ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (6): 501-509
0114-5916/11/0006-0501/$49.95/0

Risk of Depressive Episodes with Rimonabant

A Before and After Modified Prescription Event Monitoring Study Conducted in England

Yvonne Buggy,[1,2] *Victoria Cornelius*,[1,2] *Lynda Wilton*[1,2] and *Saad A.W. Shakir*[1,2]

1 Drug Safety Research Unit, Bursledon Hall, Southampton, UK
2 University of Portsmouth, School of Pharmacy and Biomedical Sciences, Portsmouth, UK

Abstract

Background: Marketing authorization for rimonabant was withdrawn in October 2008, mainly because the psychiatric adverse effects could not be addressed by further risk minimization.

Objective: The aim of the study was to compare the risk of major and minor depressive episodes in the 6 months prior to and the 6 months after starting treatment with rimonabant.

Methods: We conducted a before and after study using the observational cohort technique of Modified Prescription Event Monitoring to compare the risk of major and minor depressive episodes in new users of rimonabant reported in the 6 months before to the 6 months after starting treatment with rimonabant. Patients were identified from dispensed prescriptions issued by primary care physicians from June 2006 to October 2008. Patient demographics and information on depressive episodes were requested 6 months after the date of the first prescription for each patient. Risk ratios (RR) were calculated by comparing before and after events using a matched analysis.

Results: The cohort comprised 10 011 patients. The number of patients who had major depressive episodes before and after starting treatment were 147 and 168, respectively (RR 1.14; 95% CI 0.94, 1.39) and the number of patients who had minor depressive episodes were 825 and 829, respectively (RR 1.00; 95% CI 0.93, 1.10). For patients who had a previous history of psychiatric illness (n = 1132), 91 and 73, respectively, experienced major depressive episodes (RR 0.80; 95% CI 0.62, 1.03), and 367 and 220, respectively, experienced minor depressive episodes (RR 0.59; 95% CI 0.53, 0.68). For patients without a previous history of psychiatric illness (n = 8879), 56 and 95, respectively, experienced major depressive episodes (RR 1.7; 95% CI 1.2, 2.3), and 458 and 609, respectively, experienced minor depressive episodes (RR 1.33; 95% CI 1.20, 1.48).

Conclusions: When comparing all patients in the cohort, there was no increased risk of developing a depressive episode whilst taking rimonabant.

However, when considering subsets of patients with and without a previous history of psychiatric illness, the risk profiles were different. In patients without a previous history of psychiatric illness, there were more depressive episodes in the 6 months after starting treatment compared with the 6 months before starting treatment with rimonabant.

Background

Rimonabant (Acomplia®; Sanofi-Aventis, Guilford, Surrey, UK) was launched in the UK in June 2006. It was licensed as an adjunct to diet and exercise for the treatment of obese (body mass index [BMI] ≥30 kg/m^2) and overweight (BMI >27 kg/m^2) patients with associated risk factors, such as type 2 diabetes or dyslipidaemia.[1] Marketing authorization was withdrawn in October 2008 because the psychiatric adverse effects could not be addressed by further risk minimization.

Rimonabant is a selective cannabinoid-1 receptor antagonist that has been shown to suppress endogenous activation of the endocannabinoid system.[2,3] The endocannabinoid system maintains a homeostatic state, and response to stressful stimuli is maintained through the release of endogenous cannabinoids. Blocking this system with rimonabant has the potential to interfere with the response to stressful stimuli, making anxiety, depression and other psychiatric effects more likely.[4]

Obesity is a chronic multifactorial disease[5] and as standards of living continue to rise, weight gain and obesity are posing a growing threat to public health worldwide. The WHO has estimated that approximately 300 million people worldwide are obese, which has considerable economic consequences for healthcare systems.[5] The most recent figures for the UK show that 24% of men and women were obese in 2007 (BMI ≥30 kg/m^2). In addition, 46% of men and 32% of women were overweight (BMI >27 kg/m^2).[6] Obesity is associated with a significant increase in morbidity and mortality and has also been linked to an increased risk of hypertension, heart disease, diabetes mellitus and cancer.[7-11] As a consequence of the growing public health impact of the obesity pandemic, the development of safe and effective anti-obesity medications is paramount.

