Drug-induced Obesity

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INTRODUCTION

Weight gain is a common, but often overlooked side effect to many widely used drugs. In susceptible individuals the weight gain may result in clinically significant obesity and associated comorbidities. Both tricyclic antidepressant medications and antipsychotic compounds are those prominently cited for producing persistent and problematic body weight gain in many treated patients and have a serious impact on medication compliance to an otherwise beneficial treatment. Furthermore, weight gain is often seen as an improvement of the psychiatric disease and therefore not recognized before the initial body weight is exceeded by several kilos. The mechanisms behind the weight gain are poorly understood. Many of these drugs interfere with central appetite-regulating neurotransmitters and may also produce sedative and anticholinergic effects, ultimately contributing to changes in energy expenditure. The incidence of weight gain during acute and chronic treatment with different classes of frequently prescribed drugs will be reviewed (Table 19.1), as will the possible mechanisms by which such drugs alter energy intake and expenditure, contributing to drug-induced weight gain (Table 19.2). Newer, effective medication classes, without the side effect of weight gain will also be discussed.

ANTIDEPRESSANT MEDICATIONS

Change in body weight is a frequent symptom of major depression, most likely a result of alterations in appetite. Patients typically lose weight (1–3), although some do gain weight during a depressive episode (3–5). As a pharmacologic treatment, the tricyclic antidepressants remain, even after almost 40 years, the first choice of medication for the treatment of severe major depression throughout the world (6). Although very effective agents for restoration of normal mood, there are numerous side effects associated with this drug treatment, particularly unwanted and excessive weight gain. Previously, weight gain during antidepressant treatment had been interpreted as a positive sign of improvement, so prevalent and predictable was the effect. Such weight gain is of concern to both patient and clinician, as this is the reason often cited for medication non-compliance. It is important to point out that over the past 15 years, several newer medications of a different drug class, the selective serotonin reuptake inhibitors (SSRIs), have become available. These drugs are effective as antidepressants, usually (but not always, see below) without the side effect of weight gain, but with other problematic side effects (6,7).
Table 19.1  Drugs causing obesity

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
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<tr>
<td>Antipsychotics</td>
<td>All subgroups</td>
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<tr>
<td>Antidepressants</td>
<td>Tricyclic antidepressants</td>
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<td></td>
<td>Lithium</td>
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<td>MAO inhibitors</td>
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<tr>
<td>Anticonvulsants</td>
<td>Valproate, carbamazepine</td>
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<tr>
<td>Antimigraine and antihistaminergic drugs</td>
<td>Cyproheptadine, flunarizine, pizotifen</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>Sulfonylurea agents, all insulin preparations, glitazones</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Pharmacological doses</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Non-specific, e.g. propranolol</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Estrogen (high dose), megestrol acetate, tamoxifen</td>
</tr>
<tr>
<td>Other</td>
<td>Some antineoplastic agents</td>
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</tbody>
</table>

Table 19.2  Putative mechanisms involved in drug-induced obesity

- Decreased serotonergic and dopaminergic activity
- Impaired mitochondrial beta-oxidation of fatty acids and other changes in substrate oxidation
- Reduced sympathetic nervous system activity
- Reduced energy expenditure
- Sedation
- Anticholinergic side effects causing dry mouth and increased intake of caloric beverages
- Altered activity of hypothalamic leptin and neuropeptide Y

Tricyclic Antidepressants

Two frequently prescribed tricyclic drugs, amitriptyline (8-11) and imipramine (11-13), have most often been associated with increasing body weight during treatment. Moreover, within the tricyclic drug class, amitriptyline appears to promote weight gain to a much greater degree than the others. Importantly, in a series of studies, no relationship between clinical response and weight gain was observed (9,11,13). In fact, weight change during drug treatment was not negatively correlated with that occurring at disease onset; that is, weight gain was not simply a reflection of weight lost during the depressive episode. These results suggest that drug-induced changes in weight probably result from a pharmacologic action of the drug independent of its effect on mood. The mechanism(s) by which tricyclic antidepressants promote weight gain are not well understood and can reflect changes in energy balance produced by increases in caloric intake, reductions in energy expenditure, or both. As described in the following sections, a reduction in energy expenditure is a key factor associated with the weight promoting effects of the tricyclic drugs, while changes in food intake probably contribute to a much smaller degree.

