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Review article

Behavioural management of antipsychotic-induced weight gain: a review

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Objective: Although psychiatrists are aware of weight gain induced by atypical antipsychotics, only few studies on behavioural interventions in this patient group are published. This review aims to summarize the evidence on effectiveness of behavioural interventions for weight gain in the general population and in-patients treated with atypical antipsychotics.
Method: Medline and Cochrane databases search for evidence on effectiveness of behavioural interventions.
Results: In general, behavioural approaches including, diet, exercise and drug treatments may be effective. There were only 13 studies of behavioural interventions for patients taking antipsychotic medication. No study met the criteria for a RCT. Calorie restriction in a controlled ward environment, structured counselling combined with cognitive behavioural therapy and counselling on life style and provision of rewards may potentially lead to weight loss.
Conclusion: Currently only limited, methodologically flawed, evidence is available that behavioural interventions in overweight patients treated with antipsychotics, although intuitively appealing, actually work.

U. Werneke[1], D. Taylor[2], T. AB. Sanders[3], S. Wessely[4]

[1]Centre for the Economics in Mental Health, Institute of Psychiatry, [2]Pharmacy Department, Maudsley Hospital, [3]Department of Nutrition and Dietetics, King's College, and [4]Academic Department of Psychological Medicine, King's College School of Medicine and Dentistry and Institute of Psychiatry, London, UK

Key words: weight gain; atypical antipsychotics; diet; exercise; review; randomized controlled trial

Dr Ursula Werneke, Homerton Hospital, East Wing, Department of Psychiatry, Homerton Row, London E9 6SR, UK
E-mail: ursula.werneke@elcmht.nhs.uk

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Introduction

In psychiatric practice, weight gain is a long recognized and commonly encountered problem (1, 2). Weight gain has become increasingly prominent with the advent of the newer atypical antipsychotic agents. Of these, clozapine, olanzapine and zotepine, seem to cause substantial weight gain, more than risperidone, amisulpride and most conventional neuroleptics (3–6). Ziprasidone, aripiprazole and possibly quetiapine produce less weight gain, however, clinical data are still scarce (4, 7). Generally, weight gain usually occurs in the first months of treatment (1, 8, 9), the pattern of weight gain varying between different agents. For instance, Clozapine often results in continuous weight gain (10, 11), whereas olanzapine associated weight gain usually plateaus after 40 weeks (12, 13).

Atypical antipsychotics may have marked central, metabolic and endocrine effects. Centrally-acting mechanisms include the blockade of serotonergic, dopaminergic, adrenergic, histaminergic, cholinergic and glutaminergic receptors (1, 4, 14) resulting in increase in appetite, ingestion of high caloric drinks because of dry mouth and decrease in energy expenditure as a result of sedation. Metabolic effects include an initially increased insulin sensitivity leading to relative hypoglycemia and thus to craving. This may lead to insulin resistance as a compensatory mechanism to prevent further weight gain (15). Particularly, clozapine and olanzapine appear to result in insulin resistance, being characterized by an increase in serum triglyceride levels (16–18) and impaired glucose tolerance. Resistance to the antilipolytic action of insulin causes an increase in the flux of non-esterified fatty acids (NEFA) into the liver which stimulates triglycerides synthesis and very low density lipoprotein secretion, which results in elevated serum triglyceride concentration and a concomitant fall in high density lipoprotein cholesterol concentration. Elevated plasma NEFA may further aggravate insulin resistance because of their inhibitory effects on both glucose transport

and glucose metabolism in skeletal muscle. Thus elevated plasma NEFA may both be a cause or a consequence of insulin resistance. Insulin resistance is associated with an increased risk of coronary heart disease and may lead to type 2 diabetes mellitus (19–22). Insulin resistance is also characterized by an enlarged visceral fat pool which is characterized by an increased waist circumference or waist/hip ratio. This may particularly put women at risk shifting towards central (abdominal) obesity (23, 24). Sex hormone dysregulation shifts the balance between oestrogens and androgens and can lead to further weight gain and altered fat patterning.