An association between obesity and depression has long been proposed; however, the exact nature of this association has not been established.[12-15] The risk of depression appears to be increased in obese patients;[16-18] however, it has also been hypothesized that depression may be a predictive factor for future obesity.[13] At the time of rimonabant approval, psychiatric adverse effects, particularly depressive episodes, anxiety and sleep disorders, were identified as the main safety concerns.[1] This Modified Prescription Event Monitoring (M-PEM) study, which started in June 2006, was included in the risk management plan for rimonabant with the aim of expanding the safety knowledge and calculating the risk of depressive episodes occurring in patients prescribed rimonabant in general practice. In July 2007, the Committee for Medicinal Products for Human Use (CHMP) recommended the contraindication of rimonabant in patients with major depression or those being treated with antidepressants.[19] In October 2008, the marketing authorization was suspended because the available data indicated that rimonabant was less effective in clinical practice than was predicted from clinical trial data, and the psychiatric adverse effects could not be addressed by further risk minimization.[20]

At the time of withdrawal, the available post-marketing safety information was limited. Van Gaal et al.[21] reported anxiety, mood alterations with depressive symptoms and depressive disorders among the most common adverse events experienced by users of rimonabant (20 mg/day) in a phase III trial.[1,21] In a further study by Després et al.,[22] depression, anxiety and nausea were identified as the three most common reasons for discontinuing rimonabant therapy. In this M-PEM study, the most commonly reported reasons for discontinuing therapy were depression,

nausea and mood change. A meta-analysis of four double-blind, randomized, controlled trials (RCTs) for rimonabant (20 mg/day) showed an increased risk of psychiatric adverse events, including depressed mood and anxiety.[15,23]

PEM is a non-interventional observational methodology and typically collects information on large cohorts of patients (frequently over 10 000). The prescribing decisions of general practitioners (GPs) are not influenced by this methodology. PEM studies are conducted on a national scale and include patients prescribed newly marketed medicines in everyday clinical practice. Hospital prescriptions are not included in PEM studies. M-PEM methodology can be employed to investigate a variety of drug-related issues.[24] During this study, patient characteristics 6 months prior to exposure to 6 months after starting treatment with rimonabant were collected. In addition, information about medical history of psychiatric illness 6 months prior to starting treatment with rimonabant was collected.

The objective of the study was to compare the risk of major and minor depressive episodes[25] in the 6 months prior to and the 6 months after starting treatment with rimonabant.

Methods

A before and after study on an inception cohort of patients prescribed rimonabant in England was conducted, using the technique of M-PEM, described in more detail previously.[24] The key steps are outlined in figure 1.

Between June 2006 and October 2008 all dispensed National Health Service (NHS) prescriptions for rimonabant, issued by GPs in England, were collected and data supplied in confidence to the Drug Safety Research Unit (DSRU) by the NHS Prescription Services (NHSRxS) [part of the NHS Business Services Authority]. At least 6 months after the initial prescription for each patient, rimonabant study questionnaires were sent to prescribing GPs requesting information on major and minor depressive episodes that occurred in the 6 months before and the 6 months after starting treatment with rimonabant. Information about ongoing treatment for depression at the time of starting rimonabant and a previous history of psychiatric illness 6 months prior to the first prescription was also collected. Patient demographic details and drug utilization characteristics (indication for prescribing, BMI,

