

Review

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Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review

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Summary

Several drugs, or categories of drugs, listed by the WHO and other writers and used in the treatment of chronic disease, are consistently associated with weight gain as a side effect and considered 'obesogenic'. The extent to which they may contribute to the multifactorial process behind obesity is not well documented. We systematically reviewed papers from Medline 1966–2004, Embase 1980–2004, PsycINFO 1967–2004, and Cochrane Register of Controlled Trials, to determine the effect on body weight of some drugs that are believed to favour weight gain. We included randomized controlled studies of adult participants (>18 years) prescribed a drug considered obesogenic, that compared the 'obesogenic' drug with placebo, an alternative drug or other treatment, and that had a duration of at least 3 months: 43 studies totalling

25 663 subjects met these criteria. The main objective of the majority of studies was to compare the efficacy and safety of drug therapy, with weight change recorded under safety outcomes; weight change was a primary outcome measure in only six studies. There was evidence of weight gain for all drugs included, up to 10 kg at 52 weeks. Differences in dosage, patient population, duration of treatment and dietary advice make generalization of the results difficult. Data on body weight are often not recorded in published clinical trials or is reported in insufficient detail. This side-effect has potentially serious consequences, and should be mentioned to patients. Weight management measures should be routinely considered when prescribing drugs known to promote weight gain. Future clinical trials should always document weight changes.

Introduction

Obesity continues to increase in prevalence.^{1–3} In the UK, around half of women and two-thirds of men are overweight or obese.^{4,5} Recent Scottish data show that the figure for women has risen to 60%.⁶ In addition to being a major health problem in its own right, obesity is associated with a range of serious symptoms and co-morbid conditions. The estimated cost to the UK Health Service of obesity and related conditions at present is immense.^{5,7} If the rise in obesity continues, it is thought that by the

year 2010 one third of all adults in the UK will be obese,⁸ and the costs to health care services will rise to an estimated £3.6 billion.⁵

Obesity is a consequence of energy imbalance, when energy intake exceeds energy expenditure over a prolonged period of time. Social and environmental forces have a powerful influence over energy intake and expenditure, and individuals vary in their susceptibility to these influences due to genetic and biological factors. It is the interaction of

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Table 1 Drugs known to favour weight gain

Drug	Main use
Insulin, sulphonylureas, thiazolidiniones	Diabetes
Beta-blockers	Hypertension
Corticosteroids	Inflammatory disease
Cyproheptadine	Allergy, hay fever
Antipsychotics	Psychosis
Sodium valproate	Epilepsy
Tricyclic antidepressants	Depression
Lithium	Bipolar disorder

From references 3, 9, 10, 11, 12.

all these elements that gives rise to obesity.³ Many prescription drugs in current use are associated with weight changes. For some (e.g. certain serotonin reuptake inhibitors, oral contraceptives), the evidence of an effect on body weight is less consistent,⁹ while others are consistently associated with weight gain, and are considered obesogenic^{3,10–12} (Table 1). This effect can arise as a consequence of differing mechanisms, such as increased appetite (corticosteroids) or reduced metabolic rate (beta-adrenoceptor blockers).¹¹ For some drugs, weight loss may have occurred as a result of the underlying disease and recovery on effective treatment will include weight regain, which would not be considered an adverse effect. However, in many cases, weight gain is an unwanted side-effect. These drugs are used in the management of chronic disease and therefore prescribed on a long-term basis. In previous research, 9% of adults attributed weight gain to drugs they were prescribed.¹³

The development of obesity is a long-term multifactorial process in which obesogenic drugs play a contributory role. This review quantifies the adverse effects on body weight of those drugs that are consistently reported as obesogenic, and that are used in the treatment of chronic disease (Table 1).

Methods

We electronically searched Medline 1966–2004, Embase 1980–2004, PsycINFO 1967–2004, and the Cochrane Register of Controlled Trials. The drug name or drug category was the primary key word for each search. This was mapped to relevant subheadings. The second keyword search used the terms 'weight adj2 gain' or 'weight adj2 change'. Primary and secondary searches were then combined and limited to human, English language, adults, clinical trial, randomized controlled trial or controlled clinical trial. Reference lists of all relevant papers

were checked. We did not hand-search journals or search the 'grey' literature as part of this review.

