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ORIGINAL RESEARCH ARTICLE

Safety Profile of Modafinil Across a Range of Prescribing Indications, Including Off-Label Use, in a Primary Care Setting in England

Results of a Modified Prescription-Event Monitoring Study

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Abstract

Background Modafinil (Provigil) was marketed in the UK in 1998 to promote wakefulness in the treatment of narcolepsy. In April 2004, the licence was extended to include chronic pathological conditions; 2 years later, the prescription of modafinil was restricted to patients with shift work sleep disorder, narcolepsy and obstructive sleep apnoea/hypopnoea syndrome. Following a recent review of the safety data, the licence has been further restricted to only treat patients with narcolepsy. The review highlighted the degree of off-label usage of modafinil, including patients with multiple sclerosis.

Objective The aim of this study was to examine the safety profile of modafinil in real-world clinical usage and across a range of prescribing indications, including multiple sclerosis.

Methods The study was conducted using the observational cohort technique of Modified Prescription-Event Monitoring. Patients were identified from dispensed prescriptions issued by primary care physicians from July 2004 to August 2005. Patient demographics and information on prescribing behaviour were included in the questionnaire sent to the prescribing general practitioner (GP) 6 months after the initial prescription for each patient. The questionnaire sought data on any events that patient may have experienced during that time, reasons for stopping treatment with modafinil, adverse drug reactions (ADRs), potential interaction with contraceptives, and pregnancies. Incidence densities (IDs) were calculated for all events, and stratified according to indication and dose. Specific events were evaluated by requesting further information.

Results Of the 4,023 questionnaires sent to GPs, 2,416 were returned (response rate 60.1 %). Of these, only those patients issued modafinil after April 2004 (with the associated broadening of the indications for treatment) were included in the study, resulting in a final cohort of 1,096 patients: 497 (45.3 %) male, median age of 52 years (interquartile range [IQR] 41–63), and 599 (54.7 %) female, median age of 47 years (IQR 38–57). Nine patients were aged 16 years or younger; no serious skin reactions were reported in this group. Thirty-four percent of the cohort had an indication of multiple sclerosis. In this study, the majority of the clinical events that were most frequently reported as ADRs or reasons for stopping or that occurred in month 1 have been previously documented with modafinil. The results of the study show that less than half of the women of child-bearing potential were established on a recommended contraceptive programme; three women became pregnant whilst taking modafinil and the oral contraceptive pill. Stratification of IDs by dose revealed certain additional events occurred during month 1 of treatment at the higher dose only. Assessment of individual cases of cardiac, psychiatric and skin events indicated causal associations with modafinil.

Conclusions This study provides important additional safety data on the use of modafinil in patients in 'real-world' use, including those for whom the prescribing indication is outside the terms of licence, as per recent changes to the licensed indications for treatment. In addition to safety data, our study provides useful utilization data. Results from this study indicate that a significant number of women of child-bearing potential had not been commenced on appropriate

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contraceptive programmes prior to starting modafinil. There were three pregnancies that occurred whilst taking contraception, highlighting the necessity of ensuring effective contraceptive cover for women during and after stopping treatment with modafinil. Analysis of the data showed that the majority of events reported as ADRs or reasons for stopping and ranked events during the first month of treatment had been previously documented with the use of modafinil. Stratification of events according to dose revealed a number of events that occurred at the higher dose only, including serious events such as psychosis. The targeted events for which causality assessments were undertaken confirmed the potential of modafinil to induce certain types of events in individual patients, including cardiac and psychiatric events.

1 Introduction

Modafinil is a centrally acting sympathomimetic agent originally marketed to promote wakefulness in the treatment of narcolepsy. In some countries, including the USA, modafinil is also approved for use in excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and shift work sleep disorder (SWSD). In Europe, however, following a review of the safety of modafinil in 2007, the Committee for Medicinal Products for Human Use's (CHMP's) Pharmacovigilance Working Party recommended that modafinil should no longer be used for these extended indications since the available data from clinical trials supported a favourable benefit–risk profile only for narcolepsy [1]. This was primarily due to concerns that the modafinil-containing medicines may be associated with severe skin reactions in children and with serious psychiatric disorders (suicidal thoughts, mania and symptoms of psychosis such as delusions) [1].

From the date of initial marketing (December 1998) to 30 January 2007, the US FDA received six cases of severe cutaneous adverse reactions associated with modafinil, involving adult and paediatric patients. Although some cases were potentially confounded by drugs known to be associated with serious skin reactions, all cases had features that implicated modafinil [2]. The FDA continues to monitor cases of serious skin reactions, including erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in its postmarketing reviews of adverse event reports associated with the use of modafinil.

