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Amitriptyline, Weight Gain and Carbohydrate Craving: A Side Effect

By E. S. PAYKEL, P. S. MUELLER and P. M. DE LA VERGNE

Introduction

Increase in weight is a well-known side effect of phenothiazine drugs (Dally, 1967). There have been scattered reports of weight gain on tricyclic antidepressants (Arenillas, 1964; Dally, 1967; Kline, 1969), but this possibility has received little systematic study. Investigation is confounded by the fact that depression itself often produces weight loss. Crammer and Elkes (1968) reported weight gain in responders to desipramine, but regarded this as a limited phenomenon which never built up to obesity and was due to reversal of depression-induced weight loss.

This paper will report findings derived from a therapeutic trial in which amitriptyline was used as a maintenance treatment in recovered female depressives. Unexpectedly, reports of excessive weight gain and craving for carbohydrates emerged as frequent complaints by patients soon after recovery, and were sufficiently marked in some cases to result in refusal to take further medication. A systematic study was therefore undertaken, both of the clinical side effect and of a possible mechanism in glucose and insulin metabolism. The design of the maintenance trial, involving medication maintenance and withdrawal in well subjects, enabled drug effects to be investigated free of the effects of depression.

Method

Subjects

Subjects were 51 female depressives aged 26–60, derived from one of two clinics partipating in a larger out-patient therapeutic trial of maintenance amitriptyline and social casework, of which details have been described elsewhere (Paykel *et al.*, 1973). Inclusion in the trial was limited to patients achieving an initial rating of at least 7 on a three area scale of severity of depression of range 3–15 (Raskin *et al.*, 1970) and responding with at least 50 per cent improvement to four weeks preliminary treatment with amitriptyline. In order to confine the analyses reported to patients who were well during maintenace treatment, subjects were also excluded who at any point underwent clinical relapse, defined as persistent return of symptoms to the initial criterion severity rating of 7.

Medication

Patients were treated with amitriptyline in a flexible dose within the range of 100–150 mg. daily. Mean doses were 123 mg. in the third month of treatment and 117 mg. in the seventh month. For the first three months (including initial treatment when depressed) all patients received amitriptyline. They were then assigned by randomization to three groups: maintenance on active amitriptyline; withdrawal double blind to placebo; and open withdrawal to no medication. In both cases drug withdrawal was in two steps, the dose first being halved for one month. Treatment continued in these three groups for a total of nine months. Preliminary analyses showed no differences in the present side effect between open withdrawal and placebo groups, and these were therefore combined, leaving two groups, maintenance amitriptyline (N = 19) and drug withdrawal (N = 32). In addition, half the subjects in each group received weekly psychotherapy from social workers, but this treatment was also found in preliminary analyses not to influence the side effect.

Ratings

Subjects were weighed monthly and were rated by the treating psychiatrists. Symptom ratings included the 13-point depression scale, a global rating of severity of illness, the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), and a modified version of the Hamilton Rating Scale for Depression (Hamilton, 1960). Systematic appetite ratings were made on later subjects after the side effect was recognized. These included a bipolar thirteen point rating of appetite increase and decrease, and ratings on four point scales of craving for carbohydrates and feelings of faintness relieved by eating. They were made on

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initial assessment, after two months and six months treatment. Additional self-report ratings of appetite increase and decrease were obtained at two-month intervals on all patients.

Insulin tolerance tests

Intravenous insulin tolerance tests were carried out on a partial sample of subjects. Twelve subjects were tested during the third month when all were on amitriptyline, and retested during the seventh month when 5 were still on amitriptyline and 7 had been withdrawn. An additional 11 were tested in the third month but not retested, due in all except two cases to supervening relapse.

Subjects were admitted to hospital overnight. The test was begun between 9.00 a.m. and 10.00 a.m., and was preceded by 10 hours of no medication, food or smoking. Patients rested for at least one hour before the test to avoid alterations in growth hormone related to exercise (Schalch, 1967). Blood samples of 10 ml. were drawn through a Cournand needle situated in an arm vein. After removal of an initial blood sample, glucagon-free regular bovine insulin (Regular Iletin) was injected in a dose of 0·1 unit per kilogram of body weight. Further blood samples were removed at intervals of 15, 30, 45, 60, 90 and 120 minutes. Serum glucose was determined by the glucose oxidase method of Fales *et al.* (1961). Serum free fatty acids were determined by the method of Mueller and Watkin (1961). Serum insulin and growth hormone were measured by double-antibody immuno-assay (Soeldner and Slone, 1965; Boden and Soeldner, 1967).