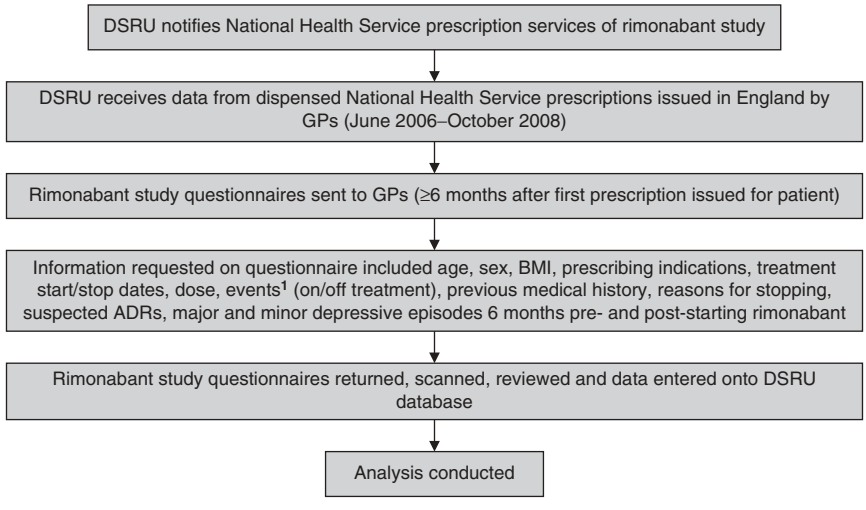

Fig. 1. Key steps in Prescription Event Monitoring (PEM). **1** In PEM, an event is defined as 'any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction that was considered of sufficient importance to enter in the patient's notes. Patient confidentiality is maintained throughout. **ADRs** = adverse drug reactions; **BMI** = body mass index; **DSRU** = Drug Safety Research Unit; **GPs** = general practitioners.

duration of treatment and reasons for discontinuing therapy if treatment was stopped) were among the data collected.

Information on patients for whom a rimonabant study questionnaire was returned was included in this study regardless of the dose or frequency of administration of rimonabant, and irrespective of whether any medicines were concurrently administered. Patients for whom any of the following applied were not included in the study: the rimonabant study questionnaire was returned with no information; the GP reported either that the patient did not take, or was never prescribed rimonabant; or the GP reported that the patient was no longer registered with the practice and no information was provided.

The *Diagnostic and Statistical Manual of Mental Disorders* was used to define major and minor depressive episodes[25] and this was attached to the rimonabant study questionnaire sent to the GP. GPs were offered £20 as reimbursement for administration costs for completing the study questionnaires. An event was coded as an adverse drug reaction (ADR) if the GP specified on the study questionnaire that the event was attributable to the drug. This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by CIOMS in collaboration with the WHO.[26]

Analysis

All analyses were pre-specified and conducted according to the study protocol. A before and after study was conducted comparing depressive episodes in the 6 months before to the 6 months after starting treatment with rimonabant. Depressive episodes were counted once according to the 'tick-box' question on the study questionnaire, which requested the GP to provide information on the first episode of major or minor depression that occurred in the 6 months before and the first episode after starting treatment with rimonabant. Using a before and after study design allows each individual patient to act as their own control. The same patients were being compared between the two time periods and, as a consequence, a matched-pair analysis was performed. The Mantel-Haenszel risk ratio (RR) between the two time periods and appropriate 95% confidence intervals (CIs) were calculated.[27] This analysis assumes that the decision to treat (with rimonabant) was not related to the event of interest (e.g. major or minor depressive episode). RRs and 95% CIs were computed using Stata's csmatch command.[28] The cohort was then stratified by patients with a previous history of psychiatric illness, and RR calculated for these subsets. Depressive episodes were only counted once according to the tick-box question on the study questionnaire.

Results

Study Cohort

Of the 21 535 study questionnaires posted, 11 207 (52.0%) were returned. Of these, 1196 (10.7%) were classified as void because they did not contain any data and were excluded from the study. Therefore, useful information was available on a cohort of 10 011 patients. The cohort consisted of 32.6% (n = 3266) males, 67.4% (n = 6743) females and for 0.02% (n = 2) sex was not specified. The median age of the cohort was 51 years, with an interquartile range (IQR) of 41–60 years. The median age was 54 years (IQR 46–61) for males and 49 years (IQR 39–59) for females. The median BMI prior to starting rimonabant was 38.7 (IQR 34.3–44; ranging from 20.8 to 116). The median was 38.4 (IQR 34–44; ranging from 20.8 to 116) for females and 39.2 (IQR 35.2–43.9; ranging from 22.3 to 116) for males. Thirteen percent (1132/8687) of the cohort (where specified) had a history of psychiatric illness prior to inclusion in the study. After 6 months, 43% of the cohort (n = 4292) were still taking rimonabant. There were 284 depressive events reported as reasons for stopping rimonabant, and 23 events were recorded as ADRs to rimonabant.