Tricycles, Ingestive Behavior, and Weight Gain

Much of the available information on antidepressants and ingestive behavior has been based on abundant anecdotal accounts. Unlike metabolic rate, where reasonable quantitative analyses are achieved, evaluating feeding behavior in drug-treated patients is much more difficult. Prior to the studies by Fernstrom (11,13,14), several reports described the presence of food cravings, particularly for ‘sweets’ or carbohydrates, associated with weight gain in some patients treated with tricyclic antidepressants. The inference of these reports is that weight gain resulted from excessive food consumption, based on increased desire. Only an occasional published report, however, has actually attempted to examine this issue with any precision. Paykel et al. (8), who coined the term ‘carbohydrate craving’, reported a craving for ‘carbohydrates’ among patients treated with amitriptyline. However, the desired ‘carbohydrate’ foods reported contained substantial amounts of fat (sometimes more than the carbohydrate) and were uniformly sweet tasting, like chocolate and pastry. Berken et al. (12) observed an increase in ‘sweets’ consumption in some patients treated with antidepressants, although no further description of the desired foods was provided. Such changes in food preference were reported to be large, and obvious to both patient and clinician.

These early studies lacked an accurate nutritional basis for defining food groups and evaluating food preferences. For example, numerous definitions
have been proposed for ‘carbohydrate’ foods (Table 19.3). This confusion in terminology indicates only that people eat foods not macronutrients, with many factors involved in preference. Certainly, once a food is eaten, the individual macronutrients are handled biochemically in the same manner, regardless of its presentation in the original food. However, the interesting and relevant study is to define which components of foods (e.g. macronutrient composition, sweetness, palatability) are driving the consumption behavior.

To address these questions a series of studies were conducted to determine how appetite changes during antidepressant treatment. A sound database for evaluating food preference changes during treatment was generated using a validated survey, the Pittsburgh Appetite Test (PAT) (14). The aims were to identify, systematically, the extent to which changes in food preference occur during tricyclic antidepressant treatment and how these might impact on subsequent weight gain. The PAT was not designed to quantitate food intake, but rather to focus on the issue of reported food cravings, and what foods these might be. Such information can help in identifying particular components generating food selection. This instrument can detect shifts in appetite and food preference, providing a reasonable index of eating attitudes and preferences. The food categories are based on macronutrient content and taste (i.e. a sugar-rich high fat food (chocolate) is different from a starch-rich high fat food (potato chips)) and were easily recognizable to the patients. Patients completed the PAT two to three times during the medication-free period, and then monthly during treatment with imipramine.

The results from the PAT at the end of 4 months of treatment (the period of time associated with the greatest incidence of weight gain) do not show marked changes in preference for calorically dense (high fat) foods with or without a sweet taste, nor for any of the foods in the other categories. Although no significant changes were noted in preference for sweets, a small percentage of patients (15%) did experience a notable change in preference toward carbohydrate-fat rich sweet tasting foods (13). It is important to point out that the craved food items contained both carbohydrate (mostly sucrose) and fat, while no preference was expressed for sweet foods containing sucrose and little fat (fruit, gum drops), nor for sweet foods without sucrose or fat (i.e. fruit, which contained fructose). It thus seems unlikely that sweetness alone is the determinant of choice. Both sweetness and fat content apparently motivate preference in these patients, a result compatible with those obtained by Drewnowski and Greenwood in normal subjects (15). It is noteworthy that shifts in food preference toward carbohydrate-fat rich sweet foods are also found in another group: the actively ill depressed patient. A marked increase in cravings for these foods was present in more than a third of depressed patients (14).

Clinical outcome was not correlated with preference for sweet/fat food items: when comparing those with cravings to those without, no changes in clinical improvement were noted. Moreover, although substantial weight gain (> 5 lb (2 kg)) was noted in 43% of patients, neither weight gain nor the presence of obesity predicted who would seek such palatable, calorically dense foods (13).

Presently, it is unclear the extent to which increases in food intake, prompted by food cravings promote antidepressant-induced weight gain. Generally, a craving for sweet, calorically dense foods does not appear a significant problem for most treated patients, although this association can be seen in an occasional patient treated with a tricyclic medication, and could promote weight gain in the susceptible individual.