Serious psychiatric disorders, including psychosis, mania and precipitation of manic/mixed episodes in existing bipolar disease, have also been associated with treatment, in addition to suicide-related behaviours [3]. The development of certain cardiac disorders has also been reported with the use of modafinil, including tachycardia, changes in blood pressure and arrhythmias. Most of the published case reports for modafinil involve psychiatric events [4–6]; however, there has also been one published report on the potential for abuse [7] and one report of ventricular contractions [8].

As well as the change to prescribing indications, the CHMP also recommended risk minimization measures to ensure the safe and effective use of modafinil-containing medicines [1]. These included updates to the Summary of Product Characteristics (SPC) to reflect the skin, hypersensitivity, neuropsychiatric and cardiovascular adverse reactions observed as well as a contraindication in patients with uncontrolled hypertension or cardiac arrhythmia, and a clear statement that modafinil is not recommended for use in children and during pregnancy and lactation.

Despite the removal of the extended indications in the EU, there is some evidence to suggest that there may be considerable off-label use of modafinil [1]. The CHMP, at the time of its assessment, found that of all the adverse event reports contained in the Marketing Authorization Holders' database, 80 % (5,381) provided the indication for use and, of these, 49 % did not correspond to an approved indication. It also quoted UK data (an estimated 64,569 prescriptions) where the highest percentage of prescriptions for specified prescribing indications was noted to be for multiple sclerosis (27 %); there were 32 % for which the indication was not specified.

Use of modafinil in children is also of interest. The current SPC, updated in March 2012 [3], states that because safety and effectiveness in controlled studies in children have not been established, and because of the risk of serious cutaneous hypersensitivity and psychiatric adverse reactions, use of modafinil is not recommended in children. However, several studies have been published examining the use of modafinil in children for the treatment of attention deficit hyperactivity disorder [9–11]. There have been very few studies examining the long-term effects and safety profile of modafinil in children. One small study (13 children) examined the effectiveness of modafinil in the treatment of excessive daytime sleepiness (EDS) in children. This study found modafinil to have a modest, yet significant, effect on EDS [12].

The present study, conducted by the Drug Safety Research Unit (DSRU), was designed to examine the real-life use of modafinil prescribed in general practice in England. This study was performed during the period when modafinil was licensed in the UK for use in both narcolepsy and as a treatment for excessive sleepiness associated with chronic pathological conditions (including SWSD). Thus, the safety data provided from this study is important not only as modafinil is still licensed in the USA for some of these extended indications but also because there is evidence of off-label use elsewhere.

2 Methods

This study was conducted on a cohort of patients prescribed modafinil in England, using the technique of Modified Prescription-Event Monitoring (M-PEM), which has been described in more detail previously [13]. The key steps are outlined in Fig 1.

Patients were identified by means of data from dispensed National Health Service (NHS) prescriptions for modafinil, written by general practitioners (GPs) in England between July 2004 and August 2005. Following a period of at least 6 months after the prescription had been issued, questionnaires were sent to GPs. This prescription information was supplied in confidence to the DSRU by the NHS Business Services Authority. Patients were admitted to the study regardless of the dose or frequency of administration of modafinil, and irrespective of whether any medicines were concurrently administered.

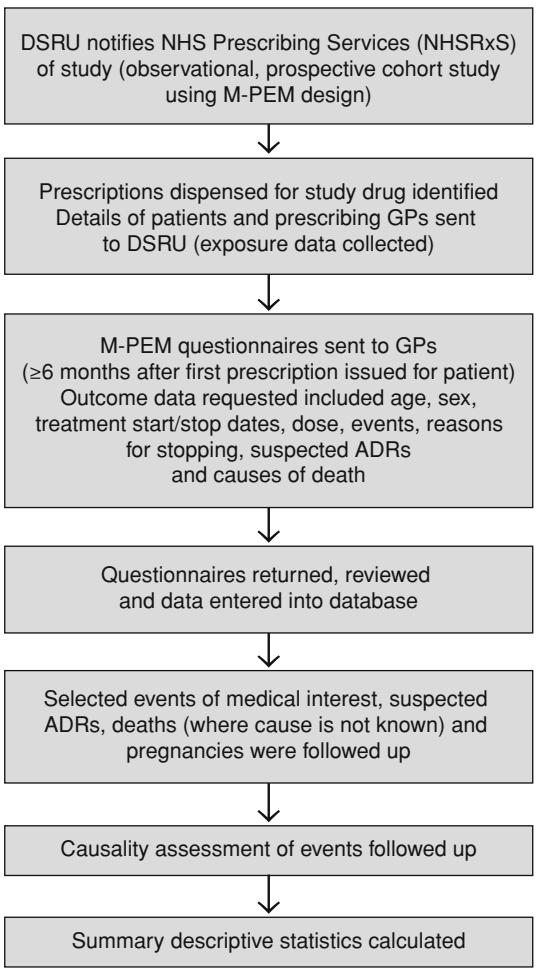

Fig. 1 Process of Modified Prescription-Event Monitoring (M-PEM) study. Patient confidentially was maintained throughout. *ADR* adverse drug reaction, *DSRU* Drug Safety Research Unit, *GP* general practitioner, *NHS* National Health Service

Patients for whom any of the following applied were not included in the study: if the questionnaire was returned blank; if the GP reported that the patient did not take, or was never prescribed, modafinil; or if the patient was no longer registered with the practice.

