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Chapter 9

The Effect of Psychopharmacological Agents on Appetite and Eating

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INTRODUCTION

Many medications increase or decrease appetite and/or weight. Some of these have been tested in anorexia nervosa and bulimia. To date, no well-controlled, large-scale studies with successful results have been replicated. In general, there is as yet, no accepted medication for the treatment of anorexia or bulimia (see Chapter 42, this volume).

This chapter reviews medications that influence weight and/or appetite, including some that have been given to patients with eating disorders. The presentation is chronological, dealing first with medications generally used before 1970, second during the 1970s and third after the 1970s. Therefore, the text is divided into three sections.

Rather than separating medications by whether they increase or decrease appetite or weight, I have retained chronology as the standard within each section. Those that increase appetite could help patients with restrictive anorexia, and those that decrease appetite could help with bulimia.

SECTION I: MEDICATIONS USED BEFORE 1970

Insulin

One of the earliest medications used for eating disorders was insulin. A review in 1946 indicated insulin's use in 1942 in small doses before meals, without success. Some patients seemed to respond to deep insulin shock with increased appetite and weight, though there was no change in personality. Insulin was also of no value in ambulatory subjects. The authors felt treatment with insulin should be followed by psychotherapy to be successful. They also felt that since patients with anorexia did not respond to insulin as schizophrenics did, anorexia was not a form of schizophrenia [1].

In 1960, Dally and Sargant proposed the combination of modified insulin and large doses of chlorpromazine. They found modified insulin alone was of little value. Twenty anorectic patients were given varying doses of chlorpromazine, up to 1000 mg per day, and remained on bed rest until regaining their normal weight. They were also given modified insulin therapy, starting with five units and progressively increasing the dosage until the patient was sweaty and drowsy. They were then given a large meal, and precautions were taken to avoid hypoglycemia. The dose range was 40 to 80 units, with the average being 60. When weight was regained, medication was stopped and psychotherapeutic work was begun. The combined treatment yielded an average weight gain of 4.4 lb per week, compared with treatment by other methods, which yielded an average gain of 1.3 lb per week [1]. Crisp, in 1965, disagreed with this program on the basis that most of those patients were already hungry. He was concerned that insulin use

might lead to bulimia [2].

In 1966, Dally and Sargant performed a follow-up study on some of the patients who received insulin in their 1960 study. The method was as described above, and the patients were compared with patients on bed rest and high-calorie diets. Patients receiving insulin and chlorpromazine gained twice as much weight as the non-medication group. There were no adverse reactions to the insulin. It was felt that most of the effect was due to the antipsychotic actions of the drug and that insulin alone was not much more effective than bed rest alone [3]. In 1967, Dally reported that weight was gained with this program, but there was no difference in final outcome between the methods of weight gain that were compared. That is, follow-up indicated that weight may have been gained rapidly with this treatment, but the weight was not necessarily maintained over several years. He felt that insulin and chlorpromazine were certainly not a cure [4].

Chlorpromazine

Chlorpromazine, an antipsychotic medication, often produces weight gain as one of its side effects. A study in 1958 of 73 chronic schizophrenics showed increases in weight and appetite. After discontinuing the drug, patients began losing weight. Some have suggested that the medication lowers metcholic rate, and thus weight gain occurs. Possibly, these schizophrenic patients' behavior became more organized with the antipsychotic drugs and they were better able to eat and care for their nutritional needs [5].

Other studies have shown weight gain in crossover, placebo- controlled comparisons. One study also found more weight gain with chlorpromazine than with promazine and more weight gain with promazine than with either placebo or phenobarbital. Another comparison showed a greater increase in weight with chlorpromazine than with trifluprомazine and mepazine. The largest absolute gain occurred early and averaged 1.4 to 5 lb in 12 weeks in these several studies. Again, weight returned to previous levels after stopping the drug. Mechanisms suggested in these studies include fluid retention, effect on appetite regulatory mechanisms in the brain, and changes in food consumption. However, if the medication were directly stimulating the brain, appetite and weight gain would be dose related, a result not found [6].

As noted above, Dally and Sargant used insulin and chlorpromazine in their program. The dose of chlorpromazine used was up to 1000 mg a day. They felt that improvement in weight may have been related to fluid retention, but they also attributed it to better acceptance of treatment. One side-effect was hypotension. The combination of the two drugs was more effective than either insulin or chlorpromazine alone [1].