Risk Ratio (RR) for Major and Minor Depressive Episodes

There was no statistically significant difference detected in the risk of developing either a major

a

		6 months before		Total
		event	no event	
6 months after	Event	36	132	168
	No event	111	9732	9843
Total		147	9864	10011

Cohort matched-pair risk ratio 1.14; 95% CI 0.94, 1.39

b

		6 months before		Total
		event	no event	
6 months after	Event	255	574	829
	No event	570	8612	9182
Total		825	9186	10011

Cohort matched-pair risk ratio 1.00; 95% CI 0.93, 1.10

Fig. 2. Number of (**a**) major and (**b**) minor depressive episodes reported in the 6 months before and after starting rimonabant for all patients in the matched-pair analysis.

or minor depressive episode in the 6 months before compared with the 6 months after starting treatment with rimonabant (see figures 2a and b). However, the risk of a major depressive episode was 14% greater in the period after starting treatment compared with the period before starting treatment; this could be as low as 6% less or as high as 39% greater. The risk of minor depressive episodes was estimated to be the same between both time periods; however, this could have been as low as 7% less or 10% greater. The number of patients who had a major depressive episode was 147 before/168 after starting treatment (cohort matched-pair RR 1.14; 95% CI 0.94, 1.39) and the number of patients who had a minor depressive episode was 825 before/829 after starting treatment (cohort matched-pair RR 1.00; 95% CI 0.93, 1.10).

RR for Patients With and Without a Previous History of Psychiatric Illness

Major Depressive Episodes

In patients with a previous history of psychiatric illness, there were a higher number of patients with major depressive episodes in the 6 months before compared with the 6 months after starting treatment with rimonabant (91 before/73 after [cohort matched-pair RR 0.80; 95% CI 0.62, 1.03]). Treatment for depression was ongoing in 72.5% (66/91) of the patients who had a major depressive episode before starting treatment with rimonabant (figure 3a).

In patients without a previous history of psychiatric illness there were a lower number of major depressive episodes in the 6 months before compared with the 6 months after starting treatment with rimonabant (56 before/95 after [cohort matched-pair RR 1.70; 95% CI 1.20, 2.30]). Treatment for depression was ongoing in 48.2% (27/56) of the patients who had a major depressive episode before starting treatment with rimonabant (figure 3a).

Minor Depressive Episodes

In patients with a previous history of psychiatric illness, there were a higher number of minor depressive episodes in the 6 months before compared with the 6 months after starting treatment with rimonabant (367 before/220 after [cohort matched-pair RR 0.59; 95% CI 0.53, 0.68]). Treatment for depression was ongoing in 59.4% (218/367) of the patients who had a minor depressive episode before starting treatment with rimonabant (figure 3b).

In patients without a previous history of psychiatric illness there were a lower number of minor depressive episodes in the 6 months before compared with the 6 months after starting treatment with rimonabant (458 before/609 after [cohort matched-pair RR 1.33; 95% CI 1.20, 1.48]). Treatment for depression was ongoing in 37.3% (181/485) of the patients who had a minor depressive episode before starting treatment with rimonabant (figure 3b).

Discussion

To our knowledge, this is the first postmarketing observational cohort study including patients (n = 10 011) who were prescribed rimonabant in general practice in England soon after market launch up to the date of marketing authorization withdrawal (i.e. from June 2006 to October 2008). This study focuses on new users of rimonabant who had a major or minor depressive episode

reported in the 6 months before and/or after starting treatment for obesity.

Rimonabant was approved throughout the EU in June 2006, and in November of that year the first reports of psychiatric adverse effects were received by the European Medicines Agency (EMA). Contraindication in patients with major depression and also in patients taking antidepressants was subsequently recommended by the EMA in July 2007, with the marketing authorization being withdrawn in October 2008. The main reasons for withdrawal were that the psychiatric adverse effects could not be addressed by further risk minimization, and rimonabant was less effective in clinical practice than was predicted based on clinical trial data.[20] At the time of withdrawal, 44% of the spontaneous adverse event reports received for rimonabant by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK were psychiatric reactions, the most common being depression.[29] The most commonly reported reason for discontinuing rimonabant in this M-PEM study was depression. Overall, we detected no statistically significant difference in the risk of developing either a major or minor depressive episode in the 6 months before compared with the 6 months after starting treatment with rimonabant (see figures 2a and b).

