

Postgrad Med J 2005;81:545–546.
doi: 10.1136/pgmj.2004.031161

Correspondence to: Dr S Rajagopal, South London and Maudsley NHS Trust, Adamson Centre for Mental Health, St Thomas's Hospital, London SE1 7EH, UK; Sundararajan. Rajagopal@slam.nhs.uk

Funding: none.

Competing interests: none.

REFERENCES

- 1 Kane J, Honigfeld G, Singer J, *et al*. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45:789–96.
- 2 National Institute for Clinical Excellence. *Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. Clinical guideline 1*. London: NICE, 2002.
- 3 Alvir JM, Lieberman JA, Safferman AZ, *et al*. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* 1993;329:162–7.
- 4 Atkin K, Kendall F, Gould D, *et al*. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996;169:483–8.
- 5 Gillman K. Paradoxical pattern of haematological risk with clozapine. Authors' reply. *Br J Psychiatry* 2000;177:88.
- 6 Munro J, O'Sullivan D, Andrews C, *et al*. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br J Psychiatry* 1999;175:576–80.
- 7 Alvir JM, Lieberman JA, Safferman AZ. Do white-cell count spikes predict agranulocytosis in clozapine recipients? *Psychopharmacol Bull* 1995;31:311–14.
- 8 Pirmohamed M, Park K. Mechanism of clozapine-induced agranulocytosis. Current status of research and implications for drug development. *CNS Drugs* 1997;7:139–58.
- 9 Claas FH. Drug-induced agranulocytosis: review of possible mechanisms, and prospects for clozapine studies. *Psychopharmacology (Berl)* 1989;99(suppl):S113–17.
- 10 Meged S, Stein D, Sitrota P, *et al*. Human leukocyte antigen typing, response to neuroleptics, and clozapine-induced agranulocytosis in Jewish Israeli schizophrenic patients. *Int Clin Psychopharmacol* 1999;14:305–12.
- 11 Banov MD, Tohen M, Friedberg J. High risk of eosinophilia in women treated with clozapine. *J Clin Psychiatry* 1993;54:466–9.
- 12 Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med* 1999;133:15–22.
- 13 Shoenfeld Y, Alkan ML, Asaly A, *et al*. Benign familial leukopenia and neutropenia in different ethnic groups. *Eur J Haematol* 1988;41:273–7.
- 14 Kuno E, Rothbard AB. Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. *Am J Psychiatry* 2002;159:567–72.

Single subject design

Should the single subject design be regarded as a valid alternative to the randomised controlled trial?

R G Newcombe

For debate.

In an accompanying article Janine Janosky sets out the case for the use of single subject designs.¹ I was asked by my colleague Dr John Mayberry, the editor of the journal, to referee this paper, but felt it would be more appropriate to respond to it, largely to stimulate debate on this issue. I would suggest that the proper applicability of single subject designs is much narrower than this article would imply. I would furthermore warn readers of the dangers of a view that if left to grow unchecked could result in an important undermining of the dominance of the multi-patient randomised clinical trial that is now, with very strong justification, accepted as the cornerstone of evidence based clinical practice—with serious consequences for the choice of appropriate management for future patients. The two key issues are equivocation regarding the ambit of the single subject design, and the robustness of the inference to be drawn from data such as figure 1 in Janosky's paper.

It is well accepted that clinical expertise is needed to apply the findings of large clinical trials to the individual patient. The doctor's initial training,

ongoing CPD, and clinical experience facilitate the recognition of patients who are not "average" and for whom current evidence based guidelines, which are optimised for patient populations, may not be optimal. How to decide on management for a specific patient may be problematic. When the issue relates to maintenance treatment, the single patient design certainly has a role. For example, the patient may have two coexisting conditions for which the therapeutic requirements conflict. Another context is polypharmacy—perhaps the patient is currently taking four drugs, and the clinician suspects that one could be withdrawn without diminution of therapeutic effect.

In some parts of the article, including the six listed "possible research questions", Dr Janosky clearly implies that the research issue only applies to a specific patient. In other places, a broader scope is implied by phrases such as "unique study populations", "choosing the patient to participate", and "typical in terms of the practice demographics (and) for disease presentation and progression". Dr Janosky concedes that there is an issue of limited

generalisability. I would argue that a study of this kind cannot provide any reassurance that we can extrapolate the findings to other patients. One could say, to other similar patients, but what does similar mean in this context? Demographic, physiological, and diagnostic similarity are of little relevance here, the only similarity that matters relates to propensity to respond to the treatment in question, and this can neither be observed nor ensured. Conversely, the conventional large clinical trial relates to patients drawn from a population defined by well defined eligibility criteria, and random allocation ensures groups are comparable within limits of chance variation in respect of all possible variables, including counterfactual treatment response. This is what justifies applying the conclusions of the trial to patients at large who fulfil the eligibility criteria used in the trial.