The questionnaire sought information on the age and sex of the patient, the date of the first dispensed prescription for modafinil, indication, initial and maintenance doses of modafinil, who initiated treatment, date treatment was stopped (including the reason for discontinuing therapy if treatment was stopped), events[1] that occurred during modafinil therapy, events reported after the drug was stopped (if treatment had been discontinued), past medical history and suspected adverse drug reactions (ADRs). The GP was offered a modest £20 payment for each modafinil study questionnaire that was completed and returned to the DSRU to partly cover his/her expenses. Frequently and rarely reported events were quantified, with the aim of defining the adverse reaction profile and, therefore, helping clinicians to judge more effectively the benefit–risk ratio of pharmacotherapy to the patient.

2.1 Analysis

Summary statistics were used to describe the patient demographics, including prescribing indication and reasons for stopping. The reasons for stopping modafinil were stratified by indication to assess whether patients discontinued treatment for different reasons. The data were also stratified by past medical history (hypertension, arrhythmia, coronary heart disease, psychiatric illness and skin reactions) to assess if the percentages of patients who stopped treatment differed between these subpopulations. Because of the small numbers of patients involved, this analysis was purely descriptive. Information on concomitant medication was also collected, in addition to that on ADRs and drug interactions. In addition, all events reported by GPs, including pregnancies, were collected. For specific events of interest, including pregnancies, further information was sought from the prescribing GP, to enable assessment of causality and the outcomes of pregnancy.

In contrast to spontaneous reporting of ADRs, Prescription Event Monitoring (PEM) provides a numerator (the number of reports of an event) and a denominator (the number of patient-months of exposure to the drug). This enabled calculation of incidence densities (IDs) (person-time incidence rates) for each event in the current study.

[1] The term '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, any alteration of clinical importance in laboratory values or any other complaint that was considered of sufficient importance to enter in the patient's notes.

IDs are expressed as the number of reports of an event per 1,000 patient-months of treatment (Eq. 1).

$$ID_t = \frac{\text{Number of reports of an event during treatment for period t}}{\text{Number of patient} - \text{months of treatment for period t}} \times 1,000 \quad (1)$$

IDs were calculated for all events reported during treatment in the first month (ID_1) after the initial prescription for modafinil was issued. These were also calculated for specific indication groups and for patients receiving different doses of modafinil.

Individual clinically significant adverse events reported on the questionnaires were further evaluated by sending an additional questionnaire, in order to assess causality [14]. These clinically significant events were defined within the protocol; they included any serious or unexpected (currently unlabelled in the UK SPC) adverse events, rare and iatrogenic ADRs, and cardiovascular, psychiatric and serious skin reactions.

Any patients commenced on modafinil prior to April 2004 were excluded from subsequent analysis, as the aim of the study was to collect data on new users of modafinil following the licence extension at that time. This study was conducted in accordance with the *International Ethical Guidelines for Biomedical Research* prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (2002) [15].

3 Results

3.1 Patient Demographics

A total of 4,023 questionnaires were sent to GPs, of which 2,416 questionnaires were returned (60.1 %). Of these 2,416 questionnaires, 324 were invalid, most commonly because of the GP having no record of this drug, or through the return of a blank form. However, the objective of the study was to collect data on the prescription of modafinil following the licence extension to include chronic pathological conditions; thus only prescriptions issued after April 2004 were included for analysis. Thus the final study cohort comprised 1,096 patients.

Of the 1,096 patients, 497 (45.3 %) were male, with a median age of 52 years (interquartile range [IQR] 41–63), and 599 (54.7 %) were female, with a median age of 47 years (IQR 38–57). The youngest patient in the cohort prescribed modafinil was aged 8 years; the prescribing indication for this patient was narcolepsy. In total, there were nine patients aged 16 years or younger; no serious skin reactions were reported in this group. One patient stopped treatment because of depression.

3.2 Drug Utilization

Within the cohort of 1,096 patients, the majority had their treatment initiated by a hospital specialist ($n = 877$, 80.0 %), with 179 patients (16.3 %) having their treatment initiated by a GP. The most frequently prescribed primary indication was for narcolepsy ($n = 268$, 24.5 %), followed by lassitude ($n = 265$, 24.2 %) and multiple sclerosis ($n = 147$, 13.4 %), as shown in Table 1. In addition to the 147 patients with a primary indication of multiple sclerosis, there were a further 225 patients for whom multiple sclerosis was listed as a secondary/tertiary indication.