Results

Weight gain

Weight gain was examined separately for the first three months when all patients were on amitriptyline, and the next six months when some had been withdrawn. During the first three months most patients gained weight rapidly. This gain might well have been associated with recovery from depression. When the groups were compared, the patients later to be withdrawn from amitriptyline showed a slightly higher mean weight gain (4·59 kg.) than those destined to be maintained on the drug (3·33 kg.). The difference was not statistically significant and reasons for it are uncertain.

Weight changes from the third month onward are illustrated in Fig. 1. The subjects maintained on amitriptyline continued to gain weight steadily. Their mean weight gain over the last six maintenance months was 2·50 kg., almost doubling their total weight gain. By contrast, subjects withdrawn from amitriptyline did not show this continuing gain. After a smaller gain during the month of withdrawal, when the medication dose was halved, they lost a little weight and then regained it. Their mean weight gain over the last six months was 0·20 kg. The difference between the two groups in weight gain over these six months was highly significant ($t = 2·82$; $p < ·01$).

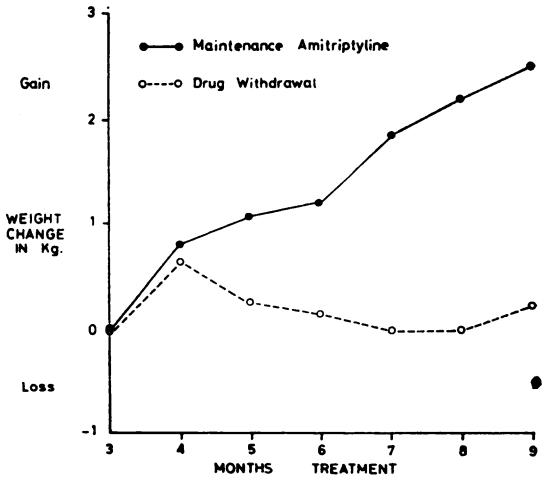


Fig. 1.—Weight gain from third month (start of drug withdrawal).

These subjects were also followed up six months after the termination of maintenance treatment. Weight changes were examined in a sub-sample of 11 subjects who withdrew from active medication and remained off it over the follow-up period. They lost weight, the mean loss being 2·38 kg. By contrast 17 patients who have been off medication in maintenance treatment, and remained off it during the six months follow-up period, remained almost steady in weight (mean weight gain = 0·45 kg.). The difference between the two groups fell minimally short of statistical significance ($t = 2·01$; $p = 0·57$). This finding would support the view that weight gain in the amitriptyline group was due to the drug; the mean weight loss of 2·4 kg. was close to the excess gain shown by maintenance amitriptyline patients.

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These mean values do not fully convey the severity of the weight gain in some subjects. Thus, one patient started treatment with an initial weight of 68 kg., 2 kg. below her usual weight, gained 6 kg. (14 lb.) in the first three months and a further 6 kg. in the next six months. She then stopped the medication and in the following six months lost 10 kg. Another women presented initially with a weight of 63 kg., 6 kg. below her normal weight. In the next four months she gained 18 kg. (39 lb.), and she then refused to take the medication any longer or to attend the out-patient clinic. A year later her weight had dropped 5 kg. A third patient put on 11 kg. (24 lb.) over three months. She attended a weight-watchers organization twice, and after the second session, when her continuing weight gain was apparent to all, became very upset, ultimately developing a major depressive relapse.