Tricyclics, Energy Expenditure, and Weight Gain

Alterations in energy expenditure can directly contribute to body weight change. Reductions in one or more compartments of energy expenditure (resting metabolic rate, diet-induced thermogenesis, exercise) can produce increases in body weight. Depressed patients treated with tricyclic medications might well produce weight gain via this mechanism, since these drugs might be predicted to alter sympathetic nervous system function and thus metabolic rate. Thus, the positive energy balance resulting in weight gain might be accounted for by a decrease in caloric utilization, making an individual more energy efficient and promoting weight gain. Resting metabolic rate (RMR) represents the greatest energy compartment, with at least 70% of daily energy use dedicated to maintenance of body systems (16); RMR probably accounts for an even greater proportion of calories in hospitalized patients due to their greater inactivity. Thus, should a
reduction in energy expenditure occur during anti-depressant treatment, RMR measurements are likely to reveal it. RMR is a technique which is reliable, and readily quantitated under controlled conditions. In one of the few clinical studies, a consistent reduction was found in the resting metabolic rate of patients treated with tricyclic antidepressants (17).

Because metabolic rate has a relatively wide range of 'normal' values, it is important to use each subject as his or her own control. Comparing triplicate measurements obtained during a 2-week medication-free period with those obtained during the second and fourth weeks of drug treatment, the drug-free, control measurements are quite reproducible, and RMR values are within the normal range for each patient's height and weight. After treatment with a tricyclic drug for 2–4 weeks, sizable reductions in RMR were observed (18). Consistent with the observed reductions in RMR is the notable decrease in diet-induced thermogenesis (DIT) (the naturally occurring increase in RMR after food ingestion) in some treated patients. Such reductions in RMR are remarkably large, and exceed by far changes in RMR produced by other stimuli. Exercise, for example, produces a 5–10% change in RMR, an effect considered to be robust. These results suggest that the magnitude of the change in RMR after drug treatment is physiologically important, and could have important ramifications in overall metabolic activity. Such changes, translated into calories, predict a reduction in daily caloric need of about 300–400 kcal/day. Thus, an individual might be expected to gain a pound every 10–14 days, independent of a change in food intake. The reductions in DIT after a single meal, although modest (accounting for about 10–25 kcal), would likely be repeated every time food is ingested (four to seven times/day), supporting an additional contribution to the decline in energy expenditure. These results support the idea that reductions in caloric expenditure during drug treatment probably contribute to problematic weight gain. In fact, an increase in body weight would normally be expected to raise, not lower, RMR (16), suggesting further that the effect on metabolic rate is drug-related.

Although the underlying mechanism(s) eliciting changes in metabolic rate are presently unknown, it is apparent that alterations in caloric expenditure do contribute to weight change in patients treated with tricyclic medications. Because both RMR and diet-induced thermogenesis seem to be altered, it is reasonable to suggest that reductions in sympathetic nervous system (SNS) tone contribute to these effects.

### Serotonin Specific Reuptake Inhibitors (SSRIs)

The SSRIs have proven to be effective treatment for depression, without the problematic side effect of excessive weight gain. The apparent lack of appetitive effects and perhaps an enhancement of resting metabolic rate contribute to the lack of weight gain observed. However, there are atypical responders to particular SSRIs, which do occasionally produce significant weight gain (19,20). This seems unrelated to changes in sympathetic tone, as reported for the tricyclic drugs. Thus, because the SSRI drugs are not usually associated with weight gain, this class of serotonergic drugs may be a more attractive treatment alternative, particularly in patients where drug-induced weight gain has been problematic.

### SSRIs, Ingestive Behavior, and Weight Gain

For paroxetine, 2% of treated patients experienced weight gain over 6 weeks, while weight gain is highly variable by the end of one year (20). Thus, although the incidence is low, it is possible for susceptible individuals to experience some weight gain during treatment with paroxetine. Fisher et al. (21) reported an increase in weight during treatment with either sertraline or fluoxetine, while weight promoting properties of citalopram (22) have also been reported.

Multiple hypotheses exist to explain the incidence of SSRI-induced increases in body weight. Blockage of 5HT2C receptors can increase appetite (23) as demonstrated by the upregulation of these receptors in rat brain (24). Alternatively, dopamine (D2) receptors antagonized, indirectly by 5HT cont-

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<th>Table 19.3</th>
<th>Definitions of 'carbohydrate' foods</th>
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<tr>
<td>Carbohydrate/fat rich; sweet taste</td>
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<td>Carbohydrate/fat rich; savory taste</td>
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<td>Carbohydrate rich/low fat; sweet taste</td>
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<td>Carbohydrate rich/low fat; savory taste</td>
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nections, can also increase appetite (as demonstrated for antipsychotics, see below). Histamine may also explain these effects, with H1 receptor antagonism also associated with an increase in appetite (22).