Of the 309 patients who stopped taking modafinil, 83 had no reason for stopping provided by the GP; for the remaining 226 patients, 274 reasons for stopping modafinil were provided. The most common reason for stopping modafinil was 'not effective' ($n = 111$, 31.1 %); the most common clinical event was headache ($n = 11$), followed by nausea ($n = 8$), malaise ($n = 7$), dizziness ($n = 5$) and insomnia ($n = 5$). The reasons for stopping treatment with modafinil were examined for the indication groups of narcolepsy, sleep apnoea, lassitude and multiple sclerosis. Furthermore, the reasons for stopping treatment were examined for patients with a past medical history of hypertension, arrhythmia, coronary heart disease, psychiatric illness and skin reactions. Across all these groups, the most frequently reported reason for stopping was a lack of efficacy. The percentages of patients who stopped treatment within the latter five sub-cohorts based on past medical history ranged from 16 % with a history of arrhythmia to 33 % of patients with a history of psychiatric illness or skin reactions (compared with the overall cohort in which 28.2 % of patients discontinued treatment).

Of the 1,096 patients, 822 (75.0 %) were reported to be taking concomitant medication (there were 67 patients for

Table 1 Ten most frequent primary prescribing indications

Indication (primary)	No.	%
Narcolepsy	268	24.5
Lassitude	265	24.2
Multiple sclerosis[a]	147	13.4
Obstructive sleep apnoea/hypopnoea syndrome	113	10.3
Drowsiness	75	6.8
Sedation	35	3.2
Chronic fatigue syndrome	28	2.6
Parkinson's disease	17	1.6
Insomnia	14	1.3
Shift work sleep disorder	10	0.9

[a] In addition to the 147 patients with a primary indication of multiple sclerosis, there were a further 225 patients for whom multiple sclerosis was listed as a secondary/tertiary indication

whom this was not known/unspecified). Individual agents were examined, and the most widely prescribed concomitant medication included baclofen ($n = 106$), fluoxetine ($n = 84$), amitriptyline ($n = 78$), gabapentin ($n = 74$) and aspirin ($n = 72$).

As the effectiveness of steroidal contraceptives may be impaired because of induction of cytochrome P450 (CYP) 3A4/5 by modafinil, the questionnaire sought information on whether the patient was of child-bearing potential, and if so, whether they were established on a recommended contraceptive programme. There were 223 women (40.2 % for whom this was known) who were reported to be of child-bearing potential, 97 of whom were reported to be established on a recommended contraceptive programme.

3.3 Events

An event was coded as an ADR if the GP specified on the questionnaire that the event was attributable to a drug. We acknowledge the limitation to this data; this classification of an ADR is solely based on the opinion of the GP. We do not undertake any further validation of these events. Twenty-seven events, in 17 patients, were specified by GPs as being ADRs to modafinil (Table 2).

Most of the ADRs reported in Table 2 have been previously documented with the use of modafinil [3]. However, there is no specific mention of euphoria or hyperactivity. Possible synonymous events that are documented include hyperkinesia, agitation and mania. Events attributed to other medication were examined to detect possible interactions between modafinil and specific medicines; three ADRs to other medicines were reported. Fluid retention, vaginal haemorrhage and malaise were attributed to the use of desmopressin, norethisterone and prednisolone, respectively.

All events reported by GPs during the first month of treatment were ranked by number, as shown in Table 3, along with whether the event was included in the SPC [3].

Most of the clinical events have been previously documented with the use of modafinil. Of the events not previously documented, some may be related to the underlying condition, e.g. multiple sclerosis. Additional undocumented events include malaise/lassitude and urinary tract infection. Although visual defect is not specifically documented for modafinil, both blurred vision and abnormal vision have been included in the product information as events that occur commonly ($\geq$1/100 to $\leq$1/10) and uncommonly ($\geq$1/1,000 to $\leq$1/100), respectively.

3.4 Statistical Analysis

The clinical events with the highest ID in the first month of treatment were headache/migraine (9.45), nausea/vomiting (7.09), dizziness (5.91) and palpitation (5.91) (these figures were calculated using all these events reported during this time period).

Table 2 Events reported as adverse drug reactions (ADRs) to modafinil

ADR	No.	%[a]
Unspecified adverse effects	6	0.5
Headache	4	0.4
Dizziness	2	0.2
Visual disturbance	2	0.2
Diarrhoea	1	0.1
Nausea	1	0.1
Vomiting	1	0.1
Pain abdomen	1	0.1
Hypertension	1	0.1
Drowsiness	1	0.1
Sedation	1	0.1
Insomnia	1	0.1
Agitation	1	0.1
Anxiety	1	0.1
Euphoria	1	0.1
Hyperactive	1	0.1
Malaise	1	0.1
Total	27	

[a] Denominator used is 1,096

The cohort was stratified according to the four indication groups of narcolepsy, OSAHS, lassitude and multiple sclerosis (lassitude and multiple sclerosis were the second and third most frequently reported primary indications in the study, respectively). Patients were included in the indication group if they had that indication reported, regardless of whether it was the primary, secondary or tertiary indication provided. Therefore, it is possible for a patient to appear in more than one indication group. IDs for events reported during the first month of treatment were calculated (ID_1) (see Table 4). Because of the small numbers of patients included in these groups, and the low event counts reported during month 1, no formal statistical comparison was performed. It was noted that the nature of the events reported for the narcolepsy and the OSAHS groups were different; there was no obvious link between the types of events reported in each group and the underlying condition.

