▶ Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in Mexican parolees.

Brodie J.D., Case B.G., Figueroa E. et al.

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Severely cocaine-dependent Mexican parolees were the test bed for an epilepsy medication known after long-term use to damage vision in a substantial proportion of patients. It seemed to help at least interrupt cocaine use and also cut drinking, but are the risks worth it?

Summary Vigabatrin is an antiepileptic medication which raises the concentration of a neurotransmitter (GABA) in the brain, in turn blunting the effects of cocaine. Previously tried with some apparent success in Mexico for patients dependent on cocaine or methamphetamine, this was the first trial to randomly allocate patients to the drug versus a placebo – the best way to tell whether the drug is the active ingredient rather than influences such as the patient's expectations of the treatment and contact with the clinic.

Patients were 103 cocaine-dependent former inmates of a prison in Mexico who were now out on parole, recruited through ads and word of mouth at a parole centre. Participation in the study was voluntary, and neither participation nor response to treatment as assessed by urine tests (confidential to the study) had any effect on the patients' parole or other legal status or privileges. Patients had to be currently using cocaine as indicated by urine tests, but not heroin or methamphetamine, not dependent on drugs other than cocaine, alcohol, nicotine, or cannabis, and to have had no previous treatment for cocaine use. Nearly all men, patients averaged 30 years of age and had been dependent on cocaine for about nine years. All had previously tried to stop using the drug. Typically they scored as suffering relatively severe mental health problems.

Consumption of drug and placebo were supervised by staff during twice-weekly clinic visits, but other doses were taken away to be used at home. The study treatments lasted nine weeks, after which patients were followed up for another four weeks. Throughout patients were also offered weekly individual cognitive-behavioural therapy focused on supporting abstinence, in accordance with routine practice at the clinic.

Main findings

The primary outcome was sustained urine-confirmed abstinence from cocaine over the last three weeks of the nine-week treatment phase; similar measures had previously been found indicative of longer term abstinence.

Of the 50 vigabatrin patients, 31 completed treatment compared to 22 of the 53 placebo patients, a statistically significant difference of 62% versus about 42%. All the patients who did not finish treatment had been terminated because they did not attend the clinic for a week. They were transferred to usual parole procedures and neither prescribed the study's medications nor urine tested or otherwise assessed by the study.

Missed urine tests were counted as indicative of cocaine use. On this basis, many more vigabatrin patients achieved sustained end-of-treatment abstinence – 28% versus 7.5%, a statistically significant difference. Though a few of these patients later relapsed, the advantage gained by vigabatrin continued in to the four-week follow-up phase. Results were similar whether or not pre-treatment intensity of cocaine consumption and years of dependence had been taken in to account (these were unrelated to outcomes), and when patients were 'allowed' one lapse during the last three weeks of treatment.

Only during two of the last three weeks of the trial did weekly abstinence rates significantly favour the vigabatrin patients, and the two groups did not significantly differ when cocaine use was assessed by the number of urine tests which were free of cocaine, or by the patients' own accounts.

Among pre-treatment drinkers, those taking vigabatrin were seven times more likely (44% versus 6%) than placebo patients to say they had not drunk alcohol at all in the last three weeks of treatment. Vigabatrin patients also experienced greater average reduction in irritability and improvement in appetite, but there were no significant differences in cocaine craving, other measures of psychological health, or in the frequency of possible side-effects, none of which were serious.

The authors' conclusions

The trial provides evidence of the efficacy and safety of vigabatrin in promoting short-term cocaine abstinence in patients with long-standing and severe dependence on cocaine. Compared to placebo patients, proportionately four times as many patients taking vigabatrin achieved sustained end-of-trial abstinence from cocaine, and the chances of abstinence in any particular week were almost three times higher by the end of treatment.

Vigabatrin was well tolerated by the patients, and there were no significant safety differences compared to a placebo. The major serious adverse effect which has been recorded is defective peripheral vision which remains even when the drug is stopped. That risk is (but not universally) believed to emerge only after patients have taken 1500g of the drug in total. In this study where doses totalled 131.5g, and in another with the same doses, tests revealed no such abnormalities.

Short-term tolerability, ease of administration (in this study, dissolved in fruit juice), long duration of action, renal excretion without metabolism, and the fact that it itself seems unlikely to be abused, contribute to vigabatrin's promise. However, important questions remain. Treatment of cocaine dependence characterised by binges rather than stable chronic use has not been evaluated, and the risk of visual defects after long-term vigabatrin treatment remains unclear. Moreover, the trial was conducted in a non-academic setting in a resource-poor nation. There was regular oversight of the conduct of the study, but no independent, daily on-site monitoring, so the results must be treated with caution.

FINDINGS The as yet unsuccessful search for a drug to which can be recommended for cocaine dependence prompts yet further trials of compounds which would not normally be considered, of which vigabatrin is an example. Its apparent effects also on drinking (often alcohol and cocaine are taken together) add to its potential attractions, but the risk of serious side effects is likely to limit routine use.

An editorial in the same journal issue says the featured trial "brings up several ethical issues", recalling that side effects which commonly (30% to 50% of patients) cause severely limited vision mean the drug now has only a restricted role in the management of epilepsy – in the USA, only for treatment-refractory partial seizure disorders in adults and infantile spasm of sufficient severity that the benefits outweigh possible vision loss.

The editorial says such defects have only been seen after over 12 months on the drug, but nevertheless asks, "Can the benefits of the treatment of cocaine and alcohol dependence ever outweigh the risk of vision loss?" Given the consequences of severe cocaine dependence, the answer for this authority seems to be that it can.

Britain's national formulary says vigabatrin-linked visual field defects have emerged after "from 1 month to several years after starting" on the drug, are generally irreversible, and may get worse. Visual field testing before treatment and at six-month intervals is recommended, patients should be warned to report any new visual symptoms that develop, and those with symptoms should be referred for an urgent ophthalmological opinion. Particular caution is also warranted in patients with a history of psychosis, depression, or behavioural problems, all of which can be aggravated by the drug, and are common among dependent substance users.

Cocaine dependence is not particularly resistant to psychosocial interventions plus for the more severe cases ongoing and residential care. Using any medication would need to be justified against this background, especially one which demands such careful monitoring and raises such risks. It does however remain conceivable that very severe cases resistant to other forms of treatment would warrant trying vigabatrin *if* it were likely to be effective, especially cases in which damaging cocaine use is entangled with heavy drinking.

The featured study cannot be considered a sufficient guide to likely effectiveness, partly because of the particular nature of the sample (male former prisoners from a single prison), and partly because it is unclear whether vigabatrin really did generate cocaine abstinence, or whether it was just that more placebo patients dropped out and their missing urine tests were assumed positive for cocaine. When attention was focused on the tests actually taken, there was no significant difference in the number free of cocaine, and nor was there any when the patients' own accounts were the criterion.

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