Selection of studies

Articles were selected on the basis of title and abstract. Studies were included according to the following eligibility criteria: only randomized controlled studies; adult participants (>18 years) prescribed a drug considered obesogenic; duration ≥ 3 months; comparison of the 'obesogenic' drug with placebo, an alternative drug or other treatment. Outcome measures had to include measured weight change, reported quantitatively. Studies that primarily investigated the use/effect of a combination of 'obesogenic' drugs were excluded, as were studies in which body weight was self-reported. Studies where the drug was used to treat diseases characterized by weight loss (e.g. type 1 diabetes) were also excluded.

Quality assessment

Two reviewers checked independently that the studies identified by the search strategy met the inclusion criteria, and assessed the methodological quality of the included studies. Quality assessment focussed on the adequacy of the randomization procedure.¹⁴ As the identified studies involved different populations, drugs and dosages, no quantitative meta-analyses were done.

Results

A total of 628 titles and abstracts were reviewed, and 139 publications were retrieved and reviewed in greater detail. From these, 43 studies (total 25 663 subjects) were identified that met our inclusion criteria. The main reasons for exclusion were: study duration <12 weeks; non-randomized study design; weight gain not reported or not quantified (Figure 1).

Valproate

All four studies compared valproate with an alternative drug; no placebo-controlled studies were identified. Comparison was made with olanzapine in the treatment of bipolar disorder¹⁵ and acute mania.¹⁶ The objective of both these studies was to compare the drugs in terms of efficacy and safety. Biton *et al.*¹⁷ compared valproate with lamotrigine in patients with epilepsy. The aim of the fourth study¹⁸ was to determine the efficacy and safety of topiramate, in comparison with cabamazepine and valproate monotherapy, in the initial treatment of newly diagnosed epilepsy.

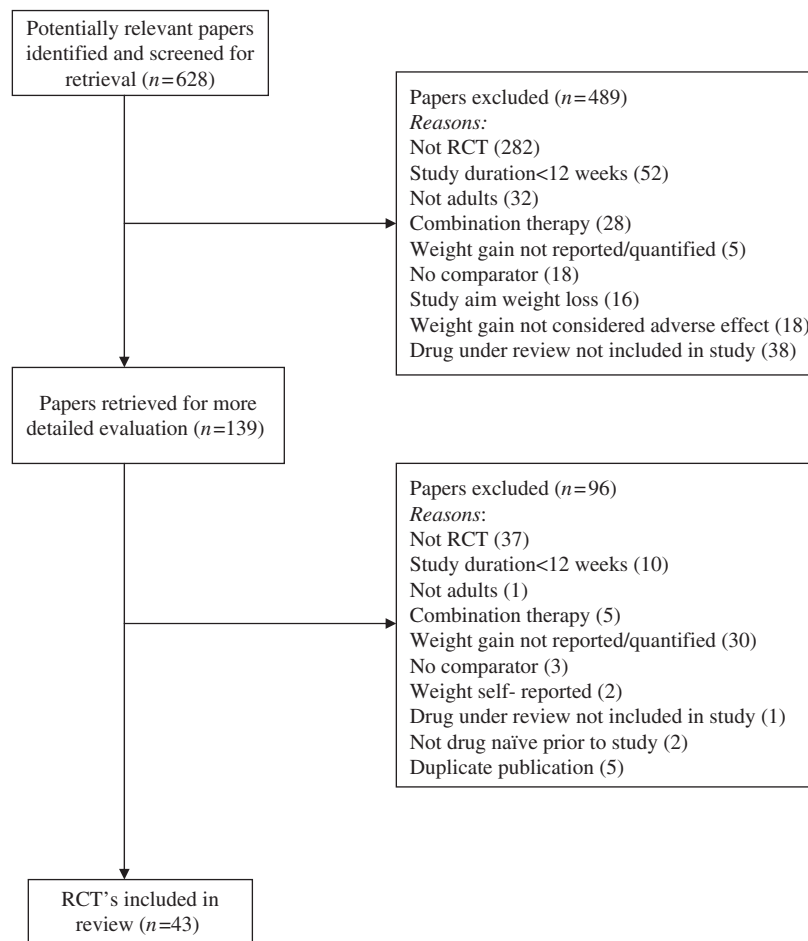


Figure 1. Flowchart of progress of papers through the review.

Weight change was the primary outcome measure in only one study,¹⁷ and a secondary measure to assess safety in the remaining studies. The mean dosage of valproate differed in each study (Table 2).