**MONOAMINE OXIDASE (MAO) INHIBITORS**

Weight gain has been described in a relation to older MAO inhibitors, whereas this side effect seems to be less prominent with the selective, reversible drugs such as moclobemide. These compounds may therefore represent an alternative treatment modality.

**LITHIUM**

Weight gain with lithium treatment is quite common, with estimates ranging between one-third and two-thirds of treated patients (25). Weight gain appears to be dose-related, and this side effect remains a leading reason for medication non-compliance (26). Interestingly, weight gain is more likely to occur in patients already overweight, and seems more problematic in female patients (25,27). The weight gain may be as much as 10 kg during a 2- to 10-year period.

The mechanism(s) responsible for lithium-induced weight gain are diverse and relatively inconsistent (25). These include increased appetite, increased fluid intake, altered energy metabolism and endocrine changes, including medication-induced hypothyroidism (28).

**ANTIPSYCHOTIC MEDICATIONS**

Weight gain as a side effect of antipsychotic treatment has been well documented for over 40 years (29,30) but its importance in the clinical management of chronic schizophrenia has been downplayed (31). Like antidepressants, it is also a common reason for medication non-compliance (31–33). Although numerous mechanisms have been proposed to explain such medication-induced weight gain, the mechanism(s) involved are even less clear than those for antidepressants; some data support a role for changes in appetite and food intake, as well as energy expenditure. Mefferd et al. (29) have suggested that increased appetite can account for weight gain, although this is poorly understood. It is possible that increases in thirst (resulting from the anticholinergic action of many drugs) result in increased caloric intake through increased fluid consumption (34), or from inactivity resulting from medication-related sedation (34), although these are presently only hypotheses.

**Conventional Antipsychotics**

Phenothiazines have been shown to be weight promoting during the chronic treatment of schizophrenia. Chlorpromazine (35), chlordiazepoxide (36) and thioridazine (36) increased weight significantly, compared to placebo. Ganguli (37) reported weight gain with haloperidol, thiothixane and fluphenazine. It has been suggested that weight gain is not proportional to dose, since depot injections of varying dosages did not correlate positively with weight gain (37–39). The weight gain can vary between 1–5 kg over several years to exorbitant weight increases in a few months of more than 28 kg, as illustrated in the cases shown in Figure 191.

**Novel Antipsychotics**

Clozapine is clearly associated with weight gain during treatment, and is among the greatest weight promoters of the antipsychotics (40,41), while molindone appears to be the only novel compound without weight promoting effects (41). Both clozapine and olanzapine appear to increase body weight through a leptin-mediated mechanism, since serum leptin levels increased during treatment with these compounds (42,43). A recent review ranked weight gain among the novel antipsychotics as follows: clozapine and olanzapine, risperidone and sertindole (44). The authors suggest a strong correlation with the histamine binding properties of these compounds (44) as a possible mechanism of action. Finally, weight gain and obesity may also arise in children after prenatal exposure to antipsychotic drugs such as haloperidol, which in the case reported by Breum (45) was prescribed as an
Two cases of drug-induced obesity in previously normal-weight women. Patient 1 (solid line) was treated with levomepromazine for only 7 months and increased her body weight by 28.7 kg. Patient 2 (dashed line) was treated for 4 years with chlorprothixene and was finally referred to a department of endocrinology due to ‘unexplained’ weight gain and a suspected endocrine disturbance.

Weight Gain and Clinical Improvement

It has been suggested, as with antidepressants, that weight gain during neuroleptic treatment is a positive sign of improvement (3), and is necessary for a positive outcome, an observation confirmed by Leadbetter et al. (40). However, more recent data suggest that, in fact, weight gain is not necessary to achieve effective pharmacologic activity and improvement in symptoms (40,41).

