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Evidence needed for treatment strategies in refractory depression

Matthews & Elijamel (2003) lucidly describe the origin, mechanism and role of vagus nerve stimulation (VNS) in the treatment of refractory depression.

Lack of evidence for strategies to treat refractory depression and lack of perceived options necessitate a fresh look into research on the efficacy of existing treatments and development of new ones. Vagus nerve stimulation may prove to be an effective option and a major advancement, but it is too early even to speculate on recommending it for general use.

The authors state, "If any treatment for chronic, refractory depressive disorder were to offer the prospect of sustained, clinically significant changes in 20–30% of patients, this would represent a major therapeutic advancement". However, our systematic review of treatment of refractory depression (Stimpson *et al*, 2002) showed an overall placebo response rate of 15% with 95% CI of 7.9–23.4%. This rate is even higher in relatively less chronic depression, reaching up to 30–40% in some trials. Hence, the response rate of 31% in open trials for VNS may largely be due to placebo response and may not result in a satisfactory 'number needed to treat' in randomised trials.

The need for further research in this area cannot be overemphasised. Authors have highlighted the difficulty of finding an appropriate control condition. Even if we can satisfy the need for an appropriate placebo control, these trials should not be considered sufficient. For evidence to be robust, any new treatment for refractory depression should at least be compared with the existing active treatments, such as augmentation strategies, in addition to placebo control. Non-inferiority trials without active treatment comparison are not only unethical, they do not help clarify the question of what is the next best strategy in a particular patient with refractory depression. The second half of the past century saw a number of commonly used treatment strategies based only on preliminary evidence. Let us not perpetuate the same mistake in the 21st century.

Matthews, K. & Eljamel, M. S. (2003) Vagus nerve stimulation and refractory depression. Please can you switch me on doctor? *British Journal of Psychiatry*, **183**, 181–183.

Stimpson, N., Agrawal, N. & Lewis, G. (2002) Randomised controlled trials investigating pharmacological and psychological interventions for treatment refractory depression. Systematic review. *British Journal of Psychiatry*, **181**, 284–294.

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Drug misuse in pregnancy

I read with interest the recent editorial by Johnson *et al* (2003) and I agree with the authors that substance misuse, including in women of reproductive age, has increased markedly over the past 20 years. In my practice of obstetrics and obstetric anaesthesia, I have provided care to many drug-misusing parturients and would like to add some comments on this timely topic.

Five million Americans are regular users of cocaine, 6000 use the drug for the first time each day and more than 30 million have tried cocaine at least once. Approximately 250 000 women in the USA meet the criteria for intravenous drug abuse. Nearly 90% of these women are of childbearing age (Kuczkowski, 2003). Psychological personality characteristics seem to predispose to, rather than result from, drug addiction. Most often, drug misuse is first suspected or diagnosed during medical management of another condition such as hepatitis, HIV/AIDS or pregnancy. Most parturients with a history of drug misuse deny it when interviewed preoperatively by primary care physicians, obstetricians or obstetric anaesthesiologists. A high index of suspicion for drug misuse in pregnancy, combined with non-judgmental questioning of every parturient, is therefore necessary (Kuczkowski, 2003). Risk factors suggesting substance misuse in pregnancy include lack of prenatal care, history of premature labour and cigarette smoking. Substances most commonly misused in pregnancy include cocaine, amphetamines, opioids, ethanol, tobacco, marijuana, caffeine and toluene-based solvents. Polysubstance misuse is very common. The diverse clinical manifestations of substance misuse, combined with the physiological changes of pregnancy and the pathophysiology of coexisting pregnancy-related disease, might lead to life-threatening complications and significantly affect the pregnancy outcome.

Johnson, K., Gerada, C. & Greenough, A. (2003) Substance misuse during pregnancy. *British Journal of Psychiatry*, **183**, 187–189.

Kuczkowski, K. M. (2003) Anesthetic implications of drug abuse in pregnancy. *Journal of Clinical Anesthesia*, **15**, 382–394.

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The article by Johnson *et al* (2003) was disappointing as they failed to present a balanced view of this topic. It is, of course, important to discuss possible effects of drug misuse on pregnancy, but to emphasise them without due and thorough consideration of the many confounding factors in this area is misleading. These include smoking, alcohol use, social deprivation, poor nutrition, quality of antenatal care and drug treatment, as well as accessibility of services. Clearly, these are additional factors that drug-misusing women will have to contend with. Well-designed, unconfounded studies in this area are rare, which means that findings on the specific effects of illicit drugs are inconsistent and contradictory (Ford & Hepburn, 1997).

The article failed to reflect that much of the recent work in this area has looked at flexibility of treatment services and equity of access. Women drug users are deterred from engaging with health and social care providers because of judgmental attitudes (Klee *et al*, 2002). We felt that the article

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