Lithium

Only one study fulfilled the inclusion criteria and compared lithium with carbamazepine as a prophylactic agent in bipolar disorder.¹⁹ The main outcome measure was relapse, with weight gain recorded as an assessment of side-effects. The initial dose of lithium was 400 mg twice daily.

Atypical antipsychotics

In three studies, olanzapine was compared with placebo in the treatment of alcohol dependence disorder,²⁰ and borderline personality disorder.^{20,21} Ziprasidone was compared with placebo in the treatment of schizophrenia.²³ In the remaining studies, comparisons were made between an atypical antipsychotic and an alternative drug: clozapine, olanzapine, and risperidone vs. haloperidol,²⁴ olanzapine vs. sodium valproate,^{15,16}

olanzapine vs. haloperidol,^{25,26} risperidone vs. amisulpride,²⁷ clozapine vs. chlorpromazine,²⁸ olanzapine vs. aripiprazole²⁹ and olanzapine vs. amisulpride.³⁰

Only two studies^{24,29} specifically examined weight change as a primary outcome; in the remainder of the studies, clinical response was the primary outcome with weight change recorded as a means of assessing safety.

Corticosteroids

Only one randomized controlled trial was identified,³¹ comparing prednisone with radiotherapy in the treatment of Graves' ophthalmopathy. The objective of the study was to compare the efficacy and tolerability of the treatments: clinical response was the primary outcome measure, with weight change recorded as a side-effect.

Insulin

The studies included were restricted to the treatment of type 2 diabetes. In all studies, insulin therapy alone was compared with either oral agents^{32–34} or with

Table 2 Drugs and their effect on body weight

Drug	Reference	Condition	Follow-up (weeks)	<i>n</i>	Dose	Weight change (kg)
Valproate	Zajacka 2002 ^{15,#}	Bipolar disorder	12	120	2115 mg/day*	+2.5**
	Biton 2001 ¹⁷	Epilepsy	32	141	1822 mg/day*	+5.8 (SD 4.2)
	Tohen 2003 ¹⁶	Bipolar disorder	47	251	1500 mg/day*	+1.2(SE 1.2)
	Privitera 2004 ¹⁸	Epilepsy	26	621	1250 mg/day	+2.0**
Lithium	Coxhead 1992 ¹⁹	Bipolar disorder	52	32	≥400 mg/day	+4.0**
Clozapine	Czobor 2002 ²⁴	Schizo-affective disorder	14	151	200–800 mg/day	+4.2 (SD 4.7)
	Lieberman 2003 ²⁸	Schizophrenia	52	160	≤400 mg/day	+9.9**
Olanzapine	Zajacka 2002 ^{15,#}	Bipolar disorder	12	120	14.7 mg/day*	+3.9**
	Lieberman 2003 ²⁶	Psychosis	12	263	9.1 mg/day*	+7.1 (SD 6.1)
	Czobor 2002 ^{24,#}	Schizo-affective disorder	14	151	30.4 mg/day*	+5.4 (SD 4.6)
	Zanerini 2001 ²²	Borderline personality disorder	24	28	5.3 mg/day*	+2.8 (SD 5.7)
Olanzapine	Tohen 2003 ^{16,#}	Acute mania	47	251	16.2 mg/day*	+2.8**
	Tran 1999 ²⁵	Schizo-affective disorder	51	110	11.5 mg/day*	+5.0 (SD 7.3)
	Guardia 2004 ²⁰	Alcohol dependence	12	60	5–15 mg/day	+4.3**
	Bogenschutz 2004 ²¹	Borderline personality disorder	12	40	2.5–20 mg/day	+3.7 (SD 3.4)
Risperidone	McQuade 2004 ²⁹	Schizophrenia	26	317	10–20 mg/day	+4.2**
	Mortimer 2004 ³⁰	Schizophrenia	26	377	5–20 mg/day	+3.9 (SD 5.3)
	Czobor 2002 ^{24,#}	Schizo-affective disorder	14	151	7.9 mg/day*	+2.3 (SD 2.8)
Ziprasidone	Sechter 2002 ²⁷	Schizophrenia	24	309	4–10 mg/day	+2.1**
	Arato 2002 ²³	Schizophrenia	52	294	40 mg/day	–2.7**
Prednisone	Prummel 1993 ³¹	Graves ophthalmopathy	24	56	80 mg/day	–3.2**
					160 mg/day	–2.9**
					Decreasing	+2.0**
Insulin	Yki-Jarvinen 1992 ³⁶	Type 2 diabetes	12	153	2 injections	+1.8 (SD 0.5)
					Multiple injections	+2.9 (SD 0.5)
					2 injections	+5.2(SD 4.1)
					1 injection	+6.6**
					2 injections	+3.9**
					2–4 injections	+5.1 (non-obese) (SD 0.6)
Glipizide	UKPDS 1998 ^{34,#}	Type 2 diabetes	10 yrs	3867	1–2 injections	~+6.5**
					5–60 mg/day	–0.3 (SD 0.2)
	Simonson 1997 ³⁸	Type 2 diabetes	16	143	5–20 mg/day	–0.1 (SD 0.1)
					204	5–20 mg/day
	Campbell 1994 ⁴²	Type 2 diabetes	52	48	5–30 mg/day	+2.6**
	Marbury 1999 ⁴³	Type 2 diabetes	52	576	0.5–12 mg/day	+3.6**
	Johnstone 1998 ⁴¹	Type 2 diabetes	52	411	1.25–20 mg/day	+2.3**
	Nathan 1988 ^{32,#}	Type 2 diabetes	36	31	2.5–10 mg/day	+3.8**
Glimepiride	Bautista 2003 ³⁹	Type 2 diabetes	14	70	1–4 mg/day	+2.3**
					Tan 2004 ^{48,#}	Type 2 diabetes
Glibenclamide	UKPDS 1998 ^{34,#}	Type 2 diabetes	10 yrs	3867	2.5–20 mg/day	~+4.0**
					Segal 1997 ⁴⁰	Type 2 diabetes
Chlorpropamide	UKPDS 1998 ^{34,#}	Type 2 diabetes	10 yrs	3867	100–500 mg/day	~+5.0**
Troglitazone	Iwamoto 1996 ⁴⁵	Type 2 diabetes	12	284	400 mg/day	+0.06 (SD 1.6)
Rosiglitazone	Patel 1999 ⁴⁴	Type 2 diabetes	12	380	0.05 mg/day	–0.95**
					0.25 mg/day	–0.54**
					1.0 mg/day	+0.18**
					2.0 mg/day	+0.36**