Antiepileptic Drugs

Weight gain is one of the most prevalent side effects of several antiepileptic drugs, but has been particularly related with the use of valproate (valproic acid), a short-chain fatty acid widely used as an antiepileptic drug, and sometimes for the treatment of mania (46–49). In retrospective studies, treatment with valproate has been found to increase body weight by 4.0 to 7.5 kg in more than 60% of the patients (47,48). It has not been possible to detect any differences between weight-gainers and weight-stable patients with regard to family history, sex, age, reported appetite, duration, dosage or serum levels of valproate (48,50). The weight gain varies between different individuals and study populations, but might often amount to 20 kg and not infrequently resulting in discontinuation of the treatment (49). The pathogenetic mechanism is still largely unknown. Changes in thyroid hormones have earlier been proposed as an explanation (51), but a subsequent clinical study by Breum has not supported this theory (52). Valproate interferes with the gamma-amino butyric acid neurotransmitter system, which might affect the appetite regulation, but this remains unstudied. In one of the few physiological studies performed in patients before and during valproate treatment, it was not possible to demonstrate any significant differences in either energy intake obtained by food records or energy expenditure during a glucose load and under basal conditions (52). It has been suggested that a reduced beta-oxidation of fatty acids, as found in the above study, could be of etiological importance since valproic acid is known to enhance the excretion of carnitine, which is an essential cofactor for the transport of fatty acids across the mitochondrial membrane (53,54). The impact of valproate on serum leptin and insulin levels has also been measured, but it seems to reflect the obese state more than any specific effect of valproate treatment (55).

Animal studies are of limited interest due to difficulties in interpreting the results since drug treatment decreases food intake and enhances energy expenditure in many animals (56–58).

Weight gain is also a commonly described side effect to carbamazepine treatment of both epilepsy and mania. However, both the size of the problem as well as the number of studies are limited compared to valproate. In a study from the Veterans Affairs Epilepsy Cooperative Study Group it was shown that long-term treatment with carbamazepine was associated less frequently with weight gain more than 5.5 kg than with valproate (20% vs. 8%) (59). In susceptible individuals, the weight gain can be very pronounced and has been associated with a sharp increase in food intake and weight gain up to 15 kg over a few months (60). It is often necessary to stop the treatment before normal body weight can be achieved.
As with valproate, the mechanisms contributing to the weight gain are unknown, but since carbamazepine shares some chemical properties with tricyclic antidepressants it might affect body weight regulation through the same serotoninergic and noradrenergic pathways increasing the appetite, as suggested in some cases (60).

During the last decade, several new antiepileptic drugs have been introduced into clinical practice. One of those drugs, vigabatrin, is normally better tolerated than the older compounds, but has recently been shown to be more frequently associated with weight gain than carbamazepine (61). In contrast to this finding, weight gain has not been yet been described with lamotrigine and this drug may therefore represent an alternative treatment modality at least in some types of epilepsy.

ANTIANXIETY DRUGS

Benzodiazepine and its derivatives have in short-term experiments been shown to promote hyperphagia and weight gain in rodents due to an effect on dopamine D2 receptors (62) or gamma-aminobutyric acid neurons (63), whereas long-term animal experiments have not been able to confirm these findings (64). Very few clinical human studies have been published reporting changes in body weight during treatment with anxiolytics. In a small study with myelopathy patients, a reduction or discontinuation of the diazepam medication in high doses resulted in a weight loss of 5 to 16 kg during a 10-month period. In a subgroup of the patients, who were reintroduced to the pharmacological treatment, body weight increased by 3 to 12 kg (65). However, in other larger human studies comparing various anxiolytics with other psychotropic drugs in subjects without severe physical handicaps, weight gain has not been reported as a side effect (66,67). Weight loss has also been described (68). Thus, in summary, benzodiazepines are unlikely to cause any significant weight gain in clinical practice.

ANTIMIGRAINE AND ANTIHISTAMINERGIC DRUGS

Weight gain is a common and early side effect of drugs such as sumatriptan (69) and cyproheptadine (70) probably due to their combined antihistaminergic and serotoninergic effect. The weight changes are, however, rather modest and the clinical importance of the problem is limited. Because to its ability to increase appetite attempts have been made to use cyproheptadine as a pharmacological support in the treatment of both anorexia nervosa (71) and cancer cachexia (72), but so far without encouraging results. Newer, non-sedating antihistaminergic agents such as loratadine and astemizole also produce weight gain, but to a lesser degree than the older compounds (73). The calcium antagonist flunarizine, used in migraine prophylaxis, has in several studies (74,75) been shown to increased appetite and induce a dose-dependent weight gain of up to 4 kg during the first months of the treatment period (74,76). The mechanism is not known, but an appetite stimulating effect involving brain dopamine and other central neurotransmitters has been suggested.

