Royal College of General Practitioners Unit for Mental Health Education, Division of General Practice and Primary Care, St George's Hospital Medical School, London SW17 0RE
André Tylee, *director*

Lilly Industries, Dextra Court, Basingstoke RG21 2SY
Hiram Wildgust, *depression adviser*

Encouragingly, the percentage of patients receiving an effective dose of antidepressant increased, but this is accounted for entirely by the much greater increase in prescribing of selective serotonin reuptake inhibitors than tricyclic antidepressants. Although for the older tricyclic antidepressants the proportion of prescriptions for an effective dose and the average doses prescribed were unchanged, we note that the *British National Formulary* still has not adopted the consensus guidelines on antidepressant doses. However, Kerr found that only 52% of general practitioners would prescribe tricyclic antidepressants at a dose lower than that recommended by the consensus guidelines[3] compared with 86% in our study. This may reflect a difference between actual prescribing practice and what general practitioners say about their practice. Doctors may consider that low doses of tricyclic antidepressants offer effective treatment. They may be unaware of, or do not believe, the consensus guidelines or the results of clinical trials showing that tricyclic antidepressants prescribed at these doses are not beneficial in the treatment of depression. They may also lack confidence in prescribing at higher doses or fear that patients will find effective doses intolerable because of side effects.

So far as we are aware low doses of tricyclic antidepressants are ineffective. Failure to treat depression effectively contributes to relapse and the development of recurrent and chronic depression[1] and may be a contributory factor in suicide.[4] One study found that a large proportion of patients receiving long term treatment with antidepressants at low doses were still moderately to severely depressed during follow up.[5] Further research is urgently needed to determine why general practitioners continue to prescribe tricyclic antidepressants at low doses and to investigate the consequences of such prescribing on a large scale.

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1 Paykel ES, Priest RG. Recognition and management of depression in general practice: consensus statement. *BMJ* 1992;**305**:1198-202.
2 Turton P, Tylee A. Evaluation in setting up a large scale educational programme—principles and problems. *Education for General Practice* 1995;**6**:226-9.
3 Kerr MP. Antidepressant prescribing: a comparison between general practitioners and psychiatrists. *Br J Gen Pract* 1994;**44**:275-6.
4 Isacsson G, Holmgren P, Wassermen D, Bergman U. Use of antidepressants among people committing suicide in Sweden. *BMJ* 1994;**308**:506-9.
5 Ali IM. Depression in primary care: a study of long term antidepressant users [MSc thesis]. Cardiff: University of Wales, 1994.

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Statistics Notes

Interaction 3: How to examine heterogeneity

John N S Matthews, Douglas G Altman

This is the 26th in a series of occasional notes on medical statistics

Department of Medical Statistics, University of Newcastle, Newcastle upon Tyne NE2 4HH
John N S Matthews, *senior lecturer in medical statistics*

ICRF Medical Statistics Group, Centre for Statistics in Medicine, Institute of Health Sciences, PO Box 777, Oxford OX3 7LF
Douglas G Altman, *head*

Correspondence to:
Dr Matthews.

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In preceding *Statistics Notes* we introduced the concept of interaction[1] and explained why a common approach to the assessment of interaction is incorrect.[2] In this note we give details of the correct approach using the same two examples.

In a study of the effect of maternal vitamin D supplementation on neonatal serum calcium concentrations[3] the researchers were interested in the possible difference between the effect of supplementation on breast and bottle fed babies. We define the treatment effect in each feeding group to be the difference in the mean serum calcium concentration of babies receiving supplements and those receiving placebo in that group: the treatment means and observed effects in the feeding groups are given in table 1.

The first step is to compute the difference between the two treatment effects—that is, 0.10 − 0.04 = 0.06 mmol/l. The standard error of this difference is 0.056 mmol/l, found from the standard errors of the separate effects using the usual method for the standard error of a difference.[4] This is the same method that provides the standard error of a treatment effect from the standard errors of the treatment means. The P value can found from the ratio of the difference to its standard error, namely 0.06/0.056 = 1.07, again using standard methods,[4] which gives P = 0.28, showing there is no evidence that the effects are different between the two feeding groups. An approximate 95% confidence interval can be found for the difference in the treatment effects in the usual way,[4]—that is, as 0.06 ± 1.96 × 0.056, or − 0.05 to 0.17 mmol/l.

A similar approach is adopted with a binary outcome measure. In a controlled trial of antenatal steroid therapy for neonatal respiratory distress syndrome 27.3% (9/33) of babies born to mothers with pre-eclampsia and 14.1% (37/262) of babies born to mothers without pre-eclampsia in the control group developed neonatal respiratory distress syndrome; the corresponding figures in the steroid group were 21.2% (7/33) and 7.9% (21/267) respectively.[5] Once standard errors of each of these percentages have been found in the usual way[4] the method for assessing an interaction between steroid therapy and mother's pre-eclampsia is the same as for continuous outcomes. The treatment effect in babies of mothers with pre-eclampsia is 27.3 − 21.2 = 6.1% (standard error 10.5%) and in babies born to unaffected mothers it is 14.1 − 7.9 = 6.2% (standard error 2.7%), so the difference in treatment effects is 6.2 − 6.1 = 0.1% (standard error 10.9%), from which the P value for the difference in treatment effects is P = 0.99. Thus there is no evidence in this trial that the effect of antenatal steroids depends on whether the mother suffered from pre-eclampsia: the 95% confidence interval for the difference in the treatment effects can also be constructed as before, giving 0.1 ± 1.96 × 10.9 or − 21.3% to 21.5%.

Table 1—*Serum calcium concentrations (mmol/l) at 1 week in babies born to mothers given vitamin D supplements or placebo and analysed according to whether they were breast fed or bottle fed*

	Breast fed		Bottle fed	
Serum calcium	**Supplement**	**Placebo**	**Supplement**	**Placebo**
Treatment mean	2.45	2.41	2.30	2.20
Standard error	0.036	0.032	0.022	0.019
No	64	102	169	285
Treatment effect	0.04		0.10	
Standard error	0.048		0.029	
P value	0.40		0.0006	

1 Altman DG, Matthews JNS. Interaction 1: heterogeneity of effects. *BMJ* 1996;**313**:486.
2 Matthews JNS, Altman DG. Interaction 2: compare effect sizes not P values. *BMJ* 1996;**313**:808.
3 Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL, *et al.* Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. *BMJ* 1980;**281**:11-4.
4 Altman DG. *Practical statistics for medical research*. London: Chapman and Hall, 1991:160-7.
5 Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. *Am J Obstet Gynecol* 1981;**141**:276-87.