Craving for carbohydrate

Ratings of overall appetite failed to differentiate the two groups significantly, although they showed trends towards increased appetite in the maintenance amitriptyline group. However, there were striking findings with respect to craving for carbohydrates. These are shown in Table I. Ratings were made on a sub-sample of patients, using a scale range 1–4 (none, mild, moderate, severe). They were made initially, after two months and six months treatment. At initial rating during the acute episode there was little craving for carbohydrates in either treatment group. Both groups reported some craving during the second month, when both were on active medication. At the sixth month the group remaining on active medication still reported the craving, while the medication withdrawal group showed little evidence of it. The difference between the two groups was highly significant.

TABLE I

Ratings of craving for carbohydrate (1–4 scale)

	Maintenance amitriptyline N = 15		Drug withdrawal N = 17		t value
	Mean	S.D.	Mean	S.D.	
Initial rating ..	1·43	0·79	1·30	0·68	0·36
Second month..	2·73	1·10	2·50	1·16	0·51
Sixth month ..	2·60	0·99	1·41	0·71	3·94*

* $p < ·001$

The magnitude of this difference is best appreciated by comparing the frequency with which subjects reported any degree of this craving, of borderline or greater extent. In these terms 87 per cent of the maintenance amitriptyline patients reported this effect in the sixth month, as opposed to 29 per cent of non-drug patients (χ^2 with Yates' correction = 8·42; $p < ·01$). Moreover, in the amitriptyline patients there was a significant correlation between the amount of weight gain in the six months after drug withdrawal and the degree of craving for carbohydrate in the sixth month ($r = ·59$; $p < ·05$).

As these findings would suggest, spontaneous reports by patients of craving for carbohydrate were among the most prominent complaints clinically. They usually developed after between one and two months treatment. There was a ravenous appetite for a variety of sweet substances, including chocolates, cake, pastry and ice-cream. One patient reported being unable to wait for frozen pastry to thaw before eating it. Although these cravings suggested the possibility of hypoglycaemia, they were not associated with feelings of faintness or dizziness.

Relationship to dose and to depression

Relationship to dose of medication was examined by product moment correlations. Carbohydrate craving in the second month was significantly related to dose of amitriptyline ($r = ·42$; $N = 27$; $p < ·05$). At the sixth month the relationship fell short of significance owing to the small number of subjects ($r = ·44$; $N = 14$; NS). Weight gain however, was not related significantly to dose.

A further set of analyses were made to exclude effects of depression. The subjects had been selected for absence of clinical relapse, but it was possible that a greater prepondernace of sub-clinical depression in the subjects withdrawn from drug might explain differences. To explore this possibility, symptom ratings were used; on these no significant differences were

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found between amitriptyline and withdrawal groups. As a further precaution depression ratings were used as covariates to adjust group means for weight gain and sugar craving. The between-group differences remained significant, indicating their independence of depression. It should not, incidentally, be concluded that amitriptyline was ineffective. These patients comprised only a selected and limited sample of subjects from the drug trial biased by omission of relapses. Evidence from the main trial reported elsewhere showed therapeutic efficacy for the maintenance drug treatment (Paykel *et al.*, 1973).

Intravenous insulin tolerance

Two tests were available, in the third month when all patients were on amitriptyline, and in the seventh month when some had been withdrawn. For analysis, third month tests were used as baselines to examine the effect of drug withdrawal, using changes over the same time in patients maintained on amitriptyline as controls. There were no significant differences in fasting values of glucose or insulin, or in serial changes over the two hours following the insulin injection. Patients on amitriptyline showed the normal responses with decrease in serum glucose and free fatty acids to a nadir 15–30 minutes after the insulin infusion and the usual compensatory rise in growth hormone reaching a peak 45–60 minutes after insulin.

Correlations were also examined between insulin tolerance parameters and degree of carbohydrate craving, at the time of the first test, using all 23 subjects on whom tests were carried out at that time. Only two correlations were significant at the 5 per cent level; 45 minute growth hormone ($r = \cdot44$) and 60 minute growth hormone ($r = \cdot49$). Both these suggested that in patients on amitriptyline greater carbohydrate craving was associated with a higher growth hormone response to exogenous insulin.