For the narcolepsy group, the clinical events with the highest ID_1 included dyspnoea, skin infection and abdominal pain (ID_1 of 8.27). Skin infection has not been previously documented [3]; however, rash and pruritis are both known to occur uncommonly with modafinil [3]. Within the OSAHS group, the clinical events with the highest ID_1 included euphoria, headache and visual defect (ID_1 of 19.20). Blurred vision had been documented with

Table 3 Twenty most frequently reported events during month 1 of treatment

Event	No. during month 1 of study	Listed undesirable effect in SPC	Frequency as per SPC	Overall frequency in study cohort ($n = 1,096$) (%)	Frequency
Not effective	19	NA	NA	1.7	Common
Headache, migraine	8	Y	Very common/uncommon	0.7	Uncommon
Non-surgical admissions	7	N	NA	0.6	Uncommon
Nausea, vomiting	6	Y	Common/uncommon	0.5	Uncommon
Dizziness	5	Y	Common	0.5	Uncommon
Palpitation	5	Y	Common	0.5	Uncommon
Dose increased	4	NA	NA	0.4	Uncommon
Intolerance	4	NA	NA	0.4	Uncommon
Malaise, lassitude	4	N	NA	0.4	Uncommon
Sleep disorder	4	Y	Uncommon	0.4	Uncommon
Visual defect	4	N	NA	0.4	Uncommon
Pregnancy	2	NA	NA	0.2	Uncommon
Condition improved	3	NA	NA	0.3	Uncommon
Multiple sclerosis	3	NA	NA	0.3	Uncommon
Muscle weakness	3	Y	Uncommon	0.3	Uncommon
Pain abdomen	3	Y	Common	0.3	Uncommon
Urinary tract infection	3	N	NA	0.3	Uncommon
Agitation	2	Y	Uncommon	0.2	Uncommon
Diarrhoea	2	Y	Common	0.2	Uncommon
Dreams abnormal	2	Y	Uncommon	0.2	Uncommon

Very common (≥1/10), common (≥1/100 to ≤1/10), uncommon (≥1/1,000 to ≤1/100)

NA not applicable, *SPC* summary of product characteristics

modafinil as occurring commonly. Euphoria has not been previously documented, although mania is reported to occur rarely [3].

Patients with multiple sclerosis comprised approximately one-third of the entire cohort. There is some overlap between the nature of the clinical events with the highest ID_1 in the multiple sclerosis and lassitude treatment groups; this may be due to the fact that some patients were included in both groups, i.e. those patients for whom lassitude was reported as an indication, who had an underlying diagnosis of multiple sclerosis. The nature of some of the clinical events reported is likely to represent the features of the underlying condition of multiple sclerosis, such as muscle weakness and tremor.

IDs were also calculated for those patients receiving 200 mg per day and for those receiving the higher daily dose of 400 mg. Headache, visual defect and muscle weakness were among the most frequently reported events in month 1 for the 200 mg daily dose (ID_1 of 5.1). However, patients receiving 400 mg daily also reported dehydration, dermatitis, dizziness, drowsiness, dyspnoea, pain abdomen, oedema, psychosis, rash and sweating as clinical events with the highest ID_1 (6.71).

3.5 Selected Events of Interest: Cardiac, Serious Skin and Serious Psychiatric Events

Certain events were selected a priori for further evaluation. Cardiac events and serious skin and serious psychiatric conditions were amongst those events that were flagged for further evaluation. All of the previously documented cardiac events that have been associated with modafinil were found to occur in our study at the same or a lower frequency than previously documented. The characteristics of the patients who experienced a selected cardiac or psychiatric event of interest are included in Table 5.

Further information on the events of interest in Table 5 was requested for those events for which an alternative explanation was not provided by the GP. Of those events for which this information was requested and formal causality assessment was undertaken, eight cardiovascular events were considered to be either possibly or probably related to the use of modafinil.

Serious psychiatric events reported during this study included mania ($n = 1$), psychosis ($n = 2$) and overdose ($n = 1$). Mania and psychosis are reported to occur rarely with modafinil [3].

