very difficult, often becoming a matter of trial and error – this is where the art of psychiatry meets the scientific evidence base.
Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest
Mark Taylor, Richard Hodgson and Jari Tiihonen have received hospitality and/or fees from various manufacturers of antipsychotic medication including Eli Lilly. Jonathan Cavanagh has no conflicts to declare.

References


Davis JM, Chen N and Glick ID (2008) Issues that may determine the outcome of antipsychotic trials: industry sponsorship and extrapyramidal side effect. Neuropsychopharmacology 33: 971–975.