Correlations between insulin tolerance parameters and symptom ratings of depression were also examined in view of previous work indicating insulin resistance in severely depressed patients (Mueller *et al.*, 1969). Symptom ratings, made at a monthly rating within three weeks of the insulin tolerance test, included the thirteen point depression severity scale, the global rating of severity of illness, and individual ratings from the modified Hamilton Depression Scale and the Brief Psychiatric Rating Scale. Findings for the depression severity scale and the global rating of severity of illness are shown in Table II. Glucose values showed a consistent pattern indicative of insulin resistance. More severely depressed patients showed higher glucose values, particularly from 30 minutes on. They also showed smaller falls in glucose expressed as a percentage of baseline. There was also a tendency to lesser growth hormone values at 90 and 120 minutes. These findings, especially those for glucose, appeared specific to depression. When a variety of ratings of individual symp-

TABLE II

Correlations between insulin tolerance and symptom ratings in third month

Test	Time in minutes	Global severity of illness	Depression severity scale
Insulin ..	Baseline	·20	·12
Glucose ..	Baseline	·25	·49*
	15	·18	·35
	30	·37	·61**
	45	·69***	·72***
	60	·65***	·60**
	90	·70***	·64***
	120	·70***	·70***
% Fall in glucose from baseline ..	30	−·34	−·51*
	45	−·65***	−·57**
	60	−·58**	−·40
Free fatty acid ..	Baseline	·14	·03
	15	·34	·19
	30	·22	·10
	45	·28	·10
	60	·11	−·01
	90	·11	·07
	120	·04	·10
Growth hormone ..	Baseline	·13	·05
	15	·37	·22
	30	·11	·01
	45	−·23	−·16
	60	−·32	−·30
	90	−·50*	−·52*
	120	−·47	−·51*

* $p < \cdot05$; ** $p < \cdot01$; *** $p < \cdot001$

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toms were examined they were consistently found for ratings of depressed mood, but were absent for such other symptoms as anxiety, psychomotor retardation and hostility. The findings were in keeping with those previously cited for severe depression, but were here extended to the mild range, since these patients were all substantially recovered. This sample did, however, include the 11 additional subjects excluded from the main study on account of later relapse, and many of these showed some symptoms at the time of rating.

Discussion

This study indicates that continuing treatment with amitriptyline after recovery from depressive illness results in significant unwanted weight gain. Even more striking is a considerable craving for carbohydrate foods which is more marked than any general increase in appetite and which is dose-related. When the drug is withdrawn the carbohydrate craving subsides and the excessive weight gained is lost. The mechanism for this side effect remains unclear. It is not merely a reflection of recovery from depression. Neither is it mediated through hypoglycaemia or any direct effect on insulin tolerance. Minor depression in these patients was, however, associated with insulin resistance.

The design of the present study enabled effects of recovery from depression to be separated from effects of continuing treatment. The most rapid weight gain occurred, in fact, in the first three months, during clinical recovery and before the period shown in Fig. 1. A little over half the total mean weight gain could be attributed to this. The remainder occurred only after the third month and in patients maintained on the drug. An additional control was provided by the group withdrawn double blind on to placebo. Although in the main analyses these subjects were pooled with patients withdrawn overtly, separate analyses showed no difference between the two withdrawal groups and confirmed that findings for the relatively crude rating of carbohydrate craving were not due to observer bias or patient expectations.

Increased appetite and weight gain are certainly not effects of all mood-elevating drugs in well patients; the amphetamines are well known for their anorectic effects. Weight gain is, however, a recognized concomitant of treatment with another group of psychotropic drugs, the phenothiazines (Dally, 1967). The mode of action is not clear. Tricyclic antidepressants show some similarities to phenothiazines in ring structure and pharmacological action (Klerman and Cole, 1965). Recently, cyproheptadine, a drug with a tricyclic structure and antihistaminic action, has also been found to produce weight gain (Bergen, 1964; Benady, 1970). The mechanism by which cyproheptadine produces the weight gain remains uncertain. Drash *et al.* (1966), reported a slight reduction in fasting blood sugar levels, but Bergen (1964) did not confirm this.