Little is known about patients' and clinicians' attitude towards weight gain as an antipsychotic-induced side effect. Weight gain has previously been seen as a necessary 'evil' (hence the common description- 'rather overweight and mentally present') (25–27). However, clinicians are now concerned about the associated health risks including diabetes mellitus, cardiovascular disease, hypertension and cancer to ensure that the achievements of the new medications are not to be offset by the increased risks of physical diseases. For instance, Fontaine et al. (28) have estimated that the lives saved by using clozapine might be offset by the associated deaths because of weight gain. Furthermore, weight gain adversely affects compliance (6, 29, 30).

There are many recommendations on how to prevent or treat weight gain. Interventions suggested include weight monitoring and behavioural measures such as diet and exercise but their effectiveness remains unclear (31, 32). A recent claim that weight gain could be successfully managed in the majority of cases in patients with psychiatric disorders if clinicians monitored and treated promptly (33), may be over-optimistic. In a previous paper, we have reviewed the potential role of pharmacological interventions (14), and in this paper we aim to (i) summarize the evidence on the effectiveness of behavioural interventions to prevent and treat weight gain as applied to the general population; and (ii) to review the potential of behavioural interventions in patients gaining weight when treated with antipsychotics.

Material and methods

We searched the Medline and Cochrane databases for evidence in regard to the effectiveness of behavioural interventions for the prevention and treatment of overweight patients treated with antipsychotic medication and individuals in the general population. We included the following search terms, 'obesity', 'overweight', 'adiposity', 'weight loss', 'weight gain', 'prevention', 'behavioural intervention', 'diet', 'exercise', 'trial' 'antipsychotic'. All recovered papers were reviewed for further relevant references. All evidence was collated and ranked as available. Information on effectiveness of prevention and treatment of overweight individuals in the general population was mainly derived from systematic review by Glenny et al. 1997 from the NHS Centre for Reviews and Dissemination, University of York (34, 35) and summarized. Reviewing behavioural interventions in patients taking antipsychotic medication we considered and abstracted all studies identified.

Results

Effectiveness of behavioural interventions for the prevention and treatment of overweight

The systematic review by Glenny et al. (34, 35) examined behavioural prevention and treatment of obesity as well as maintenance of treatment effect. The review was restricted to trials with weight change as the principal outcome measure and at least 12 months of follow-up. Key strategies include education, weight monitoring, food diaries, dietary changes towards reduction of fat intake to no more than 30% and an increase in fruit, vegetable and high fibre intake. Exercise programmes aim at increasing energy expenditure. Cognitive strategies enhance the understanding into maladaptive eating patterns and assist monitoring progress through regular review.

Prevention of adult onset obesity. The systematic review identified three studies addressing prevention of adult onset obesity. Community-based education programmes including use of mass media, direct mailing, classes, seminars and school curricula were suggested to be effective in preventing obesity (36–38). These interventions may be combined with weight monitoring and linked with financial incentives. However, the success of such measures may depend on educational attainment and intellectual capacity.

Treatment of adult obesity. Behavioural approaches including, diet, exercise and drug treatments have all been shown to be effective to some extent. Promising approaches included food provision (39) or meal plans and grocery lists (40). There was no evidence that restriction of fat intake is superior to restriction of overall calorie intake (41, 42). Equally, it remains unclear whether increase of dietary fibre can be beneficial (43, 44). Exercise on

its own may prevent weight re-gain (45). Combined diet and exercise programmes were superior to diet alone, but only if accompanied by a behavioural programme (46, 47).

It is important to note that, the risk of physical illness does not only depend on the degree of overweight but also the distribution of the fat pool. For instance, individuals with an increase in visceral fat are at higher risk of type 2 diabetes and cardiovascular disease (48–50). Smith and Zachwieja (51) reviewed strategies to reduce the visceral adipose tissue preferentially. They found energy restricted diets (800–1000 kcal/day) to be effective, but very low calorie diets (400 kcal) did not offer any advantage. Physical exercise may also be important in the reduction of abdominal obesity even if no overall weight loss is achieved (52).