(Continued)

Table 2 Continued.

Drug	Reference	Condition	Follow up (weeks)	<i>n</i>	Dose	Weight change (kg)
Pioglitazone	Wallace 2004 ⁴⁶	Type 2 diabetes	12	30	45 mg/day	+0.70 (SE 0.6)
	Tan 2004 ^{48,#}	Type 2 diabetes	52	244	15–45 mg/day	+1.5**
	Schernthaner 2004 ⁴⁷	Type 2 diabetes	52	1199	≤45 mg/tid	+1.9**
Nortriptyline	Weber 2000 ⁴⁹	Depression	12	32	NA	+3.7 (SD 2.3)
Doxepin	Feighner 1986 ⁵⁰	Depression	13	147	100–225 mg/day	+2.7**
Amitriptyline	Montgomery 1998 ⁵¹	Depression	104	217	max 280 mg/day	+1.7 (SD 4.1)
Atenolol	Houston 1991 ⁵³	Hypertension	13	49	56 mg/day*	+1.0**
Atenolol or metoprolol	Wilhelmsen 1987 ⁵⁷	Hypertension	45 months	6569	100/200 mg/day	+1.1**
Metoprolol	Wikstrand 1988 ⁵⁶	Hypertension	208	3234	174 mg/day*	+1.5**
	Foss 1990 ⁵⁰	Hypertension	26	114	50–200 mg/day	+0.5 (females)** +0.7 (males)**
Propranolol	Rossner 1990 ⁵⁴	Post myocardial infarction	52	3837	Not stated	+2.3**
	Berglund 1986 ⁵⁵	Hypertension	10 yrs	106	80 mg/bd*	–0.6**

*Mean dose. **SD or SE not reported. #Duplicate reporting of studies as a result of the comparator in each study.

insulin plus oral agents.^{35–37} The dosage of insulin varied in each study, and was calculated according to the participant's body weight, subsequently adjusted according to blood glucose results.

Sulphonylureas

Treatment with a sulphonylurea was compared with placebo alone in two studies,^{38,39} with another oral hypoglycaemic agent and placebo in two studies,^{40,41} with insulin in two studies,^{32,34} and with an alternative oral hypoglycaemic agent in three studies.^{42,43,48} Weight change was a primary outcome measure in only one study.⁴² In the UKPDS study, the main objective was to determine the risk of micro or macro-vascular complications, with weight change recorded under adverse events. The objective of the remaining studies was to determine efficacy, safety and tolerability, with clinical response as the primary outcome measure and weight change recorded under safety outcomes.