The other key issue relates to drawing an "obvious" conclusion from a limited dataset. This is shaky on two counts, relating to clinical liability and statistical methodology. Dr Janosky refers to the patient "in need of lower fasting blood glucose values"—but there is such a thing as regression towards the mean (strictly, a misnomer, regression towards the mode would be a more apt description). The inference that the "switch" in figure 1 is real is strongly dependent on a presupposition that patients don't just "switch" spontaneously in this way. Perhaps this is reasonable in diabetes—it would not be for remitting/relapsing conditions such as inflammatory bowel disease or multiple sclerosis, and certainly not for thyroid disease or bipolar disorder. What Dr Janosky terms the "primary A-B single subject design", as used here,

is particularly vulnerable to criticism—while it is the simplest within subject design, it is the least adequately controlled, and effective blinding is unlikely to be achieved. The methodological issues arising in the familiar multi-subject crossover design are well known. Borrowing terminology commonly used in that context, the observed treatment difference could equally be interpreted as a period effect, or could be distorted by carry-over. In the example given, the treatment difference could be considerably confounded by seasonal differences.

Furthermore, with regard to statistical methodology, what is the implied cut off between a “real” difference and one that could be attributable to chance? For the data as shown, an unpaired two sample *t* test would give a highly significant *p* value, around 0.0001 here, but we do not have sufficient evidence to decide whether an assumption of Gaussian distributional form is reasonable, without considerable extrapolation from data on others. The non-parametric Mann-Whitney test is robust, and yields a two sided exact *p* value of 1 in 35 or 0.029. This is below 0.05, but much less extreme, normally a *p* value

of this magnitude would not be regarded as strongly convincing. A decision rule approach is more relevant. This might relate to a pre-agreed clinically importantly large difference—although this would share the non-robustness problem. Alternatively, one could abandon conventional hypothesis testing with a low α level and opt for a “pick the winner” approach with implied equal α and β rates. This corresponds more closely to the less formalised “trial and error” course of events that commonly occurs in clinical practice.

Dr Janosky’s stance contrasts quite sharply with that taken by Guyatt *et al.*² This highly informative review of the appropriate use of single subject trials was restricted to double blind, randomised, multiple crossover designs aiming to optimise management of a specific patient. Decisions about efficacy were based on a combination of a signed standardised difference measure of effect size *D* and a single tailed *p* value. Although my reservation above concerning unquestioned use of parametric methods still applies. Furthermore, an effect size criterion expressed in absolute terms (for example, fasting blood

glucose units) would be much more directly interpretable for clinical importance than a relative measure such as *D*.

Clinicians are forever “trying” patients with different treatments. Use of a single subject design, with additional rigour ensured by multiple periods, randomisation of treatments to periods and blinding, and perhaps some statistical analysis, is certainly one stage more formal and rigorous. But we should not imagine it is anything more than that: we can only validly draw conclusions about that one patient, in their present state, it would be very risky to extrapolate to ostensibly “similar” cases.

Postgrad Med J 2005;**81**:546–547.
doi: 10.1136/pgmj.2004.031641

Correspondence to: Professor R G Newcombe, Centre for Health Sciences Research, Department of Epidemiology, Statistics and Public Health, Wales College of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; newcombe@cf.ac.uk

REFERENCES

- 1 Janosky JE. Use of the single subject design for practice based primary care research. *Postgrad Med J* 2005;**81**:549–51.
- 2 Guyatt GH, Keller JL, Jaeschke R, *et al.* The *n*-of-1 randomized controlled trial: clinical usefulness. *Ann Intern Med* 1990;**112**:293–9.

Single subject design

Single subject trials in primary care

N A Francis

Lack of generalisability limits use.

From a GP’s perspective, the accompanying article by Janine Janosky on the single subject design is both interesting and stimulating.¹ This type of design, as Dr Janosky highlights, is infrequently used in research and has some potential advantages. Most notably, it is the only type of design that can provide information about effects at an individual level. There are obvious benefits in formalising what all GPs do on a day to day basis, namely observing the effects of individual treatments on individual patients. However, the article suggests a scope and potential for the *n* = 1 trial that I would take issue with, and the author fails to adequately describe the limits and disadvantages of this type of design.

While single subject designs have the potential of examining effects at an individual level, they do not provide

data that can readily be applied to others. The author does mention that the generalisability of results from this type of study is limited, but goes on to suggest that if a subject that is “representative of the general type of patients for which this intervention would be used” then the results become more generalisable. A person can be chosen that has a certain disease at a certain stage and with certain sociodemographic characteristics. But is this person really representative? How do we know exactly which variables are relevant to the effect being shown? And how can we judge “biological representation”. For example, are there aspects of a person’s metabolism that influences the way they respond to a drug? Furthermore, demonstrating an effect in a person, even if the person is similar to a population, provides little evidence

about the probable effects of an intervention on a population, or the effects on another, inevitably unique, person.

Other potential problems with single subject trials are problems of bias and the determination of statistical significance. Effects that are likely to lead to bias in this type of trial include regression to the mean and “carry-over” effects. Values towards the extremes are likely to normalise on repetition for statistical reasons, an effect that is described as regression to the mean. This will occur without any clinical change in the subject, and in a single subject trial is likely to lead to a false impression of treatment effect when none may be present. Secondly, the author describes using a washout period between different phases of treatment. However, treatments can have lasting effects and it can be difficult to distinguish whether any prior treatments or indeed the rotation of treatments plays a part in any observed effect. Furthermore, once a subject has “changed”, how can you ever really know what you are comparing to? Can change revert back to its original state in every way? After all, you can only ever be a virgin once!

Ways of attempting to minimise bias in *n* = 1 trials, as the author points out,