In 1965, Crisp gave 400 to 600 mg of chlorpromazine a day, without insulin, accompanied by a 3,000-calorie diet and supportive psychotherapy. Initially, all but 2 of 21 subjects returned to normal weight. At the time of follow-up, two had died, and 15 of the remaining 19 had normal weight. Eleven of these had normal eating behavior [7].

In another report, Crisp discussed possible mechanisms for chlorpromazine's actions, including increased calmness with decreased activity, leading to decreased energy expenditure or increased carbohydrate intake as a second possibility. He also noted that the medication has other effects, such as amenorrhea, galactorrhea, and hypothermia, which may be mediated by the hypothalamus. These phenomena also occur in anorexia. He postulated that chlorpromazine may affect the appetite by acting on the hypothalamus [7].

In 1966, Dally and Sargant reported rare complications from the chlorpromazine. Extrapyramidal symptoms occurred in 9 of 50 patients, and all nine responded to decreased antipsychotic medication or the addition of antiparkinsonian drugs. Five had one grand mal seizure, and occasional pitting edema occurred. Rashes, sleepiness, blurred vision, dry mouth, and jaundice were reported also. Bulimia developed in 45% of the patients [3].

Other mechanisms of drug action have been suggested. Chlorpromazine may increase fat deposition [8], increase fluid intake secondary to dry mouth [9], or change the utilization of certain foods as a consequence of changes in the basal metabolism rate [9]. Food intake is increased in animals following chlorpromazine injection into the lateral hypothalamus [10].

Not all the reports on chlorpromazine and anorexia nervosa are positive. Roland surveyed 30 cases in the literature in 1970 and found five in whom the medication was of little help [11]. Russell reported on seven patients in whom the drug was not effective without an overall treatment plan for weight gain [12].

Gross, at the Cleveland Clinic, preferred not to use the medication for several reasons. The drug increases the danger of orthostatic hypotension, and anorectics usually already have low blood pressure. Also anorectic patients have abnormal liver function and liver function tests, and neuroleptics may affect the liver. Additionally, the extrapyramidal symptoms of tightness in the throat and difficulty in swallowing may increase the anorexia. Further, anorectics may have seizures during initial refeeding, and antipsychotics decrease the seizure threshold. He suggested neuroleptic treatment for only a few weeks to encourage acceptance of therapy and the

weight gain. He uses 25 to 50 mg three to four times a day for inpatients and 10 to 20 mg three to four times a day for outpatients [13].

Amitriptyline

In 1964, a letter to the editor of The Lancet reported on 30 female patients taking amitripyline for four months. They developed voracious appetites with an apparent increase in carbohydrate intake. Weight increased as much as 28 lb in four to five weeks. Fat deposits increased, and breasts became large and tender. Some patients thought they were pregnant [14].

Paykel and associates in 1973 studied 51 depressed patients aged 26 to 60 treated with 100 to 150 mg amitriptyline daily. Most gained weight rapidly during the first three months. The authors noted that this could relate to recovery from depression. The average weight gain almost doubled after three months in comparison to the initial three-month period. Additionally, craving for carbohydrates increased significantly during the second and sixth months on the medication compared to no medication. The carbohydrate craving in the second month was significantly related to medication dose and not to hypoglycemia, as faintness or dizziness were not present. Overall weight gain was not related significantly to dose. Subjects withdrawn from the drug lost the excess weight that had been gained. Carbohydrate craving was associated with a higher growth-hormone response to exogenous insulin, that is, to hypoglycemia. This suggests that amitriptyline may alter hypothalamic sensitivity to glucose, indicating a central mechanism of drug action [15].

Nakra et al in 1977 tested Paykel's hypothesis that hypoglycemia induces weight gain. Six nondepressed healthy volunteers were given 50 mg amitriptyline twice a day for 28 days. Blood was obtained for fasting glucose and fasting blood insulin before the study and on days 14 and 28 of the study. During the study, amitriptyline levels were measured to determine compliance. Subjects were weighed weekly and asked to report changes in appetite, eating habits, and side effects. There was no significant weight gain, and only two reported increased appetite. The latter was especially in the evening and included excessive cravings for sweets. There was no significant difference in glucose tolerance curves, fasting or peak insulin, or glucose/insulin ratio curves. The authors felt these results did not support the hypothesis that hypoglycemia and hyperinsulinemia are responsible for the weight gain during amitriptyline therapy [16].