Maintenance of treatment effect. Extension of behavioural therapy into the maintenance phase may yield further benefits (53). Cue avoidance (54), i.e. avoidance of situations which may stimulate overeating, was the only effective cognitive strategy identified (34, 35). Behavioural therapy by correspondence (55) and daily weight charting (56) were identified as approaches which would warrant further research. For instance, no intention-to-treat analysis was conducted in either study. The majority of studies found weight re-gain which may already start during treatment. Effective maintenance strategies including continued contact with the therapist or self-help groups combined with therapist led booster sessions may be necessary to sustain weight loss. Long-term food provision or meal plans may not be practicable. However, it may be necessary to continue maintenance programmes life-long (57).

Behavioural interventions for patients taking antipsychotic medication

We identified 13 studies using weight change as a main outcome published over a period of 38 years (20, 58–69). Papers seemed to cluster around the 1960s and the year 2000/2001, reflecting rising awareness of side effects after the introduction of new agents. No study met the criteria for a RCT. Two studies were retrospective case-note reviews (20, 58). Five studies used a contemporary control group (58, 59, 64, 67, 68), and one study used a historical control group (62). In all studies, sample sizes were small suggesting insufficient power to detect any potential effect of the intervention chosen. Nine studies followed-up their patients for less than 1 year (59–61, 63–68). Interventions included behavioural counselling and energy restricted diets but only two studies included exercise in its intervention (20, 59) (Tables 1 and 2).

Energy restriction in a controlled ward environment led to weight loss in eight studies (58, 59, 62, 65–69) but the effect was not always significant (58, 59, 67). Counselling during routine outpatients did not lead to weight loss, but structured counselling combined with cognitive behavioural therapy (CBT) led to a significant reduction of mean BMI from 29.6 to 25.1 kg/m^2 (61). However, this study did not use a comparison group. Rotatori et al. (64) conducted an intervention study using counselling on life style and the use of rewards such as positive verbal reinforcement or extension of ward privileges leading to a significant weight reduction in the intervention group.

Discussion

Although psychiatrists seem aware of weight gain induced by atypical antipsychotics the few studies which exist are methodologically weak. Problems included small sample sizes, lack of suitable control group, insufficient duration of follow-up and, crucially, an absence of random allocation. Of the seven studies with control groups, only two studies yielded a significant result, one of which used a historical control group (62, 64). Thus, there is currently very limited evidence available that behavioural interventions in overweight patients treated with antipsychotics actually work. To our knowledge, no randomized controlled trial has been conducted to test weight control interventions in patients taking atypical antipsychotics. Clearly, this is needed, as measures such as dietary counselling, although intuitively appealing, may not be effective.

Prevention or treatment of obesity in patients on oral antipsychotics may be a daunting task as the drugs by virtue of their receptor affinities and endocrine effects produce weight gain. These effects may be so powerful as to eclipse the efficacy of behavioural interventions. Serum leptin levels increase with clozapine or olanzapine therapy, probably because of increased appetite, overeating and weight gain (70, 71). This reflects a normal physiological response increasing satiety. This mechanism can be overridden by maladaptive learnt behaviour ignoring the normal physiological clues. In atypical antipsychotics leptin increase may be independent of weight gain as the effect may be immediate (70, 72). Atypical antipsychotics would then constitute a risk factor for cardiovascular disease in their own right as

Table 1. Studies testing behavioural interventions in overweight psychiatric patients