Table 4 Events ranked according to ID_1 for the indications of narcolepsy/OSAHS/lassitude/multiple sclerosis

Higher term	N_1	ID_1
Narcolepsy ($n = 269$)		
Not effective	4	16.55
Dyspnoea	2	8.27
Infection skin	2	8.27
Pain abdomen	2	8.27
Pregnancy	1	7.38
Anaemia	1	4.14
Anorexia	1	4.14
Cardiac failure	1	4.14
Dermatitis	1	4.14
Dizziness	1	4.14
OSAHS ($n = 185$)		
Euphoria	2	19.20
Headache, migraine	2	19.20
Not effective	2	19.20
Visual defect	2	19.20
Agitation	1	9.60
Condition improved	1	9.60
Diabetes mellitus, hyperglycaemia	1	9.60
Dizziness	1	9.60
Dose increased	1	9.60
Gout	1	9.60
Lassitude ($n = 287$)		
Not effective	9	35.32
Palpitation	5	19.62
Headache, migraine	4	15.70
Nausea, vomiting	3	11.77
Dizziness	2	7.85
Multiple sclerosis	2	7.85
Muscle weakness	2	7.85
Non-surgical admissions	2	7.85
Pain chest, tight chest	2	7.85
Sleep disorder	2	7.85
Multiple sclerosis ($n = 372$)		
Not effective	8	24.03
Nausea, vomiting	4	12.02
Multiple sclerosis[a]	3	9.01
Muscle weakness	3	9.01
Palpitation	3	9.01
Intolerance	2	6.01
Non-surgical admissions	2	6.01
Sleep disorder	2	6.01
Tremor	2	6.01
Urinary tract infection	2	6.01

ID_1 incidence density for each event during the first month of treatment, *N_1* total number of first reports of each event during the first month of treatment, *OSAHS* obstructive sleep apnoea/hypopnoea syndrome

[a] Within the indication group of multiple sclerosis, there were three patients with multiple sclerosis reported as an event, with no further clinical details

There were no cases of EM, SJS or TEN reported; however, this study was not powered to detect these conditions.

3.6 Pregnancies

As stated above, only results for patients prescribed modafinil after the licence update in April 2004 were included in the analysis for this study. However, there were a significant number of patients prescribed modafinil before this date. Because of the important nature of the data, all patients for whom pregnancy data was available were analysed, irrespective of the date of the first prescription of modafinil; thus data were available on 2,092 patients.

In total, there were 13 pregnancies reported during the study for the entire cohort of 2,092 patients. Of these, one woman was not taking modafinil, and one woman had stopped modafinil prior to her last menstrual period. Table 6 shows the outcomes for the remaining 11 pregnancies.

There were three women who fell pregnant during treatment with modafinil, despite taking the oral contraceptive pill (OCP). One of these women had a spontaneous abortion; this woman subsequently fell pregnant again whilst taking modafinil, which resulted in a therapeutic termination. It was not known if there was any foetal abnormality. The second woman had an ectopic pregnancy that was an unplanned pregnancy. The mother was taking modafinil along with the OCP Cilest (ethinylestradiol and norgestimate) and dexamphetamine during her pregnancy. Finally, the third woman was noted to have had an accidental pregnancy whilst on the OCP. She stopped modafinil during her first trimester; the outcome was a live birth; the baby was noted to have a left lower lid entropion, which subsequently corrected itself.

4 Discussion

Analysis of the indication data confirms a high percentage of patients with multiple sclerosis were prescribed modafinil (34 % of study cohort), consistent with findings from the CHMP assessment report [1]. This is consistent with the most frequently co-prescribed medicine reported, baclofen, a medicine used to treat spasticity. This usage of modafinil would currently be regarded as off-label, following the licence recommendation. Further off-label prescription of modafinil was identified, as 0.8 % of the cohort was aged less than 16 years.

In this study, the majority of the clinical events that were most frequently reported as ADRs or as reasons for

Table 5 Characteristics of patients who experienced cardiac/psychiatric events of interest during treatment with modafinil

	No. of events reported during treatment	Median age at start [years (IQR)]	Gender[a]	Median time to onset [days (IQR)]	No. assessed as possibly/ probably related	Primary indication							
						N	L	OSAHS	PD	D	S	CFS	NK
Cardiovascular													
Arrhythmia	1	80	M1	99	0	1							
Chest pain	8	53 (49–63)	M3	130 (84–152)	1	3	2	1	1				1
Hypertension	6	66 (53–72)	M3	274 (226–342)	1	3	1	1				1	
Raised blood pressure	4	56 (46–66)	M3	92 (57–153)	2	1	1			1	1		
Tachycardia	1	59	F1	NK	1		1						
Palpitations	6	48 (46–50)	M3	17 (9–21)	3	1	5						
Psychiatric													
Psychosis	2	18, 38	M1	8, 88	0	1	1						
Drug overdose	1	51	M1	144	0	1							