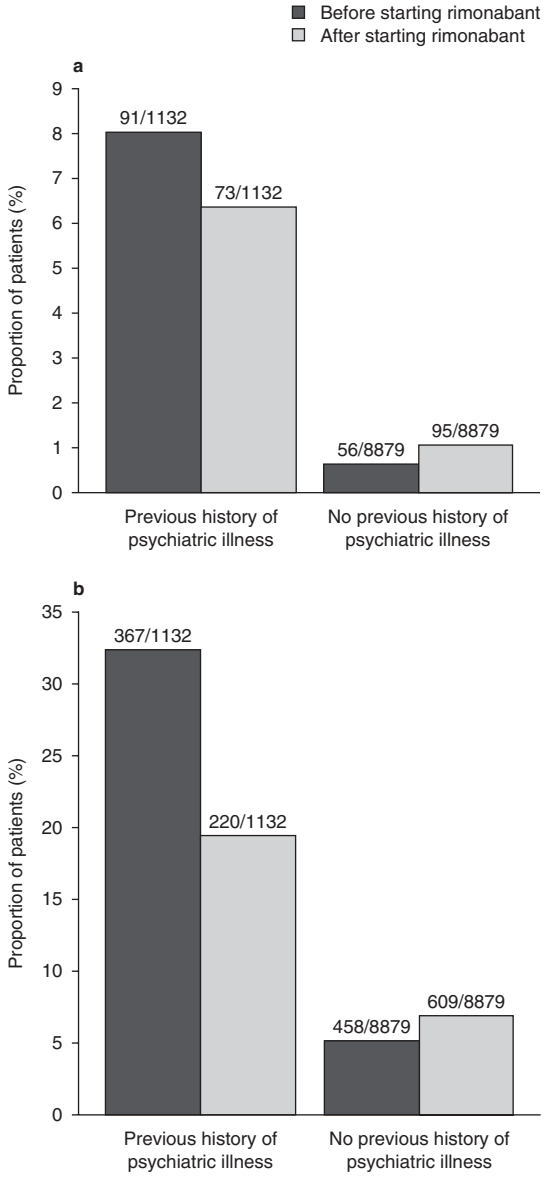

Fig. 3. Number of patients with and without a previous history of psychiatric illness who had (**a**) major and (**b**) minor depressive episodes in the 6 months before and after starting treatment with rimonabant.

However, when the data were stratified according to previous history of psychiatric illness, the risk of developing a minor depressive episode was estimated to be 41% lower (which was significant at the 5% level) in the 6 months after starting treatment with rimonabant in patients with a previous history of psychiatric illness. Likewise, the risk of developing a major depressive episode was estimated to be 20% lower in the 6 months after starting treatment with rimonabant; however, this was not significant at the 5% level (figures 3a and b). This was an unexpected finding based on the recommendation of contraindication of rimonabant in patients with major depression and in patients taking antidepressants.[19] However, treatment for depression was ongoing in the majority of patients who had either a major or minor depressive episode in the 6 months before starting treatment with rimonabant (72.5% for major depressive episodes and 59.4% for minor depressive episodes); therefore, these patients were not at the same risk of developing a depressive episode in the 6 months after starting treatment with rimonabant. Ongoing

antidepressant treatment may have accounted for the decrease in the number of reports of depressive episodes after starting treatment with rimonabant in patients with a previous history of psychiatric illness. In addition, at the time of withdrawal of the marketing authorization for rimonabant, the CHMP concluded that 'patients at an elevated risk of psychiatric illness could not be identified and introducing further restrictions would be unlikely to reduce the risk to an acceptable level.'[30] The results of this study suggest that it may be difficult to identify patients expected to have an increased risk of developing depressive episodes after starting treatment with rimonabant.

The opposite occurred in patients without a previous history of psychiatric illness. While the absolute changes in proportions were low, the relative differences were significant, indicating 70% (major depressive episodes) and 33% (minor depressive episodes) relative increases in the risk of developing a major or minor depressive episode in the 6 months after starting treatment with rimonabant, which were both significant at the 5% level. This finding suggests patients without a previous psychiatric history are at an increased risk of developing depressive episodes after starting treatment with rimonabant. These results are consistent with a meta-analysis conducted on four double-blind, RCTs for rimonabant, which suggested that rimonabant increased the risk of psychiatric adverse events, including depressed mood disorders. These trials had a highly selected enrolment process and patients with a previous history of depressed mood disorders or severe psychiatric illness were not included.[23]