Authors and ref.	Type of study	Sample	Inclusion criteria for analysis	N intervention group	N Control group
Cohen et al. (58)	Retrospective case note review	Fifty adults with mental retardation treated with risperidone	Mean weight gain of 8.3 kg in 2 years	20	19
Ball et al. (59)	Intervention study	Thirty-one out-patients with schizophrenia treated with olanzapine for 7 months at a dosage between 15 and 40 mg and who had gained at least 7% of their pretreatment weight	For intervention group, completion of intervention	11 including: seven males and four females (10 dropouts)	11 (matched)
Nguyen et al. (60)	Intervention study	Twenty-two out-patients with schizophrenia, schizoaffective or bipolar disorder treated with olanzapine with a mean BMI of 28 kg/m^2 (range 19–39.9)	All included	22 including 14 males and eight females	None
Umbricht et al. (61)	Intervention study	Nine patients with schizophrenia and one patient with bipolar affective disorder, all treated atypical antipsychotics	Completion of intervention	6 including two men and four women (four dropouts)	None
Alquila & Emanuel (62)	Intervention study	Thirty-two patients with schizophrenia or schizoaffective disorder living in a care facility for formerly homeless persons with serious mental illness	Completion of intervention	32	17 (historical)
Wirshing et al. (20)	Retrospective case note review	Ninety-two patients with schizophrenia participating in eight different drug trials producing 122 records	Six-year study period	122	None
Merriman et al. (63)	Intervention study	Six patients with diagnoses of schizophrenia, psychosis, episodic dyscontrol syndrome and psychopathic personality disorder with a BMI $\geq$ 25 receiving medication on a rehabilitation ward	Completion of intervention or weight loss at dropout at an earlier stage	6 including three men and three women (one dropout at week 9)	None
Rotatori et al. (64)	Intervention study	Fourteen patients with adjustment reaction to adult life or schizophrenia undifferentiated type in a semi-dependent residential setting randomized after selection into intervention and control group	All included	7 including three men and three women (three dropouts at follow-up)	7 including three men and three women (two dropouts at follow up)
Knox (65)	Intervention study	Seventy-four overweight psychiatric inpatients	All included	73 (one death)	None
Bernard et al. (66)	Intervention case report	One overweight female inpatient with schizophrenia	NA	1	None
Harmatz & Lapuc (67)	Intervention study	Twenty-one overweight psychiatric patients randomised into three groups after selection	All included	14 in two intervention groups	7 (diet only)
Sletten (68)	Cross-over study	Fourteen obese female inpatients treated with Chlorpromazine	All included	7	7 (matched)
Allyon (69)	Intervention case report	One overweight female inpatient with schizophrenia	NA	1	None

Table 2. Results of the studies testing behavioural interventions

Authors and year	Intervention	Duration of study	Weight change intervention group	Weight change control group	Between group significance
Cohen et al. (58)	Calorie restriction	2 years	3 ↓ at a rate of 0.1 kg/months; 17 ↑ at a rate of 0.4 kg/months	17 ↑ at a rate of 0.4 kg/months	NS*
Ball et al. (59)	Weight watchers programme: diet and exercise and 10 weekly group sessions	10 weeks	Men ↓ mean 3.3 kg SD (2.6 kg) 3 women ↑; 1 woman ↓ 5.9 kg	Not given	NS for whole group. $P < 0.5$ for ↓ in weight in men; NS for loss in BMI in men; NS for exercise
Nguyen et al. (60)	5 min education on diet and exercise on outpatient visits with a 2 min reminder on subsequent visits	7 months	Whole sample ↑ mean 2.4 kg	NA**	NA
Umbricht et al. (61)	Counselling on diet and exercise and cognitive behavioural therapy seven to nine individual sessions and 10 biweekly group sessions followed by six maintenance sessions	32 weeks (estimate)	Whole sample ↓ From baseline BMI = 29.6 kg/m^2 (SD 2.5) to after-treatment BMI = 25.1 kg/m^2 (SD 3.0)	NA	NA
Alquila & Emanuel (62)	Full medical and psychiatric care, switch to a patient optimal antipsychotic drug, low calorie monitored diet, nutritional education and supportive care	18 months	↑ in 30%	↑ in 71%	$P < 0.01$ (only limited applicable as comparison with historic controls)
Wirshing et al. (20)	Staged intervention of weight monitoring, food diaries, nutritional advice, behavioural analysis, education, exercise classes and group support	Up to 6 years	Not quantified: weight gain with clozapine but not with olanzapine and risperidone seemed to persist	Not given	$P < 0.003$ (final weight comparison for all groups)
Merriman et al. (63)	Wonderful Me! programme: diet, exercise and self-assertiveness training offered as group sessions	12 and 4 weeks FU†	Whole sample ↓ 0.6 kg 3 ↓ mean 2.3 kg with mean weight regain of 0.2 kg at follow-up; 1 ↓ 2.9 kg after 9 weeks; 2 ↑ 3 kg with further ↑ 0.4 kg at follow-up	NA	NA
Rotatori et al. (64)	Counselling on diet and exercise and life style and tokens and self-reinforcement techniques	14 and 2 weeks FU	↓ mean 3.3 kg further ↓ 0.8 kg at follow-up	↑ 2.5 kg and further ↑ 1.3 kg at follow-up	$P < 0.5$ kg
Knox (65)	1000 kcal diet	6 months	↓ in 74%; 18% achieved ideal weight; ↑ in 24% 1 patient died	NA	NA
Bernard et al. (66)	1800 kcal diet and restriction of snacks and tokens	6 months	↓ 45.9 kg (25% of original body weight)	NA	NA
Harmartz & Lapuc (67)	(1) 1800 kcal diet and group therapy, (2) 1800 kcal diet and behaviour modification using loss of money for failure to lose weight	6 and 4 weeks FU	(1) ↓ mean 2.5% and ↑ mean 1% regain at follow-up, (2) ↓ mean 4% and further ↓ mean 3% at follow-up	No weight loss	(1) NS (2) NS
Sletten (68)	1000 kcal diet in intervention group, ≥2000 kcal in control group vigorously encouraged	8 weeks (cross-over after 4 weeks)	↑ mean 5.0 kg in group A and ↑ mean 4.0 kg in group B. Significant worsening of mental state	↑ mean 3.0 kg in group A and ↑ mean 3.7 kg in group B	Not calculable from data provided
Allyon (69)	Behaviour modification programme of chronic food stealing	14 months	↓ 22.5 kg (17% of original body weight)	NA	NA