Nakra and his colleagues discussed several other possible mechanisms for the effect noted. Weight gain was not attributed to lifting of mood, because mood remained improved after medication was stopped, but the weight that had been gained was subsequently lost. Amitriptyline could have a central effect on weight-regulating mechanisms. Others have postulated that the drug inhibits nonepinephrine and blocks alpha-adrenergic receptors, leading to a relative increase in beta-adrenergic effect. This would lead to sitmulation of beta-adrenergic receptors in the pancreas, with a subsequent increase in insulin. The insulin would produce hypoglycemia and hunger.

Needleman and Waber, in 1977, studied five females and one male aged 11 to 17 who had severe aversion to food, cold extremities, weight loss greater than 20%, and in the females, amenorrhea. They were given 75 to 150 mg amitriptyline daily. Socialization and mood improved, and extremities became warmer. Weight gain occurred between 6 to 12 days after treatment was commenced. Both patients and staff reported improved eating behavior and attitude toward food. Three subjects discontinued the medication and continued to gain weight. The authors suggested that the improvement of both appetite and temperature regulation may be mediated by the hypothalamus [17].

Kendler (1978) suggested that an abnormal body weight set point occurs in the eating disorders and that the set point is altered by the various medications that affect appetite and weight. The weight set point would produce increased appetite and decreased satiety until an increased body weight is reached. He reported on a patient given amitriptyline whose appetite increased within eight days, resulting in weight gain. Over the next seven weeks she gained 1 kg a week and was rarely satisfied by large amounts of high-calorie foods. When the medication was stopped, weight gain continued to more than 25% over her ideal weight, despite the return of the depressed mood. Hunger persisted and was associated with lack of satiety. Kendler suggested that the patient's body weight set point may have been altered by the drug [18].

On the other hand, others have reported that amitriptyline was ineffective in inducing weight gain. In one study of 80 patients taking 50 to 200 mg a day of the drug, some still needed hospital admission and coercion to put on weight. Another patient, who had lost more than 30 kg and was given a six-month trial of tryptophan and amitriptyline, had minimal response.

As with all medications, amitriptyline has side effects. These include sedation, tachycardia, and postural hypotension, in addition to dry mouth. If the patient quenches this thirst with high-calorie liquids and/or increases total fluid intake, weight gain may occur.

Clomipramine

Clomipramine is widely used in Europe but is not yet available in the United States. In one report, treatment with 50 mg at bedtime yielded increased appetite and

more appropriate eating habits but produced no weight gain. Beaumont (1973) reported that its use in anorexia was first suggested in 1969 in a study of four patients in whom weight was restored to normal levels with treatment for about ten weeks. In 1971 that group was enlarged to ten cases. Another study reported that the drug antagonized fenfluramine- induced anorexia. Some studies used the intravenous form of this drug [19]. As clomipramine is a very selective inhibitor of serotonin uptake. Katz and Walsh (1978) suggested using the intravenous form after tryptophan priming, which decreases hepatic conversion of the drug to the demethylated metabolite. The demethylated compound is a weaker inhibitor of serotonin reuptake [20].

In 1980 Lacey and Crisp gave 50 mg of clomipramine or a placebo to 16 female anorectics at bedtime until they reached their target weights. They were also on bed rest, 2,600 calories a day, twice-weekly weighings, and individual psychotherapy. Half of the group was medicated, and the other half received a placebo. Hunger was significantly greater in the group receiving clomipramine. No significant difference in weight gain occurred between the two groups. The medicated group, however, tended to maintain their body weight better after leaving the trial than the placebo-treated group [10].

Studies show that clomipramine affects hypothalamic hormones, influences the neurotransmitters thought to be involved in food intake regulation, and may increase insulin peripherally by direct action on the pancreas, as is suggested for amitriptyline. It is chemically similar to chlorpromazine, which may have a direct effect on hypothalamic hunger-regulating mechanisms. Perhaps clomipramine may decrease anxiety about eating and reduce obsessional intrapsychic conflicts about weight [10].