Thiazolidinediones

Three studies compared a thiazolidinedione with placebo in type 2 diabetic patients. Patel *et al.*⁴⁴ assessed the metabolic effects of four doses of rosiglitazone, Iwamoto *et al.*⁴⁵ investigated the efficacy and safety of troglitazone and Wallace *et al.*⁴⁶ examined the effect of pioglitazone on beta cell function and insulin sensitivity. The metabolic effects of pioglitazone were compared with

metformin in one study,⁴⁷ and in the final study pioglitazone was compared with glimepiride with regard to changes in glycaemic control and insulin sensitivity.⁴⁸ In all studies, weight change was a secondary outcome.

Tricyclic antidepressants

All three studies compared the efficacy and tolerability of a tricyclic antidepressant with an alternative anti-depressant: paroxetine in comparison with nortriptyline,⁴⁹ bupropion compared with doxepin,⁵⁰ and mirtazapine with amitriptyline and placebo.⁵¹ Weight change was the primary outcome measure in one study,⁴⁹ and assessed as an adverse event in the other two. The dosage of tricyclic antidepressant was not reported in one study,⁴⁹ and differed in the other two.

Beta-adrenergic blocking agents

Two studies compared the effect on lipid profiles between a chosen beta-blocker and an alternative anti-hypertensive agent: captopril vs. metoprolol⁵² and nifedipine vs. atenolol.⁵³ The effect of long-term treatment with propranolol on body weight study was the main outcome in one study.⁵⁴ Two studies compared treatment with a beta-blocker with bendroflumethiazide: one investigated the metabolic effects,⁵⁵ the other compared the effects on mortality.⁵⁶ Wilhelmsen *et al.*⁵⁷ compared beta-blocker treatment with diuretic treatment to determine differences in the incidence of non-fatal

myocardial infarction, coronary heart disease mortality and total mortality.

Cyproheptadine

No studies were identified that fulfilled the inclusion criteria.

Methodological quality of included studies

All studies included in this review were described as randomized, but in the majority (72%) the methods of randomization and concealment were not described. In one study,³⁵ the method of randomization (consecutive and alternate) was inadequate.¹⁴ In 11 studies the method of randomization was clearly described and considered adequate. Inclusion and exclusion criteria were clearly described in all studies. Intention-to-treat analysis was used in 51% of studies.

Weight change

In the majority of studies, weight change was not a primary outcome measure, but was measured and recorded under safety outcomes; weight change was a primary outcome measure in only six studies.^{17,24,29,42,49,54} The effects on body weight differed greatly amongst the different categories of drugs. In the majority of studies, weight gain was the result of treatment, with some of the greatest weight gains seen in subjects prescribed anti-psychotic medications. However, weight loss was observed in some studies (Table 2).

Six studies investigated whether weight gain was dose-related. Results varied, with three studies reporting no relationship between drug dosage and weight gain.^{17,23,24} Some correlation was observed between dosage of insulin and weight gain.^{35,36} One study⁴⁴ suggested that a clinically significant increase in body weight might be observed at higher doses of rosiglitazone.

Discussion

Weight change occurs over time and against a background of progressive weight gain in the 'normal' population. There is no ideal time to examine the possible obesogenic effects of drugs. It can be assumed that most such drugs will have a most marked effect early in treatment, reaching a plateau effect by 6–12 months (although all healthy subjects are likely to continue to gain weight at around 1 kg/year).^{58,59}

If the underlying disease for which the drug was prescribed has caused weight loss, then recovery on effective treatment will include weight regain.

The primary treatment of type 1 diabetes is an obvious example. This was not considered an obesogenic effect, and such studies were excluded by our own inclusion criteria