CFS chronic fatigue syndrome, *D* drowsiness, *IQR* interquartile range, *L* lassitude, *N* narcolepsy, *NK* not known, *OSAHS* obstructive sleep apnoea and hypopnoea syndrome, *PD* Parkinson's disease, *S* sedation

[a] Number of male (or female) patients

Table 6 Outcome of pregnancies for 11 women taking modafinil, from total cohort of 2,092[a] patients

Exposure period	Age (years)	Smoking status	Concomitant medication	On contraception	Outcome of pregnancy
Throughout	25	Non-smoker	None	No	Termination
Throughout	28	Current	Levothyroxine	No	Termination
1st trimester	23	Current	None	NS	Live birth
1st and 2nd trimester	33	Current	Fansidar, Gaviscon, Ispaghula, Pregaday	NS	Live birth
Throughout	27	NK	Cilest, dexamphetamine	Yes	Ectopic
1st trimester	28	Ex-smoker	None	Yes	Live birth
1st trimester	35	Ex-smoker	None	NS	NK
1st trimester	18	Non-smoker	Clomipramine, fexofenadine	NS	Live birth
Unclear	23	Non-smoker	Lofepramine	Yes	Miscarriage and termination[b]
Unclear	28	NS	Sertraline	No	NK
Unclear	27	NS	NS	NS	NS

NK not known, *NS* not specified

[a] Due to the importance of pregnancy data, all patients for whom this in information was available were included in this table, including those patients prescribed modafinil prior to April 2004; hence, the study cohort comprised 2,092 patients

[b] This patient had a spontaneous abortion; this woman subsequently fell pregnant again whilst taking modafinil, which resulted in a therapeutic termination. It was not known if there was any foetal abnormality

stopping modafinil or that were reported during the first month of treatment have been previously documented with modafinil [3]. Events reported as ADRs that are not specifically included in the product information for modafinil include euphoria and hyperactivity; however, hyperkinesia, agitation and mania have been previously documented. The stratification of the reasons for stopping treatment according to past medical history showed a slightly higher cessation rate amongst patients with a past history of psychiatric illness or skin reactions (33 % vs. an overall cessation rate of 28.2 %). This may be due to the predisposition of these patients to develop certain adverse events.

Analysis of the ID_1 for patients stratified according to dose showed those patients taking the higher dose of 400 mg per day experienced additional events during month 1, including dehydration, skin reactions and psychosis.

Evaluation of the focused events of interest in this study, which included cardiac events, serious skin and serious psychiatric events, showed causal associations between these events and the use of modafinil. As stated, there were no cases of EM, SJS or TEN reported; however, as stated above, this study was not powered to detect these conditions. There were five cases of urticaria that occurred during treatment, only one of these was considered to be possibly related. The FDA has been monitoring cases of serious skin reactions with modafinil therapy, including EM, SJS and TEN, in its postmarketing reviews of adverse event reports associated with its use. In the UK, a letter to healthcare professionals was sent in February 2008 [16], containing new warnings regarding serious skin rash and psychiatric symptoms.

The effectiveness of steroidal contraceptives may be impaired because of induction of CYP3A4/5 by modafinil. Alternative or concomitant methods of contraception are recommended for patients treated with modafinil [3]. The results of the study show that less than half of the women of child-bearing potential were established on a recommended contraceptive programme. There were also three women who became pregnant whilst taking modafinil and the OCP. The product information states that alternative or concomitant methods of contraception are recommended in women taking modafinil, and that adequate contraception will require continuation of these methods for 2 months after stopping modafinil. Although it is possible that other factors contributed to this contraceptive failure, such as lack of patient compliance, this data highlights the necessity of ensuring that women who are of child-bearing potential are adequately protected against pregnancy by an effective contraceptive programme during and after stopping treatment with modafinil.

4.1 Weaknesses and Strengths of Modified Prescription-Event Monitoring Studies

The limitations of this methodology include the potential for non-response bias, reporting and channelling bias, and the inability to assess patient compliance. However, the additional questions provided on the modified questionnaire can minimize some of these, for example, information was sought in this study on past medical history of cardiovascular events, psychiatric illness and skin reactions. We also acknowledge the potential for misclassification and under-reporting of events. Also, the sample size in this study was smaller than standard PEM studies, and as such was not formally powered to detect rare events. A further potential weakness of the study was the difficulties in identifying cases of abuse. Modafinil is a Schedule IV controlled substance. Since modafinil and amphetamine-like substances share wake-promoting effects, it was important to assess whether modafinil might also have a potential for abuse. One patient was reported to have abused modafinil within the valid cohort.

