clinical state became serious with lethargy, aspontaneity, disinhibition and executive dysfunction.

Biological features were abnormal with elevated creatinine phosphokinase (3415 UI/l), increased C-reactive protein (3.7 mg/dl) and hepatic cytolysis. Her treatment consisted of cyclophosphamide and methylprednisolone, and the introduction of a titrating-dose (up to 600 mg) of quetiapine for the psychiatric symptoms was decided upon. Her creatinine phosphokinase levels returned progressively to normal, and no signs of neuroleptic malignant syndrome were observed. Six weeks after continuing this treatment, biological and clinical features were normalised.

This case illustrates the importance of differentiating delirium caused by a neuropsychiatric systemic lupus erythematosus, a steroid-induced delirium[1] (which was not the case here as the patient had not been receiving any steroids when she developed the second psychotic episode) and an alteration in the consciousness level due to neuroleptic malignant syndrome, which was the case here.

Although there are no guidelines for the treatment of the psychiatric manifestations of systemic lupus erythematosus, it usually includes immunosuppressants associated with second-generation antipsychotics.[3] The diagnosis of neuroleptic malignant syndrome is based on muscle rigidity, hyperthermia, delirium and autonomic disturbances.[4] The dopaminergic hypothesis of the syndrome is well documented.[5] Neuroleptic malignant syndrome is not an absolute contraindication for further antipsychotic treatment and some factors can reduce that risk: avoiding the long-term use of antipsychotics, using low-potency agents, adjunctive treatments and slow titration.[2]

In this case, we suggest that the introduction of quetiapine – a lower D_2-affinity antipsychotic – was an interesting alternative.

1 Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stallworth CL, Valdez CR, Escalante A, del Rincón I, Gronseth G, Rhine CB, Padilla P, McGlasson D. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. *Neurology* 2002; **58**: 1214–20.

2 Haddad PM, Dursun SM. Neurological complications of psychiatric drugs: clinical features and management. *Hum Psychopharmacol Clin Exp* 2008; **23**: 15–26.

3 Stojanovich L, Zandman-Goddard G, Pavlovich S, Sikanich N. Psychiatric manifestations in systemic lupus erythematosus. *Autoimmunity Rev* 2007; **6**: 421–6.

4 Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant ayndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004; **65**: 464–70.

5 Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry* 2007; **164**: 870–6.

Philippe Verdoot, MD, Eric L. Constant, MD, PhD and Arlette Seghers, MD, Université Catholique de Louvain, Cliniques Universitaires Saint Luc, Adult Psychiatric Unit, Belgium. Email: philippe.verdoot@uclouvain.be

doi: 10.1192/bjp.193.6.507a

Are antidepressants safe during pregnancy?

Ramos *et al*[1] report that the use of antidepressant medications by women during the first trimester of pregnancy is not associated with an increased risk for major congenital malformations in children. The authors have a good database to study this topic but have described and analysed it using a case–control framework. They assembled two cohorts, with and without exposure to antidepressants during pregnancy. They then observed the various outcomes in both groups. We calculated the relative risk (RR) for major congenital malformations following use of antidepressants during first trimester of pregnancy as 1.13 (95% CI 0.86–1.48) from their published data. Estimating such relative risk and population attributable risk (5.76%) would have bolstered their arguments, as a cohort design is superior to a case–control strategy.

However, we suggest caution in generalising these findings because of two important limitations that were not acknowledged in their paper. If antidepressants are associated with more spontaneous abortions and an increased number of minor congenital anomalies, their lack of association with major congenital anomalies will not imply safety. A previous meta-analysis of 3567 women established a significantly increased RR of 1.45 (95% CI 1.19–1.77) for spontaneous abortions following use of antidepressants during pregnancy.[2] Individual antidepressants such as selective serotonin reuptake inhibitors[3] and other newer antidepressants[4,5] have led to more miscarriages when compared with unexposed control groups. As Ramos *et al* have included exclusively women who had their pregnancies ending in delivery, they do not add any information regarding spontaneous abortions.