* Not significant; ** not applicable; † follow-up.

leptin elevation is associated with impaired vascular function, independent of the metabolic and inflammatory disturbances associated with obesity (73). However, although atypical antipsychotics may have effects on the hypothalamic response to leptin they could also affect other peptides such as melanin concentrating hormone (MCH) which is a powerful orexic agent (74). Interestingly, MCH mRNA expression increases after exposure to lithium and may explain some of the lithium associated weight gain (75).

Increasing attention should be paid to the type of behavioural intervention offered. Whereas energy restriction may lead to short-term weight loss, a regular exercise regimen may be required to maintain the weight loss long-term (76). Dietary strategies may need to take into account not only the need to restrict energy intake (77) but also to provide a diet with decreased glycaemic index. Such diet may improve insulin sensitivity (78, 79). Suffice to say that for any behavioural intervention to be effective, assessment of motivation is essential as motivation to lose weight is a predictor of later weight loss (80). At the early stage of their illness or during relapses patients may still be mentally too unwell to adhere to a diet and exercise plan. They may also correctly associate weight gain with the taking of antipsychotic drugs and hence be more inclined to discontinue the drug instead of aiming at weight control. In later stages of psychosis social isolation and negative symptoms may lead to increased eating and decreased mobility. Behavioural intervention may be a necessary, albeit deficient, tool to weight control.

Management of weight gain will be an important part of the management of psychosis, and behavioural interventions will have a major role. However, the characteristics of this population mean that this will be even more difficult to achieve than in populations without mental health difficulties. Currently, psychiatrists have little guidance on which intervention to choose and have to rely on evidence established in non-psychiatric populations which may not be transferable. Weight loss, particularly if not maintained long-term may not automatically translate into health benefits. The presumed effectiveness of behavioural interventions in the prevention and treatment of weight gain in patients on antipsychotic medication rests on the assumption that obesity is a consequence of an inability to regulate food intake rather than altered efficiency of energy utilization. For example, it has not been convincingly demonstrated that antipsychotic induced weight gain is because of increased food intake and there is little evidence of increased energy intake in pregnant women, and yet they clearly gain weight (81, 82). Furthermore, patients with schizophrenia may have a greater baseline risk of obesity. For instance, Thakore et al. (83) found in a sample of drug free or drug naïve patients with schizophrenia a significant intra-abdominal fat pool and raised plasma cortisol levels.

In consequence, further better-conducted research is needed to establish the effectiveness of behavioural methods on weight control in patients prescribed anti-psychotics. However, only sufficiently powerful randomized controlled trials will be able to overcome the methodological pitfalls presented in this paper. Even then success is not guaranteed when behavioural interventions that are tested under 'ideal' trial conditions are rolled out into practice.

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