The effect of the drug treatment on body weight was reported in all of the studies in this review, and provides evidence that weight gain is associated with some drugs, and is a major and continual burden on public health. All of the drugs included in this review are used in the treatment of chronic disease. In the UK, it is estimated that around 2.6 million people have been diagnosed with coronary heart disease,⁶⁰ and beta-blockers (unless contraindicated) have a prominent role in its management.^{61–63} Valproate is one of the first-line treatments for epilepsy,⁶⁴ and is also used in the treatment of manic episodes associated with bipolar disorder. In Scotland, around 20 000–40 000 people have active epilepsy, with about 2000–3000 new cases per year.⁶⁴ In England ~380 000 people suffer from the disease (1:130 people).⁶⁵ Bipolar disorder is the third most common mood disorder after major depression and schizophrenia, and affects around 1% of the population.⁶⁶ Around 1.3 million people in the UK suffer from either type 1 or type 2 diabetes.⁶⁰ In the light of these figures, the number of individuals in the population receiving treatment with an obesogenic drug is potentially quite high. In Scotland alone, the number of prescriptions dispensed for beta-blockers and tricyclic antidepressants between 2004 and 2005 exceeded 1 million and 2 million, respectively (Table 3) (Audrey Thompson, personal communication).

It is generally accepted that during adult life, most people will gain weight. The rate at which weight is gained varies, but a 0.5–1 kg gain per year

Table 3 Prescribing by GP practices in Scotland, April 2004–March 2005

Drug class	No. of prescriptions
Beta-blockers (BNF 2.4)	2 936 456
Atypical antipsychotics	275 114
Lithium	81 252
Sodium valproate	193 064
Tricyclic antidepressant	1 134 611
Intermediate and long-acting insulins	352 632
Short-acting insulins	105 207
Suphonylureas	442 833
Pioglitazone	36 898
Rosiglitazone	65 458
Glucocorticoid therapy (BNF 6.3.2)	517 366

is considered average in the general population.^{58,59} In some studies in this review, weight gain in excess of this was observed over a much shorter duration: in particular, those involving anti-psychotic drugs. Olanzapine and clozapine were associated with the greatest weight gains, a finding that concurs with previous reviews in this area.^{67,68} The weight gains with beta-blocker therapy were relatively small, but more marked in those prescribed propranolol. Previous research has also identified propranolol as the beta-blocker most likely to cause weight gain.^{69,70}

In the UK at present, a significant proportion of the population are considered either overweight or obese,^{5,6} and an annual weight gain of 5 kg/year or more is not uncommon. It is therefore likely that prior to treatment with a drug known to favour weight gain, many individuals will already be overweight and struggling to avoid further gain. The additional effect of obesogenic drug therapy may tip the balance to increase BMI towards the obese category, or be sufficient to make co-morbidities clinically apparent. Given the common and long-term use of many of these drugs, it is likely that they play a significant contributory role in the increasing prevalence of obesity.

Non-compliance with any drug therapy is a widespread problem,⁷¹ and around half of patients prescribed long-term medication for the management of chronic diseases do not comply fully with treatment.⁷² Poor compliance with drug therapy may lead to a worsening of the underlying condition and contribute to increased health care costs.⁷³ Non-compliance is reported as an issue with many of the drugs included in this review,^{73–76} and the weight gain associated with them may contribute to this. For those prescribed anti-psychotic medication, weight gain is acknowledged as a major cause of non-compliance.⁷⁶ It is unclear whether this known side-effect is routinely discussed with patients prior to prescription but it should be, on medico-legal grounds. The treatment of anti-psychotic-induced weight gain is now considered a treatment priority,⁷⁷ and research on approaches to address this is a growing area.^{77–81} It would seem greatly preferable to discuss the probability of weight gain as a side-effect, and to provide effective advice and support to avoid weight gain. For a number of the drug classes included, weight management should form an essential part of treatment for the underlying disease, e.g. in type 2 diabetes and hypertension, access to dietitians should be routine. For other drugs (notably anti-psychotics) provision of dietary advice is a new consideration.⁸²

Study limitations

The drugs included in the present review were those consistently reported in medical/scientific literature, used in the treatment of chronic disease and believed to affect weight.^{3,9–12} Many other drugs prescribed today may also affect weight. Few studies included in the review examined weight change as a primary outcome, and in many instances the variability of weight change was not reported. Studies that primarily investigated the effect of a combination of 'obesogenic' drugs were excluded, but it was not always possible to be certain that other drugs known to favour weight gain were not also being taken. However, the process of randomization should have ensured that any such confounding effect would have been similar in all groups

Conclusions

This review provides evidence of the weight gain potential of some common drugs. It is perhaps only now, in light of the present epidemic of obesity, that the negative effect on body weight is a pertinent issue. Body weight and height are routinely recorded in virtually all clinical trials, but seldom reported. The potential of weight gain should be discussed with patients prior to the institution of therapy, both for medico-legal grounds and to ensure that weight maintenance is promoted and adhered to.

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