Others

Other medications affect appetite and weight. Simmonds' disease (pituitary cachexia) is rare but can be confused with anorexia. In both there is loss of weight, gynecological disturbance, low basal metabolism rate, hypotension, and bradycardia. ACTH and cortisone were used in treating five patients with anorexia as an adjunct to other therapy, with mood and appetite improvement being the target symptoms for the drugs. Three of the patients received both ACTH and cortisone. In one case, cortisone was administered for seven days immediately after nine days of ACTH treatment; the other two patients took the drugs simultaneously. Two received only cortisone. One patient (described as "uncooperative") who one took the drugs immediately in sequence had no benefit; two had improved appetite, weight, and attitude with cortisone; and two benefited from ACTH. One had depression as a side effect and all five had mild to moderate generalized edema, which was controlled by potassium chloride. Two of three who had ACTH reported insomnia and nocturnal restlessness. Weight gain in one was 15 lb over one month and in another 15 lb over two months [21].

Other drugs have been tried with little or no success, or results have not been replicated. Reserpine has been used in anorexia, but the doses that produced increased appetite also produced depression. Thyroid has been tried with little effect. Benzedrine sulfate was given to two patients with depressive symptoms and was of no help. Sulfa drugs and vitamin B_{12} have also been tried without success.

Thioridizene was given to a 12-year-old female with a three-month history of obsessive eating habits and weight loss, who had been tried on chlorpromazine with some weight gain. She received 800 mg daily and in two months gained 9 lb. Gross, at the Cleveland Clinic, prefers thioridizine to chlorpramazine because orthostatic hypotension occurs more often with the latter and because thioridizine has some antidepressant effect [13].

Fifty-three obese patients were treated with an appetite-reducing product made of hydrophilic granules called Prefil, which is intended to decrease appetite by bulk. The granules are 60% dietary fibers (vegetable gum) and swell in the stomach, creating a sense of fullness and satiety when taken with water before eating a meal. Six of 26 patients had side effects (three had abdominal discomfort; two had nausea, and one had headache) [22].

Four anorectic patients were treated with glycerol. In a starvation state, glycerol turnover and conversion to glucose increases and a higher proportion of glucose is derived from glycerol. Thus, administration of glycerol to anorectics would provide a source of glucose, remove excess fatty acids, and assist repletion of carbohydrate stores. The patients tested maintained their weight and, according to family, improved in their acceptance of food [23].

A 21-year-old woman with anorexia had been ineffectively treated with the beta-blocker propranolol. She was then given the alpha- blocker phenoxybenzamine, which produced weight gain. When the drug was stopped because of nausea and postural hypotension, weight loss resumed. Treatment was recommenced at a lower dose and weight gain recurred. Theoretically, decreased norepinephrine levels would decrease satiation—that is, increase appetite [24].

SECTION II: MEDICATIONS USED DURING THE 1970s

Cyproheptadine

Cyproheptadine is an antiserotonergic, antihistaminergic agent, often used for allergy. Chemically it is sim-

ilar to LSD and the phenothiazines. It also has anticholinergic and sedative effects. In 1962, Lavenstein et al studied 28 asthmatic children taking cyproheptadine compared with chlorpheniramine in a double-blind protocol. Those receiving cyproheptadine showed a marked increase in appetite and weight. They appeared to have exogenous obesity and not fluid retention. The authors felt this was not an antihistamine effect, since the chlorpheniramine is equally potent in that respect. The median weight gain on cyproheptadine was more than twice that on chlorpheniramine. Four times as many children had increased appetite, as reported by parents and patients, with cyproheptadine as with the other drug. Appetite and weight returned to normal when the drug was stopped. The children also had an increase in linear growth, which is common in children with obesity due to increased food intake. Appetitive effects were unrelated to decreases in allergic symptoms, which occurred with both drugs [25].

Bergen, in 1964, followed up on this study. Hospitalized chronically asthmatic children were given either cyproheptadine or placebo for 15 weeks in a double-blind study. Again, cyproheptadine produced increased weight and appetite. Carbohydrate tolerance tests showed no significant differences between the groups. When the drug was discontinued, appetite and weight decreased again. They found no symptoms of hypoglycemia as well as no change in glucose tolerance tests. The authors theorized that cyproheptadine stimulates lipogenesis through stimulation of the hexose monophosphate shunt or stimulation of growth hormone secretion [26].

