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- Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70.
- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289:454-65.
- Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA* 2003;290:921-8.
- The Cochrane Collaboration. The Cochrane Collaboration—principles. www.cochrane.org/docs/tenprinciples.htm (accessed 18 Sept 2006).
- Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M, et al. Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. *JAMA* 1998;280:278-80.
- Jadad AR, Moher M, Browman GP, Booker L, Sigouin C, Fuentes M, et al. Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. *BMJ* 2000;320:537-40.
- Oxman AD, Guyatt GH. Guidelines for reading literature reviews. *Can Med Assoc J* 1988;138:697-703.
- Jadad AR, McQuay HJ. Meta-analyses to evaluate analgesic interventions: a systematic qualitative review of their methodology. *J Clin Epidemiol* 1996;49:235-43.
- Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;44:1271-8.
- Berlin JA. Does blinding of readers affect the results of meta-analyses? *Lancet* 1997;350:185-6.

- Moja LP, Telaro E, D'Amico R, Moschetti I, Coe L, Liberati A. Assessment of methodological quality of primary studies by systematic reviews: results of the metaquality cross sectional study. *BMJ* 2005;330:1053.
- Konstant MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001;104:2280-8.
- Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004;364:2021-9.
- Cochrane Collaboration. Commercial sponsorship and the Cochrane Collaboration. www.cochrane.org/docs/commercialsponsorship.htm (accessed 16 June 2005).
- Götsche PC. Steroids and peptic ulcer: an end to the controversy? *J Intern Med* 1994;236:599-601.
- Katerndahl DA, Lawler WR. Variability in meta-analytic results concerning the value of cholesterol reduction in coronary heart disease: a meta-analysis. *Am J Epidemiol* 1999;149:429-41.
- Chalmers TC, Berrier J, Sacks HS, Levin H, Reitman D, Nagalingam R. Meta-analysis of clinical trials as a scientific discipline. II: replicate variability and comparison of studies that agree and disagree. *Stat Med* 1987;6:733-44.
- Linde K, Willich SN. How objective are systematic reviews? Differences between reviews on complementary medicine. *J R Soc Med* 2003;96:17-22.
- Götsche PC, Pødenphant J, Olesen M, Halberg P. Meta-analysis of second-line antirheumatic drugs: sample size bias and uncertain benefit. *J Clin Epidemiol* 1992;45:587-94.
- Cook DJ, Reeve BK, Guyatt GH, Heyland DK, Griffith LE, Buckingham L, et al. Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. *JAMA* 1996;275:308-14.
- Olsen O, Götsche PC. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2001;4:CD001877.
- Hopayian K. The need for caution in interpreting high quality systematic reviews. *BMJ* 2001;323:681-4.

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DRUG POINTS

Epileptic seizures can follow high doses of oral vardenafil

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Case report

An otherwise healthy 60 year old man was prescribed 10 mg of vardenafil (Levitra, Bayer) for sexual dysfunction. Because this was ineffective, he increased the dose to 40 mg. Three hours later, he had a tonic-clonic seizure, seen by his relatives. On admission to hospital, neurological examination, brain magnetic resonance imaging, and electroencephalography after sleep deprivation were normal. Stress electrocardiography, echocardiography, and cardiac scan with dipyridamole test as well as carotid doppler ultrasonography did not show concomitant cardiac diseases. The man was told to stop using vardenafil.

Two months later he had a new tonic-clonic seizure, four hours after taking 30 mg of vardenafil. At eight months' follow-up he is seizure-free without treatment.

Discussion

In this man, the seizures were unlikely to be the manifestation of other diseases: a complete screening ruled this out. And in both occasions seizure occurred within a few hours after he took vardenafil.

Vardenafil is a selective oral phosphodiesterase type 5 (PDE5) inhibitor effective in erectile dysfunction.¹ Adverse events include headache, flushing, nasal congestion, and dyspepsia.¹⁻² Convulsions were not reported to Bayer during clinical trials of vardenafil.¹⁻² However, people taking sildenafil (Viagra, Pfizer), another inhibitor of this type, have had seizures.³

PDE5 inhibitors increase nitric oxide leading to increased cyclic guanosine monophosphate (cGMP), with relaxation of the smooth muscle in the corpus

cavernosum and increased blood flow to the penis.¹⁻²

Recent evidence indicates that these inhibitors may increase effects mediated by nitric oxide. Although the role of nitric oxide in the pathophysiology of epilepsy remains debated, the effects of nitric oxide and cGMP signalling pathway on seizure threshold⁴ raise the possibility that nitric oxide may mediate mechanisms that alter susceptibility to seizure. Furthermore, sildenafil has shown a pro-convulsant effect on seizure threshold, interacting with exogenously and endogenously released nitric oxide.⁵ However, the exact role of PDE5 in altering susceptibility to seizure via this pathway remains unclear.

After we submitted this drug point, a 78 year old patient presented with partial epileptic seizure after oral intake, for the second time, of 10 mg of vardenafil.⁶ This confirms that epileptic seizures may occur during treatment with phosphodiesterase inhibitors.

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- Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs* 2003;63:2673-703.
- Hatzichristou D, Montorsi F, Buvat J, Laferriere N, Bandel T, Porst H. The efficacy and safety of flexible-dose vardenafil (Levitra) in a broad population of European men. *Eur Urol* 2004;45:634-41.
- Gilad R, Lampl Y, Eshel Y, Sadeh M. Tonic-clonic seizures in patients taking sildenafil. *BMJ* 2002;325:869.
- Przegalinski E, Baran L, Siwanowicz J. The role of nitric oxide in chemically- and electrically-induced seizures in mice. *Neurosci Lett* 1996;2173:145-8.
- Riazi K, Roshanpour M, Rafiei-Tabatabaei N, Homayoun H, Ebrahimi F, Dehpour AR. The proconvulsant effect of sildenafil in mice: role of nitric oxide-cGMP pathway. *Br J Pharmacol* 2006;147:935-43.
- Koussa S, Hage Chahine S, Tohme A, Riachi M. Epileptic seizures and vardenafil. *Rev Neurol (Paris)* 2006;162:651-2.

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