animal studies should be acknowledged, since some reports[11] have suggested that rimonabant might have antidepressant or anxiolytic actions. Another observation that might provide an alternative physiological basis for increased mood disorders seen with greatest weight-loss comes from evidence that leptin, the adipose-derived hormone, had an antidepressant action after intrahippocampal but not hypothalamic injection.[12] However, direct clinical correlates are difficult to draw.

What is the significance of the findings reported by Christensen and colleagues? First, their meta-analysis has raised major questions about the safety of rimonabant in obese people, who are already at an increased risk of depression, especially since the FDA review suggests that the risk of suicide is increased by use of this agent. Moreover, at least four other companies have CB_1 antagonists in phase II or III development. The findings of Christensen and colleagues' meta-analysis suggest that phase III studies of such CB_1 antagonists should monitor psychiatric complications very carefully. Second, the link between depression and this CB_1-receptor blocker raises theoretical questions about a potential central role for the endocannabinoid system in both normal and clinical mood states.[13]

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1 Di Marzo V, Matias I. Endocannabinoid control of food intake and energy balance. *Nat Neurosci* 2005; **8:** 585–89.
2 Cooke D, Bloom S. The obesity pipeline: current strategies in the development of anti-obesity drugs. *Nat Rev Drug Disc* 2006; **5:** 921–31.
3 Curioni C, Andre C. Rimonabant for overweight or obesity. *Cochrane Database Syst Rev* 2006; **4:** CD006162.
4 Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *Lancet* 2007; **369:** 71–77.
5 Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007; **370:** 1706–13.
6 Onyike CU, Crum RM, Lee HB, et al. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2003; **158:** 1139–47.
7 Food and Drug Administration Endocrinologic and Metabolic Advisory. June 13, 2007. Briefing Information, NDA 21-888 ZIMULTI (rimonabant)—Sanofi-Aventis. 2007. http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4306b1-00-index.htm (assessed Aug 6, 2007).
8 Gobbi G, Bambico FR, Mangieri R, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad Sci USA* 2005; **102:** 18620–25.
9 Hill MN, Ho WS, Sinopoli KJ, et al. Involvement of the endocannabinoid system in the ability of long-term tricyclic antidepressant treatment to suppress stress-induced activation of the hypothalamic-pituitary-adrenal axis. *Neuropsychopharmacology* 2006; **31:** 2591–99.
10 Moreira FA, Kaiser N, Monory F, et al. Reduced anxiety-like behaviour induced by genetic and pharmacological inhibition of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) is mediated by CB1 receptors. *Neuropharmacology* 2007; published online July 19. DOI:10.1016/j.neuropharm.2007.07.005.
11 Griebel G, Stemmelin J, Scatton B. Effects of the cannabinoid CB1 receptor antagonist rimonabant in models of emotional reactivity in rodents. *Biol Psychiatry* 2005; **57:** 261–67.
12 Lu X-Y, Kim CS, Frazer A, et al. Leptin: a potential novel antidepressant. *Proc Natl Acad Sci USA* 2006; **103:** 1593–98.
13 Vinod KY, Hungund BL. Role of the endocannabinoid system in depression and suicide. *Trends Pharmacol Sci* 2006; **27:** 539–45.

Benefits and risks of homoeopathy

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Five large meta-analyses of homoeopathy trials have been done. All have had the same result: after excluding methodologically inadequate trials and accounting for publication bias, homoeopathy produced no statistically significant benefit over placebo.[1–5] And yet homoeopathy can still be clinically useful.

During the cholera epidemic in the 19th century, death rates at the London Homoeopathic Hospital were three times lower than those at the Middlesex Hospital.[6] The reason for homoeopathy's success in this epidemic is even more interesting than the placebo effect. At the time, nobody could treat cholera, and while medical treatments such as blood-letting were actively harmful, the homoeopaths' treatments were at least inert.

Similarly, modern medicine can offer little for conditions such as many types of back pain, stress at work, medically unexplained fatigue, and most common colds. Going through a theatre of medical treatment, and trying every drug in the book, will only elicit side-effects. An inert pill in these circumstances seems a sensible option.

However, just as homoeopathy has unexpected benefits, so it can have unexpected side-effects. The very act of prescribing a pill carries its own risks: medicalisation, reinforcement of counterproductive illness behaviours, and promotion of the idea that a pill is an appropriate response to a social problem, or a modest viral illness.

Similarly, when a health-care practitioner of any description prescribes a pill which they know is no more effective than placebo—without disclosing that fact to

their patient—then they disregard both informed consent and their patient's autonomy. Some could argue that this cost is acceptable, but such old-fashioned paternalism can ultimately undermine the doctor–patient relationship.