The mechanism of this side effect of amitriptyline is also not clear. An indirect action via depressed mood was ruled out by sample selection and the analyses of covariance. The weight gain did appear due to increased food intake. The factors regulating appetite are complex, but one important factor is the effect of diminished glucose levels on the hypothalamic appetite centres (Grossman, 1955). In the present case the most central side effect seemed to be the carbohydrate craving. It was more marked than weight gain or general appetite increase, and was dose-related. This craving originally suggested the possibility of hypoglycaemia. Hypoglycaemia can be produced by MAO inhibitors (Cooper and Ashcroft, 1966) and has been reported in a single case of a diabetic on insulin who was also treated with amitriptyline and perphenazine (Shader and DiMascio, 1970).

This simple explanation can be ruled out. There was no evidence from resting levels of either hypoglycaemia or hyperinsulinism. Nor was there any abnormal sensitivity to exogenous insulin as reflected in glucose or free fatty acid levels. In contrast to these two direct effects of insulin, the growth hormone rise following injection of insulin is mediated by hypothalamic stimulation in a protective response to hypoglycaemia (Frohman *et al.*, 1968). There was no direct evidence of an abnormal growth hormone response in the comparison of amitriptyline and control groups, but there was a correlation

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between height of growth hormone response and degree of carbohydrate craving in patients on amitriptyline. Patients with more carbohydrate craving showed a greater degree of growth hormone response to hypoglycaemia. This raises the possibility that amitriptyline may alter hypothalamic sensitivity to a given level of glucose. This action might well be shared by other drugs with similar structure, such as cyproheptadine and the phenothiazines. For the latter group other hypothalamic effects, such as hypothermia and endocrine changes, have been described (Goodman and Gilman, 1970). This possible action remains, however, speculative.

What the insulin tolerance tests did show was a correlation between minor depression and insulin resistance, mainly reflected in the glucose response. This finding, although incidental, is interesting. Previous studies in severely depressed untreated patients have indicated correlations between depressive manifestations (particularly psychomotor retardation) and diminished glucose response (Mueller *et al.*, 1972). The present data extend these findings to the mild range. These patients were all substantially improved from their initial depressed state, but some, particularly among the additional subjects who later relapsed, showed mild depression. The correlations were specific to depressed mood, providing further support for a more general relationship between insulin resistance and depressive affect.

Since this study involved only a single drug, we cannot say whether the side effect of carbohydrate craving and weight gain is specific to amitriptyline or characteristic of all tricyclic antidepressants. Within the group of tricyclics general similarities in pharmacological actions are high (Klerman and Cole, 1965). We did attempt, after completion of the main study, to change some patients to other tricyclic antidepressants; the results were equivocal.

In describing this side effect we would certainly not argue against the use of amitriptyline. Its efficacy in acute depression is clear (Klerman and Cole, 1965), and evidence is accumulating of maintenance efficacy (Paykel *et al.*, 1973; Mindham *et al.*, 1973). The weight gain was not large in most cases, and the therapeutic benefit would well outweight it. However, in a small proportion of cases weight gain was marked and intractable, causing considerable distress and interfering with treatment. Such complaints of weight gain and craving for carbohydrates, developing soon after recovery on tricyclic antidepressants, should not merely be discounted as return of normal appetite but recognized as a possible side effect. Although the requirements of the therapeutic trials did not permit adequate investigation of the issue, both the dose relationship found and clinical experience of the effect suggested it could be controlled to some extent by reducing the dose. For a minority of more severe cases, however, it may render early discontinuation necessary.

Summary

This paper reports excessive weight gain associated with craving for carbohydrates, occurring as a side effect of treatment with amitriptyline. Subjects were 51 depressed women who had responded to initial treatment with amitriptyline and remained well. Nineteen were maintained on amitriptyline for nine months; 32 had the medication withdrawn after three months. Both groups gained weight during recovery. Subsequently the amitriptyline group continued to gain weight excessively, while the drug withdrawal group did not. This difference was not due to persisting depression. Withdrawal of active drug after nine months treatment was followed by weight loss. Amitriptyline patients also reported a striking and dose-related craving for carbohydrates, developing within one or two months of starting the drug. Fasting insulin and glucose, and intravenous insulin tolerance were not affected, and the mechanism of the side effect is not clear. However, in confirmation of previous work, insulin resistance was found in subjects with minor residual depression.

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