The strengths and limitations of this study design have been described in detail elsewhere.[24] PEM is a non-interventional observational methodology; it does not influence the prescribing decisions of GPs. This study provided information regarding the use of rimonabant in general practice in England, irrespective of age, past medical history or concomitant medication. The before and after study design allows the patients to act as their own controls, thereby minimizing confounding by indication; however, reporting bias over time may be an issue. Patients may not have been equally likely to report a depressive episode in both time periods due to the possibility of more visits to the GP in the 'after' period as a result of follow-up appointments. The analysis assumes that the decision to treat with rimonabant was not related to the occurrence of depressive episodes. However, in July 2007, the EMA recommended against the use of rimonabant in patients taking antidepressants or those with major depression. This may have lead to a lower number of patients with a previous history of psychiatric illness being prescribed rimonabant following the communication by the EMA.[19]

This study comprised 10 011 patients, which is higher than the number of patients who were enrolled in clinical trials for rimonabant, where a meta-analysis of four RCTs for rimonabant included 4105 patients.[23] PEM studies have an advantage over clinical trials because of the greater number of patients included and also the lack of any selection criteria for inclusion in the study. Patients were included in this study regardless of any previous history of psychiatric illness.

As with all other observational studies, PEM lends itself to inherent weaknesses in the study design. One of these weaknesses may be the response rate. Of the rimonabant study questionnaires sent (n = 21 535), 11 207 (52.0%) were returned. This study did not assess the impact of non-response bias; however, the response rate is comparable to response rates reported elsewhere for GP postal surveys[31] and it is not thought that the reason for non-response is related to the outcomes of interest. Of the rimonabant study questionnaires returned, 10.7% of them were classified as void; the main reason for exclusion (29%) was because the patient was no longer registered at the practice. It is difficult to estimate accurately the exact rate of patient migration between GP practices; however, the latest figures available from the Office of National Statistics suggest a net increase in both interregional and international migration in the UK.[32] Therefore, it is reasonable to expect that a number of patients will have moved GP practice during the course of a PEM study.

In PEM, exposure is based on dispensed prescription data. These data are more accurate than exposure data based solely on written prescriptions.

However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. While it is not possible to be sure the patient used the medication, it is almost certain that the patient received it. Repeat prescriptions indicate the patient continued to obtain the medication.

If the result observed in this study is a true drug effect, the risk of depressive episodes after starting treatment with rimonabant may have been underestimated because not all patients were using rimonabant for the whole 6-month period. It was not possible to investigate this further because of the lack of dates for the occurrence of the depressive episodes supplied by the GPs. However, in this setting, it is interesting to speculate on the potential protective effect of antidepressant treatment in patients taking rimonabant who have a previous history of psychiatric illness. Counteracting the effects of one drug by another is a complex therapeutic manoeuvre that is merited in cases when the risk/benefit balance is considered favourable.

Conclusions

In this study, when comparing all patients, there was no increased risk of developing a depressive episode whilst taking rimonabant. However, when considering subsets of patients with and without a previous history of psychiatric illness, the risk profiles were very different. In patients with a previous history of psychiatric illness, there were more depressive episodes in the 6 months before compared with the 6 months after starting treatment with rimonabant. Conversely, in patients without a previous history of psychiatric illness, there were more depressive episodes in the 6 months after compared with the 6 months before starting treatment with rimonabant.

Acknowledgements

The DSRU is an independent charity (No. 327206) and is an Associate Department of the School of Pharmacy and Biomedical Sciences, University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or publication of the studies conducted by the DSRU. The DSRU has received such funds from the manufacturer of rimonabant.

Victoria Cornelius and Saad Shakir have received consultancy fees for work unrelated to this project. The other authors have no potential conflicts of interest to declare that are directly relevant to this study.