The strengths of standard PEM methodology [13] apply to the M-PEM design used in this study. These include the real-world use of the drug, the lack of strict exclusion criteria, and the non-interventional basis of the methodology. Crucially M-PEM/PEM provides the opportunity to identify reactions that may not have been suspected as being due to the drug under surveillance. Although modafinil therapy is generally initiated in hospital by a specialist, it is possible to gain access to clinical data from this time onwards from GP records as the GP receives information from the hospital via specialist correspondence. Thus where available, we have information for the entire period during which patients received modafinil.

As stated, the sample size of 1,096 patients included in this study is considerably smaller than standard PEM cohorts of 10,000 patients. This reflects the market uptake of modafinil and prescribing patterns within general practice in the UK, and also the exclusion criteria based on whether the prescription was prior to or post April 2004. However, this figure still compares favourably to many clinical trials.

Earlier studies evaluating the safety and efficacy of modafinil reported that medication-related adverse experiences were few and mostly rated mild to moderate [17, 18]. This study provides some useful data regarding the real-world usage of modafinil, and its associated safety profile. Although in the UK modafinil is only indicated for the treatment of narcolepsy, recent evidence suggests significant off-label usage, particularly in patients with multiple sclerosis [1].

By using the M-PEM methodology, specific questions sought to capture information relating to prescribing behaviour (dose, duration, indication and concomitant medication), potential interaction with oral contraceptives, and adverse events. It has also been possible to further evaluate specific events of interest by requesting further information from the GP when necessary. In this way, specific safety issues can be targeted through this methodology.

5 Conclusions

This study provides important additional safety data on the use of modafinil in patients in 'real-world' use, including those for whom the prescribing indication is outside the terms of licence, as per recent changes to the licensed indications for treatment.

In addition to safety data, our study provides useful utilization data. Results from this study indicate that a

significant number of women of child-bearing potential had not been commenced on appropriate contraceptive programmes prior to starting modafinil. There were three pregnancies that occurred whilst taking contraception, highlighting the necessity of ensuring effective contraceptive cover for women during and after stopping treatment with modafinil.

Analysis of the data showed that the majority of events reported as ADRs or reasons for stopping and ranked events during the first month of treatment had been previously documented with the use of modafinil. Stratification of events according to dose revealed a number of events that occurred at the higher dose only, including serious events such as psychosis.

The targeted events for which causality assessments were undertaken confirmed the potential of modafinil to induce certain types of events in individual patients, including cardiac and psychiatric events.

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Conflict of interest The authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. European Medicines Agency (EMA). Assessment report for modafinil containing medicinal products. London: EMA; 2011.
2. Cephalon Inc. Dear Healthcare Professional letter. Updated safety information: warnings regarding serious rash, including Stevens–Johnson Syndrome and hypersensitivity reactions, and psychiatric symptoms. Silver Spring: US FDA. 2007. http://www.fda.gov/medwatch/safety/2007/Provigil_dhcpletter091207_final.pdf. Accessed May 2012.
3. Cephalon (UK) Limited. Summary of product characteristics: Provigil®. Castleford: Cephalon UK Limited; 2012.
4. Mariani JJ, Hart CL. Psychosis associated with modafinil and shift work. Am J Psychiatry. 2005;162(10):1983.
5. Ranjan S, Chandra PS. Modafinil-induced irritability and aggression? A report of 2 bipolar patients. J Clin Psychopharmacol. 2005;25(6):628–9.
6. Vorspan F, Warot D, Consoli A, Cohen D, Mazet P. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry. 2005;162(4):813–4.
7. Kruszewski SP. Euphorigenic and abusive properties of modafinil. Am J Psychiatry. 2006;163(3):549.
8. Oskooilar N. A case of premature ventricular contractions with modafinil. Am J Psychiatry. 2005;162(10):1983–4.
9. Boellner SW, Earl CQ, Arora S. Modafinil in children and adolescents with attention-deficit/hyperactivity disorder: a preliminary 8-week, open-label study. Curr Med Res Opin. 2006; 22(12):2457–65.
10. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. Ann Pharmacother. 2006;40(10):1829–33.
11. Swanson JM, Greenhill LL, Lopez FA, Sedillo A, Earl CQ, Jiang JG, et al. Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. J Clin Psychiatry. 2006;67(1):137–47.
12. Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. Sleep Med. 2003;4(6): 579–82.
13. Layton D, Hazell L, Shakir SA. Modified prescription-event monitoring studies: a tool for pharmacovigilance and risk management. Drug Saf. 2011;34(12):e1–9.
14. Shakir S. Causality and correlation in pharmacovigilance. In: Talbot J, Waller P, editors. Stephens' detection of new adverse drug reactions. 5th ed. Chichester: Wiley; 2004. p. 329–43.
15. CIOMS, WHO. International ethical guidelines for biomedical research involving human subjects. Geneva: Switzerland. 2002. http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm. Accessed May 2012.
16. Drug Safety Update. Monthly newsletter from MHRA. Vol 1. Issue 8, March 2008.
17. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998; 43(1):88–97.
18. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000; 54(5):1166–5.