There are also more concrete harms. A routine feature of homoeopaths' marketing practices is to denigrate mainstream medicine. One study found that half of all homoeopaths who were approached advised patients against the measles, mumps, and rubella vaccine for their children.[7] A television news investigation found that almost all homoeopaths who were approached recommended ineffective homoeopathic prophylaxis for malaria, undermined medical prophylaxis, and did not even give simple advice on bite prevention.[8] Undermining medicine is a wise commercial decision for homoeopaths, because survey data show that a disappointing experience with mainstream medicine is one of the few features to regularly correlate with a decision to use alternative therapies. But it might not be a responsible choice.

Homoeopaths can undermine public-health campaigns; leave their patients exposed to fatal diseases; and, in the extreme, miss or disregard fatal diagnoses. There have also been cases of patients who died after medically trained homoeopaths advised them to stop medical treatments for serious medical conditions.[9,10]

All these problems have been exacerbated by society's eagerness to endorse the healing claims of homoeopaths, and by the lack of a culture of critical self-appraisal in alternative medicine. Publication bias in alternative therapy journals is high: in 2000, only 5% of studies published in complementary or alternative health journals were negative.[11] To my knowledge, the ethical issues of autonomy and placebo have never been discussed. Homoeopaths routinely respond to negative meta-analyses by cherry-picking positive studies. An observational study,[12] which amounts to little more than a customer-satisfaction survey, has been promoted[13] as if it trumps a string of randomised trials.

Homoeopaths can misrepresent scientific evidence freely to an unsuspecting and scientifically illiterate public, but in doing so they undermine the public understanding of what it means to have an evidence base for a treatment. This approach seems particularly egregious when academics are working harder than ever to engage the wider public in a genuine understanding of research,[14] and when most good doctors try to educate and involve their patients in the selection of treatment options.

Every criticism I have made could be managed with clear and open discussion of the problems. But homoeopaths have walled themselves off from academic medicine, and critique has been all too often met with avoidance rather than argument. The Society of Homeopaths (in Europe) has even threatened to sue bloggers,[15] and the university courses on alternative medicine which I and others have approached have flatly refused to provide basic information, such as what they teach and how.[16] It is hard to think of anything more unhealthy.

To ban homoeopathy would be an over-reaction, as placebos could have a clinical role. However, whether the placebo effect is best harnessed by homoeopaths will remain questionable until these ethical issues and side-effects have been addressed.

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1 Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homoeopathy. *BMJ* 1991; **302:** 316–23.
2 Boissel JP, Cucherat M, Haugh M, Gauthier E. Critical literature review on the effectiveness of homoeopathy: overview of data from homoeopathic medicine trials. Brussels, Belgium: Homoeopathic Medicine Research Group. Report to the European Commission. 1996: 195–210.
3 Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. *J Alter Complement Med* 1998; **4:** 371–88.
4 Cucherat M, Haugh MC, Gooch M, Boissel JP. Evidence of clinical efficacy of homeopathy: a meta-analysis of clinical trials. *Eur J Clin Pharmacol* 2000; **56:** 27–33.
5 Shang A, Huwiler-Müntener K, Nartey L, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet* 2005; **366:** 726–32.
6 Hempel S. The medical detective. London, UK: Granta Books, 2006.
7 Schmidt K, Ernst E. Aspects of MMR. *BMJ* 2002; **325:** 597.
8 Jones M. Malaria advice 'risks lives'. *Newsnight*, BBC2 July 13, 2006. http://news.bbc.co.uk/1/hi/programmes/newsnight/5178122.stm (accessed Nov 8, 2007).
9 General Medical Council Fitness To Practise Panel. Dr Marisa Viegas. 2007. http://www.gmc-uk.org/concerns/hearings_and_decisions/ftp/20070628_ftp_panel_viegas.asp (accessed Nov 8, 2007).
10 Sheldon T. Dutch doctor struck off for alternative care of actor dying of cancer. *BMJ* 2007; **335:** 13.
11 Schmidt K, Pittler M, Ernst E. Bias in alternative medicine is still rife but is diminishing. *BMJ* 2001; **323:** 1071.
12 Spence DS, Thompson EA, Barron SJ. Homeopathic treatment for chronic disease: a 6-year, university-hospital outpatient observational study. *J Altern Complement Med* 2005; **11:** 793–98.
13 Grice E. Keep taking the arsenic. *Daily Telegraph* Nov 25, 2005. http://www.telegraph.co.uk/health/main.jhtml?view=DETAILS&grid=P8&xml=/health/2005/11/25/hhomeo25.xml (accessed Nov 8, 2007).
14 Evans I, Thornton H, Chalmers I. Testing treatments: better research for better healthcare. London, UK: British Library, 2006.
15 Goldacre B. Threats, the homeopathic panacea. *Guardian* Oct 20, 2007. http://www.guardian.co.uk/science/2007/oct/20/homeopathy (accessed Nov 6, 2007).
16 Giles J. Degrees in homeopathy slated as unscientific. *Nature* 2007; **446:** 352–53.