In another study of 482 pregnant women,[6] fluoxetine caused significantly more prematurity (RR=4.8, 95% CI 1.1–20.8), more admissions to special care nurseries (RR=2.6, 95% CI 1.1–6.9) and worse neonatal adaptation (RR=8.7, 95% CI 2.9–26.6) after adjusting for all potential confounders. A total of 15.5% of infants exposed to fluoxetine had three or more minor congenital anomalies compared with 6.5% of infants who were not exposed to fluoxetine (P=0.03).[6] However, Ramos *et al* excluded minor congenital anomalies during case ascertainment without any explicit justification. Absence of association between use of antidepressants and major congenital malformations will not make a clinician confident to continue antidepressants during the first trimester of pregnancy if there are concerns over spontaneous abortions, prematurity and minor congenital anomalies. Hence, we encourage cautious interpretation of these findings as well as judicious use of antidepressants for women of reproductive age.

1 Ramos E, St-André M, Rey E, Oraichi D, Bérard A. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *Br J Psychiatry* 2008; **192**: 344–50.

2 Hemels ME, Einarson A, Koren G, Lanctôt KL, Einarson TR. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005; **39**: 803–9.

3 Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihn S, Donnenfeld A, McCormack M, Leen-Mitchell M, Woodland C. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993; **269**: 2246–8.

4 Djulus J, Koren G, Einarson TR, Wilton L, Shakir S, Diav-Citrin O, Kennedy D, Voyer Lavigne S, De Santis M, Einarson A. Exposure to mirtazapine during pregnancy: a prospective, comparative study of birth outcomes. *J Clin Psychiatry* 2006; **67**: 1280–4.

5 Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, Shakir S, Einarson A. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 2005; **192**: 932–6.

6 Chambers C, Johnson K, Dick L, Felix R, Jones KL. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996; **335**: 1010–5.

Anto P. Rajkumar, **K. S. Jacob**, Department of Psychiatry, Christian Medical College, Vellore-632002, India. Email: antoprajkumar@cmcvellore.ac.in

doi: 10.1192/bjp.193.6.508

Authors' reply: The nested case–control approach that we used is the most effective design to study rare outcomes such as major congenital malformations.[1,2] This is even truer since it was performed in a well-established cohort of women with pre-pregnancy diagnosed psychiatric disorders. We disagree with Rajkumar & Jacob that a cohort approach would have been better, based on the fact that it lacks power for research in perinatal pharmacoepidemiology. This was clearly apparent when several small human cohort studies published in the 1990s did not suggest

https://doi.org/10.1192/bjp.193.6.508a Published online by Cambridge University Press

an overall increased risk for birth defects with first-trimester exposure to any selective serotonin reuptake inhibitors but later studies with more efficient designs such as the case–control approach started showing low-to-moderate increased risks for the more commonly occurring birth defects such as heart defects, neural tube defects and oral clefts. Therefore, using a cohort approach would have resulted again in a null finding, contrary to Rajkumar & Jacob's comments.

We excluded pregnancies ending with abortion or miscarriage per design since malformation outcomes of these foetuses were not available in the Quebec Pregnancy Registry. We agree that this resulted in prevalent cases of malformations in our study but this is highly comparable to studies performed in similar populations. We do not, however, agree that this methodological choice resulted in biasing our study estimates towards the null. Indeed, although Hemels *et al*[3] reported an association between antidepressant use during pregnancy and risk of spontaneous abortion, this was based on women's self-report and likely resulted in an overestimation of the rate of miscarriage and an underestimation of the rate of abortion, hence a significant association.

Major congenital malformations are structural abnormalities that affect the way a person looks and require medical and/or surgical treatment. Minor defects are abnormalities that do not cause serious health or social problems. Major defects were the focus of interest in our study and, although the risk of minor malformations is interesting, it is a different research question. Several other authors have previously made this distinction.[4,5]

We agree that results from observational studies always need to be interpreted with caution. However, given that from an ethical point of view it is almost impossible to randomise pregnant women to receive medications not known to be safe for the foetus, the collection and follow-up of observational data is the only ethical way to close the knowledge gap between the limited value of animal studies and human pregnancy exposures.

Finally, our study was not designed to look at the effect of the duration of specific antidepressants on the risk of specific major congenital malformations. Therefore, we only looked at duration of antidepressant use during the first trimester of gestation and its risk for major congenital malformations, all types and all malformations combined. Results should be interpreted in this context.