BETA-BLOCKERS

Treatment with non-specific beta-blockers, such as propranolol, has been associated with a modest, but sustained weight gain (77,78). In a large retrospective study of 3837 patients randomized to either propranolol or placebo treatment after a myocardial infarction, a weight gain of 2.3 kg was found after the first year in the beta-blocker treated patients compared to 1.2 kg in the placebo group. The difference between the groups remained during the following 2 years (77). The mechanism behind the weight gain is thought to be mediated through an effect on beta-receptors resulting in a reduction of the energy expenditure, including facultative thermogenesis, by approximately 200 kJ/day. In the recent UKPDS 39 substudy (79), atenolol and captopril were found to be equally effective in lowering blood pressure and reducing the risk of diabetic complications. However, the patients treated with atenolol showed a larger weight gain than those treated with captopril during a 9-year study period (3.4 kg vs. 1.6 kg). During the first 4 years of the study, the glycated haemoglobin was slightly higher in the atenolol group and more patients required additional glucose lowering treatment at the end of the study. It has been suggested (80,81) that beta-blockers might worsen the already impaired insulin
sensitivity found in obese subjects, but the recent data from the UKPDS and other studies showed a reduced risk of cardiac events in beta-blocker treated patients (79).

**INSULIN AND ORAL HYPOGLYCEMIC AGENTS**

Intensive blood glucose control has, in large intervention trials, been shown to increase body weight in both type 1 and type 2 diabetic patients (82,83). In the Diabetes Control and Complications Trial (DCCT), intensive treatment with either multiple daily injections of insulin or continuous subcutaneous insulin infusion resulted in a 60% increased risk of a body weight more than 120% of the ideal body weight. On average, the intensively treated patients had a weight gain of 5 kg compared to the patients treated with conventional insulin regimens (82). Most of the weight changes appeared during the first year of treatment (82,84). In another DCCT substudy it was concluded that the changes in lipid levels and blood pressure that occur with excessive weight gain with intensive therapy were similar to those seen in the insulin resistance syndrome and may increase the risk of coronary artery disease in this subset of subjects with time (85). Not surprisingly, more female than male patients have been found to be worried about weight gain as a side effect and this may prove a significant impediment to the clinical implementation of intensive insulin treatments. It has been estimated that 70% of the weight gain can be accounted for by reduced glucosuria and that 30% is due to a reduction in energy expenditure by the reversal of the catabolic changes in carbohydrate, protein and lipid metabolism (86). Increased body weight has also been found in young type 1 patients on intensive therapy and might, especially in adolescent girls, influence adherence to good metabolic control regimens (87,88).

In type 2 diabetes, the UKPDS study showed that weight gain was significantly higher in the intensive group (mean 5.4 kg) than in the conventional group (2.5 kg), and patients assigned to insulin had a greater gain in weight (6.5 kg) than those assigned to chlorpropamide (5.1 kg) or glibenclamide (3.2 kg) (83).

In contrast to these findings, a UKPDS substudy with metformin in obese type 2 patients showed that the weight gain in metformin treated patients was similar to the conventional control group and less than the weight increases found in patients assigned to intensive treatment with insulin or sulphonylureas (89). In addition, patients who received metformin also had a more favorable outcome with respect to diabetes complications and mortality (89). If diabetes control cannot be achieved by metformin treatment alone, it should be combined with bedtime insulin since this treatment modality has been shown in a recent 12-month study to prevent weight gain and provide acceptable metabolic regulation (90). Also the newer glitazones have been associated with a modest, but significant, weight gain, although long-term data are still lacking.

**ESTROGENS AND OTHER HORMONE DERIVATIVES**

In earlier reports weight increases have been described in relation to older high dose hormonal contraceptives and weight gain is still one of the most prevalent complaints of women using oral hormonal contraceptives. However, the typical present day combination therapy contains only small doses of estrogen and progesterone and these compounds have not been associated with excessive weight gain apart from cyclic periods of moderate water retention in some individuals (91,92).

In postmenopausal women, several studies (93,94) have also demonstrated that hormone replacement therapy if anything may lead to a small weight reduction. This effect is not fully understood, but increased lipid oxidation seems to be of importance, whereas circulating leptin is not affected (95,96).

In contrast to these findings high to moderate doses of megestrol acetate have been shown to increase appetite and body weight in women with advanced cancer disease (97,98). Tamoxifen, a partial oestrogen receptor antagonist used in postmenopausal women with breast cancer, also promotes weight gain (99–101), but to a lesser extent when used as monotherapy (102).