Chakrabarty et al (1967) administered cyproheptadine to cats and measured food intake, glucose utilization, and EEG. Glucose utilization decreased in cats that had exhibited hunger behavior. EEG changes occurred in the feeding centers but not in the satiety centers of treated animals. They suggested that cyproheptadine has a chronic hypoglycemic effect and that decreases in glucose utilization induce both increases in food intake and hypothalamic feeding center activity. They suggest that glucose utilization, not blood glucose, influences the brain centers explaining why previous studies failed to find a correlation between blood glucose and appetite increase [27].

In 1969, Noble further pursued this line of thinking by measuring the effect of cyproheptadine in comparison to placebo on appetite and weight in healthy underweight adults. Both appetite and weight increased significantly. Drowsiness was a common transient side effect. Most patients were female, and appetite was self-rated. Again, weight gain appeared as exogenous obesity. There was no evidence of hyperadrenocorticism, water retention, or hypothyroidism [28].

In 1970, Benady described the first report of cyproheptadine treatment as adjunct therapy in anorexia nervosa. A 12-year-old female was 4 ft 11 in and weighted 56 lb 13 oz. She gained 18 lb in two months taking chlorpromazine, bed rest, and twice weekly psychotherapy. After initial treatment with Mellaril, she was switched to cyproheptadine and gained an average of 1-1/4 lb a week over six months. No side effects were noted. After nine months, she doubled her initial weight measured 2-1/2 years previously at age 12, and six months later she had lost only 10 lb, and her periods had returned [29].

Goldberg and his colleagues (1979) compared liquid cyproheptadine and placebo in a double-blind study of anorectics. One subgroup responded positively to treatment. This group had a history of birth delivery complications, a 41% to 52% weight loss from normal and a history of previous outpatient treatment failure. The researchers felt this drug could be more useful in a more severe form of the illness. No complications were noted [30]. The effect of the drug on attitudes was explored in a different group of patients. Fear of becoming fat was reduced (though not to normal) in the medicated group but not with placebo. Cyproheptadine also reduced resistance to eating, but the placebo had a mild effect on resistance as well [31].

Halmi et al (1983) compared amitriptyline, cyproheptadine, and placebo in the treatment of 57 anorectic females. Cyproheptadine induced weight gain and reduced depression without complicating side effects. The mechanism of action of cyproheptadine is unknown. In treated adults, serum amylase is increased and fasting blood sugar is decreased. Affects on the pancreas and on cell permeability to glucose have been postulated [33].

Side effects of the medication have been rare. However, drowsiness, dizziness, apprehension, rash, and dry mouth can occur. Occasionally, agitation, confusion, and visual hallucinations appear. Contraindications include glaucoma and predisposition to urinary retention. Patients should not concurrently use alcohol or CNS depressants, and the effect of concurrent antidepressant medication is unknown.

Lithium

Weight gain is one of the most prominent side-effects of lithium. In one study on seven patients, a substantial weight gain occurred in all initially with a leveling off over the next one to six years. Weight gain was attributed to improved general health and better appetite and diet in people no longer suffering severe, debilitating depressive disorder. The weight gain seemed to be increased fat and solid tissue, while total body water was constant. The authors suggested patients reach the weight they would have obtained if they had not been ill, and they

postulated that weight gain is related to drug effects on mood [34]. However, lithium treatment also increases weight in rats, suggesting that its action may not be related to relief from psychosis [35].

Further study shows a correlation between number of fat cells initially and subsequent weight gain with lithium tratment. There was, however, no correlation with fat cell size. Thus, patients with weight problems before using the drug tended to develop more weight problems on the medication than patients without previous weight problems. Lithium may directly stimulate deposition of fat in cells and thus those with more cells gain weight. This could occur through inhibition of adenyl cyclase activity and thus lower lipolysis [36].

The same authors also found a weak correlation between appetite increase and weight gain following lithium treatment. In this study, no link to previous history of infant obesity was observed. Nearly all patients reported increased thirst, and weight gain was correlated with liquid intake. There was no difference in weight gain by gender, diagnosis (unipolar versus bipolar depression) or improvement of mood [37].

In preliminary findings on two anorectics given lithium, Barcai reported significant weight gain in six weeks, lasting for one year. Both reported increases in food intake. No metabolic investigations were done [38].