Declaration of interest

This study was supported by the Fonds de la Recherche en Santé du Québec (FRSQ, grant number: 6263), the Réseau Québécois de Recherche sur l'Usage des Médicaments (RQRUM), and the FRSQ network for the well-being of children.

1 Ramos E, St-André M, Rey E, Oraichi D, Bérard A. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *Br J Psychitary* 2008; **192**: 344–50.

2 Hernández-Díaz S, Hernán MA, Meyer K, Werler MM, Mitchell AA. Case-crossover and case-time-control designs in birth defects epidemiology. *Am J Epidemiol* 2003; **158**: 385–91.

3 Hemels MEH, Einarson A, Koren G, Lanctôt KL, Einarson TR. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005; **39**: 803–9.

4 Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. *Am J Psychiatry* 2002; **159**: 2055–61.

5 Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996; **335**: 1010–5.

Anick Bérard, **Élodie Ramos**, Faculty of Pharmacy, University of Montreal, Pavillon Jean-Coutu, Local 2244, Montreal, and Medications and Pregnancy Research Center, Sainte Justine Hospital, Montreal, Canada. Email: anick.berard@umontreal.ca

doi: 10.1192/bjp.193.6.508a

Structural equation modelling in developmental psychiatry

The paper Green & Dunn[1] may prove to be of merit in the interpretation of causal relationships between interventions and outcomes. In particular, the recommendation that randomised controlled trial (RCT) methodology should be embedded within statistical methods from observation studies is long overdue. Such an approach would greatly assist in the interpretation of results which seem completely counterintuitive to those in everyday clinical practice. One such result is the finding of Byford *et al*[2] that cognitive–behavioural therapy provides no added or separate advantage to selective serotonin reuptake inhibitors in the treatment of adolescent depression.

I have a quibble with the length of time it has taken for basic concepts on causality introduced by Green & Dunn to appear in psychiatric research. These concepts have been commonplace in social science research for more than 20 years and their section on causal inference in analysis is little more than a primer. For a more complete coverage of principles of causality, I can recommend Judea Pearl's book, *Causality: Models, Reasoning and Inference*.[3]

Is there any particular reason why Green & Dunn, having put their toes in the water by introducing basic concepts on causality, have not taken their paper further or are we to await a follow-up? In particular, why is there no mention of structural equation modelling, otherwise known as covariance structure analysis? Structural equation modelling has been extensively used in social science research for the past 20 years and adaptations of the method such as multiple-indicator, multiple-cause (MIMIC) seem to address the issues on confounding variables adequately without the need to revert to RCT methodology. It would be interesting to hear from Green & Dunn their thoughts as to how necessary would RCT methods be in developmental psychiatry research whenever a structural equation model is being employed.

1 Green J, Dunn G. Using intervention trials in developmental psychiatry to illuminate basic science. *Br J Psychiatry* 2008; **192**: 323–5.

2 Byford S, Barrett B, Roberts C, Wilkinson P, Dubicka B, Kelvin RG, White L, Ford C, Breen S, Goodyer I. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive–behavioural therapy in adolescents with major depression. *Br J Psychiatry* 2007; **191**: 521–7.

3 Pearl J. *Causality: Models, Reasoning and Inference*. Cambridge University Press, 2000.

Don MacFarlane, Belfast Health, Social Services and Public Safety Trust, Ireland. Email: donmac@doctors.org.uk

doi: 10.1192/bjp.193.6.509

Authors' reply: We thank Dr MacFarlane for his favourable comments on our views. The development of research designs that can rigorously test the complexities of mental health intervention and also have face validity to clinicians is at the centre of our concern. In a brief editorial we could do no more than whet the readers' appetites. There was no mention of structural equation modelling because of lack of space, and not because we do not have sympathies with the technique. In fact, one of us (G.D.) has taught structural equation modelling for nearly 20 years.[1] When used wisely and with correctly specified models, structural equation modelling approaches can be very powerful – but they do not obviate the need for good design (including the randomisation in an RCT). In particular, MacFarlane is mistaken when he suggests that the use of structural equation modelling (MIMIC)