trial requires it to be viewed in the context of the totality of evidence; the estimates of effect seen in IST-3 were comparable with, and reinforced the results of, previous trials.1

Fatovich and colleagues state that we had decided “ordinal analysis was not appropriate”; this was the view of the steering committee in 2009. However, as stated in the statistical analysis plan,1 that decision was altered in 2011, and the ordinal analysis was added, before the investigators were unmasked to the data, as a secondary outcome, because empirical evidence had emerged to show that the ordinal method was not only statistically more efficient (crucial given that the sample size had been reduced relative to the original target) but also robust against even substantial deviations from the proportional odds assumption.4

Smith believes that we changed the primary measure of outcome from the modified Rankin Scale to the Oxford Handicap Scale (OHS). We did not; we merely clarified that we would use the 1990 modification of the Rankin Scale (now referred to as the OHS) throughout.5

We agree with David Barer, David Curtis, and Newman and Shreves that discussions with patients and their families about the immediate risks of death and long-term benefits of thrombolysis should be informed by good quality data. IST-3 on its own lacks statistical power to provide reliable answers on whether rt-PA is more beneficial in specific categories—eg, severe strokes—or perhaps harmful at 3·0–4·5 h; such answers could emerge from the individual patient data meta-analysis by the Stroke Thrombolysis Trialists’ Collaboration, which will also provide the independent scrutiny suggested by Smith.

We declare that we have no conflicts of interest other than those stated in the original paper.

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Antipsychotic drugs for relapse prevention in schizophrenia

In their meta-analysis on antipsychotics for relapse prevention in schizophrenia, Stefan Leucht and colleagues (June 2, p 2063) found that these treatments reduced relapse rates at around 1 year (7–12 months) from 64% (placebo) to 27% (risk ratio 0·40, 95% CI 0·33–0·49; risk difference –39%, 95% CI –46 to –32); 24 randomised trials, published from 1962 to 2010, were included in this analysis.

Since these trials covered nearly 50 years, we used standard meta-regression techniques2–5 to examine the temporal trend of the primary result of Leucht and colleagues’ study. We thought our meta-regression to be worthwhile because other meta-regression covariates were assessed by these authors, but time was not.

In our meta-regression, the proportion of relapsed patients at 1 year showed a quite surprising tendency to increase over time. In the experimental (figure A) and control (figure B) groups, the tendency towards these worsened outcomes with time did not reach the conventional threshold of significance, but was close to it (p=0.058).

Anyhow, these findings clearly suggest that there has been no therapeutic improvement over

Figure: Meta-regression analysis (random effects model) of temporal trends of outcomes in patients with schizophrenia treated with antipsychotics versus controls: data from 24 randomised trials. Endpoint (relapse at 7–12 months) is separately shown for patients given antipsychotics (A) and controls (B). C shows timecourse of risk difference. In all panels, y-axis scale is 0–1. Regression equations are: RATE=0·004 × (YEAR–1960) + 0·12 (p=0·058) in A; RATE=0·006 × (YEAR–1960) + 0·478 (p=0·092) in B; RATE=−0·002 × (YEAR–1960) −0·33 (p=0·386) in C. Each study is represented by a circle, the diameter of which is proportional to its statistical weight.
50 years; this conclusion is also supported by meta-regression of risk difference (figure C), which indicates that the incremental benefit of antipsychotics has shown no significant change for 50 years (p=0.39).

One explanation is that this tendency towards worsened outcomes from 1960 to 2010 is a casual finding. Alternatively, it could reflect differences with time in other variables that could be further explored, particularly in these 24 randomised studies.

We declare that we have no conflicts of interest.

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Authors’ reply

Andrea Messori and colleagues’ analysis is important because it shows that efficacy differences between antipsychotic drugs and placebo remained stable over time. We interpret this finding in a positive way, because in other areas early trials (of potentially lower quality) seem to have yielded larger differences than more recent ones.1

We feel that, overall, the definitions of relapse have broadened in more recent studies, making the absolute risk of relapse for both drug and placebo groups larger. Expression of the difference as a risk ratio has the advantage that relative effect measures can account for some of the heterogeneity due to varying definitions of relapse.2 That being said, we have now done a meta-regression based on relative risks, and this confirmed Messori and colleagues’ analysis based on absolute risk differences, because it found no significant association between publication year and difference in relapse reduction (mixed effects, unrestricted, maximum-likelihood regression: slope 0.003, 95% CI −0.011 to 0.016, df=1, p=0.70).

We agree that the efficacy of most new second-generation antipsychotics is identical to that of most of the older first-generation antipsychotics, with a few exceptions (clozapine, amisulpride, olanzapine, and risperidone) which are somewhat more efficacious.3 But we emphasise that the difference in relapse prevention between antipsychotic drugs and placebo for schizophrenia seems to be one of the largest effect sizes achieved by most of the commonly used drugs in medicine.4

Finally, we agree that large meta-analyses such as this one deserve further exploration. Further meta-regressions showed that the following were not significantly associated with relapse reduction at 7–12 months: sex (slope 0.003, 95% CI −0.011 to 0.016; p=0.70); mean participant age (0.003, −0.024 to 0.019; p=0.82); duration of illness in years (0.003, −0.022 to 0.024; p=0.93); good versus bad or unclear compliance (test for subgroup differences heterogeneity Q=0.85, df=1, p=0.36); and single-centre versus multiple-centre design (Q=0.10, df=1, p=0.75).


2 Funakawa TA, Akitchi T, Wagenpfel S, Leucht S. Relative indices of treatment effect may be constant across different definitions of response in schizophrenia trials. Schizophr Res 2011; 126: 212–19.


The Irish health system and the economic crisis

The Irish economy has moved from roaring tiger to half-drowned kitten in the space of a few years, with knock-on effects for the health sector. From averaging more than 5% growth in the early 2000s, the economy shrank by over 10% between 2008 and 2010. Debt has ballooned from 25% of gross domestic product (GDP) in 2005 to more than 100% of GDP in 2010. Unemployment leapt from 4% to 14% in 4 years and the government has taken on the extensive debt of the banks. The bailout by the European Central Bank in late 2010 confirmed that there are no quick fixes for the current malaise of this multidimensional crisis.1

In consequence, the Irish health system has faced cuts to public funding of more than €2 billion, or a whopping 17% of the government health budget from 2010 to 2012. Health accounted for almost 30% of cuts to public expenditure between 2010 and 2012. These cuts have been achieved through general wage and fee reductions, voluntary