References

1. Sanofi-aventis. Acomplia: summary of product characteristics [online]. Available from URL: http://www.acompliareport.com/AcompliaSPC.htm [Accessed 2011 Feb 18]
2. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 2003; 63 (4): 908-14
3. Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov 2004; 3 (9): 771-84
4. Moreira FA, Lutz B. The endocannabinoid system: emotion, learning and addiction. Addict Biol 2008; 13 (2): 196-212
5. World Health Organization. Obesity: preventing and managing the global epidemic. Geneva: World Health Organization, 2000
6. Rennie KL, Jebb SA. Prevalence of obesity in Great Britain. Obes Rev 2005; 6 (1): 11-2
7. Bergstrom A, Pisani P, Tenet V, et al. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001; 91 (3): 421-30
8. Ducimetiere P, Richard J, Cambien F. The pattern of subcutaneous fat distribution in middle-aged men and the risk of coronary heart disease: the Paris prospective study. Int J Obes 1986; 10 (3): 229-40
9. Dyer AR, Elliott P. The INTERSALT study: relations of body mass index to blood pressure. INTERSALT Co-Operative Research Group. J Hum Hypertens 1989; 3 (5): 299-308
10. Larsson B, Svardsudd K, Welin L, et al. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13-year follow up of participants in the study of men born in 1913. Br Med J (Clin Res Ed) 1984; 288 (6428): 1401-4
11. Ohlson LO, Larsson B, Svardsudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985; 34 (10): 1055-8
12. Kivimaki M, Lawlor DA, Singh-Manoux A, et al. Common mental disorder and obesity: insight from four repeat measures over 19 years: prospective Whitehall II cohort study. BMJ 2009; 339: b3765
13. Kivimaki M, Batty GD, Singh-Manoux A, et al. Association between common mental disorder and obesity over the adult life course. Br J Psychiatry 2009; 195 (2): 149-55
14. Sarwer DB, Cohn NI, Gibbons LM, et al. Psychiatric diagnoses and psychiatric treatment among bariatric surgery candidates. Obes Surg 2004; 14 (9): 1148-56
15. Wadden TA, Sarwer DB, Womble LG, et al. Psychosocial aspects of obesity and obesity surgery. Surg Clin North Am 2001; 81 (5): 1001-24
16. Roberts RE, Kaplan GA, Shema SJ, et al. Are the obese at greater risk for depression? Am J Epidemiol 2000; 152 (2): 163-70

17. Roberts RE, Deleger S, Strawbridge WJ, et al. Prospective association between obesity and depression: evidence from the Alameda County study. Int J Obes Relat Metab Disord 2003; 27 (4): 514-21
18. Ross CE. Overweight and depression. J Health Soc Behav 1994; 35 (1): 63-79
19. European Medicines Agency. European Medicines Agency recommends Acomplia must not be used in patients on antidepressants or with major depression [media release]. 2007 Jul 19 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500012384.pdf [Accessed 2011 Apr 19]
20. European Medicines Agency. The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia [media release]. 2008 Oct 23 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014774.pdf [Accessed 2011 Apr 19]
21. Van Gaal LF, Rissanen AM, Scheen AJ, et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005; 365 (9468): 1389-97
22. Després JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005; 353 (20): 2121-34
23. Christensen R, Kristensen PK, Bartels EM, et al. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet 2007; 370 (9600): 1706-13
24. Shakir SAW. Prescription-event monitoring. In: Mann RD, Andrews EB, editors. Pharmacovigilance. Chichester: John Wiley & Sons Ltd, 2007: 307-16
25. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Arlington (VA): American Psychiatric Association, 2005
26. CIOMS-WHO. International guidelines for biomedical research involving human subjects. Geneva: CIOMS-WHO, 2002
27. Greenland S. Applications of stratified analysis methods. In: Rothman K, Greenland S, editors. Modern epidemiology. 2nd ed. Philadelphia (PA); Lippincott Williams and Wilkins, 2007: 281-99
28. Cummings P, McKnight B. Analysis of matched cohort data. Stata J 2006; 4 (3): 274-81
29. Medicines and Healthcare products Regulatory Agency. Rimonabant: depression; psychiatric reactions. Drug Saf Update 2008; 5 (10): 2-4,
30. European Medicines Agency. Questions and answers on the recommendation to suspend the marketing authorisation of Acomplia (rimonabant) [media release]. 2008 Oct 23 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500014779.pdf [Accessed 2011 Apr 19]
31. McAvoy BR, Kaner EF. General practice postal surveys: a questionnaire too far? BMJ 1996; 313 (7059): 732-3
32. Office of National Statistics. Migration statistics 2008: annual report [online]. Available from URL: http://www.statistics.gov.uk/downloads/theme_population/Migration-Statistics-2008-Annual-Report.pdf [Accessed 2010 Feb 17]

Correspondence: Dr *Yvonne Buggy*, Senior Research Fellow, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK.
E-mail: yvonne.buggy@dsru.org