These compounds, especially megestrol acetate, have therefore been suggested as adjuvant treatment in patients with cancer-induced cachexia (98). Other non-hormone antineoplastic agents such as
cyclophosphamide and fluorouracil have also been associated with weight gain exceeding the pre-illness body weight in patients with early stage cancer disease (103). The mechanisms have not been elucidated and very few data are available.

GLUCOCORTICOSTEROIDS

Weight gain is a common adverse effect of long-term pharmacological treatment with glucocorticoids in patients not suffering from adrenal insufficiency (104–106). In a 12-month study of 109 patients with polymyalgia rheumatica/giant cell arteritis, a steroid-related dose-dependent weight increase of between 2 and 13 kg occurred in more than 50% of all patients (104). In a large retrospective study with 774 patients examined before and after liver transplantation, mean body mass index (BMI) increased from 24.8 kg/m² initially to 28.1 kg/m² in the second year after the operation (105). Of the 320 patients who were not obese before transplantation more than 20% became obese later. Interestingly, both donor and recipient BMIs were found to be risk factors for weight gain together with a high cumulative prednisolone dose. Other studies have suggested that intermittent use of glucocorticoids may diminish the weight gain (107), but data are not overwhelming. Glucocorticoid treatment also affects body fat distribution by predominantly increasing the abdominal fat tissue mass (108) and together with the more immediate effects on insulin resistance this may increase the risk for cardiovascular diseases and later diabetes.

The mechanisms behind glucocorticoid-induced weight increase is not fully understood, but it is well known that glucocorticoid hormones are important in obesity, since adrenalectomy will reverse or prevent the development of most forms of obesity in animals. It has been suggested that glucocorticoids may primarily exert an effect on energy balance through a stimulating effect on food intake since animal studies have shown that centrally injected glucocorticoids inhibit the hypothalamic effect of leptin and increase the activity of neuropeptide Y (NPY) (109,110). Central glucocorticoid infusion has also been shown to produce a marked decrease in the expression of uncoupling protein UCP1 and UCP3. In contrast to these results it was not possible to show any decrease in free-living energy expenditure or significant changes in substrate oxidation using the doubly labelled water method in healthy female volunteers taking 1 mg of betamethasone twice a day for 21 days (111). Other short-term human studies also failed to demonstrate an effect on energy expenditure or plasma leptin levels whereas energy intake was increased (112,113).

SUMMARY AND CONCLUSIONS

Weight gain associated with tricyclic antidepressant and certain antipsychotic medications is problematic for many treated patients, and often a reason for non-compliance. Such weight gain is associated, at least in part, with reductions in resting metabolic rate and diet-induced thermogenesis. Changes in food preference towards calorically dense (‘fattening’) sweet-tasting foods do not appear to affect a majority of patients treated with tricyclic medications, but can occur. When such preference changes do occur, though, they are not associated with the development or maintenance of obesity. Another class of antidepressants, specific serotonin reuptake inhibitors (SSRIs), have been used in the past few years as effective antidepressants, but do not promote weight gain during treatment, although this is occasionally seen. The antipsychotic medications often promote weight gain, particularly the conventional medications, but also some of the novel antipsychotics seem to have weight promoting effects. Although the mechanism(s) for antipsychotic-induced medications is poorly understood, increased caloric intake, a change in leptin response, and reduction in physical activity have all been proposed. Medication-induced weight gain is a significant problem for many treated patients, and the weight promoting effects of different psychiatric drugs should be considered in drug selection. A selection of the least weight promoting medication may promote drug compliance for many treated individuals, as well as avoid the comorbidities associated with increasing weight and obesity.

With respect to other drugs, the weight increases are often more modest, but can be a very serious problem with compounds used for chronic medication or long periods as with antiepileptic drugs such as valproate. The weight increases due to insulin or sulfonylurea agents not only might
worsen the metabolic control in diabetic patients, but are also a major factor in non-compliance. So far only very few studies have been performed elucidating specific treatment possibilities in these groups of patients. Unfortunately, none of the current available anorectic agents have so far been studied in these groups of patients. Dietary advice, including avoidance of high calorie beverages, and lifestyle and exercise programs are still the fundamentals for the treatment of medication-induced weight gain. However, the recent advance in obesity research and especially the increased understanding of brain function may provide new possibilities for further treatment.

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