Treatment of euthymics with either lithium or placebo induced weight gain only in patients taking the drug. Since mood control could not be related to drug action in this study, the authors suggested that lithium affects weight directly [39].

Amphetamine

The most frequently used drug for weight reduction is amphetamine. It is a stimulant, euphoriant, and anorectic. It causes peripheral sympathominetic action and in large doses can produce a paranoid psychosis similar to paranoid schiziphrenia. The neurotransmitters dopamine and norepinephrine seem to be involved in its action.

Most of the literature on amphetamine involves its mechanisms of actions and the influence of other drugs on amphetamine-induced anorexia. Amphetamine decreases eating at times and increases it at other times. It changes the rate of feeding, latency (time before onset of feeding), meal number, and selection of food.

The effectiveness of amphetamine in appetite reduction may be increased by administration two hours after meals. Amphetamine mobilizes fats from deposits. Amphetamine should be used only early in the course of treatment, when temptation is maximal [40].

Metoclopramide

Often patients with anorexia complain of discomfort after eating and with refeeding. These symptoms include fullness, bloating, epigastric pain, regurgitation, nausea, heartburn, and vomiting. These symptoms may be related to delayed gastric emptying. Metoclopramide (Reglan) is an antiemetic that can alleviate these symptoms.

In 1977, Moldofsky et al published a preliminary report on the use of Reglan for relief of dyspepsia in anorectics. In follow-up after three to six months, patients were free of dyspepsia while taking 10 mg at bedtime. Two patients had depressive symptoms while on the drug, but these ceased when the medication was discontinued [41].

Saleh and Lebwohl (1980) reported on five female and two male anorectics with moderate to severe gastrointestinal symptoms. Seven normal-weight people with minor GI problems served as controls. Normally, 55% or less of an ingested meal will remain in the stomach 90 minutes after ingestion. Six of the seven anorectics had greater than 85% of their meal remaining (mean was 90%) compared with mean of 42% retained in the normal controls, indicating delayed gastric emptying in the anorectics. After being given Reglan, the mean for the anorectics decreased to 64% retention, with five of the seven having a significant reduction of meal retention, indicating a facilitation of gastric emptying. One month of taking the medication yielded a significant increase in weight and marked improvement of GI symptoms, mostly in tolerance to meals, postprandial epigastric pain, excessive belching, vomiting, and satiety. Two patients had no change in gastric emptying but still gained weight, indicating that the increase in weight was not related to gastric emptying. No side effects or untoward reactions were noted [42].

Metoclopramide increases lower esophageal sphincter tone, antral gastric contractions, and the rate of gastric emptying. It also relaxes the duodenal cap, which prevents pyloric regurgitation. It does not affect gastric enzyme secretions and potentiates acetylcholine action. It makes gastric contractions more effective. The mechanism of action is through blockade of dopamine receptors, particularly in the brainstem. By blocking dopamine, metoclopramide inhibits gastric acid secretion and gastric relaxation.

Another consequence of the inhibition of dopamine by metoclopramide is increased prolactin secretion leading to galactorrhea, cardiac arrhythmias, and increased incidence of breast cancer. Thyrotropin and aldosterone may be increased. Central side-effects occur in about 10% of those under treatment and include somnolence, lassitude, dizziness, faintness, nervous-

ness, anxiety, and lethargy. Extrapyramidal symptoms may occur (metoclopramide should not be given concurrently with a neuroleptic, except with caution). Tardive dyskinesia may also follow its use, but there is no significant antipsychotic or tranqulizing effect at the dose recommended and use within two weeks of treatment with a monoamine oxidase inhibitor, tricyclic antidepressant, or sympathomimetic is not recommended. Absolute contraindications include pheochyromocytoma and organic intestinal obstruction and perforation. Relative contraindications are Parkinson's disease, CNS depressant treatment, and procaine or procainamide sensitivity. Dose should be decreased in renal disease.

Fenfluramine

Fenfluramine (Pondimin), like amphetamine, produces anorexia but is not believed to be a stimulant. The two drugs are structurally similar. Fenfluramine acts via serotonergic pathways. Kirby and Turner (1976) suggest the drug has peripheral infleunces on glucose metabolism, which may be important in the weight loss accompanying treatment. Fenfluramine increases glucose uptake into skeletal muscle in addition to its central effects. The authors felt the central changes in neurotransmitters and behavior (sedation) may be occurring through the hypothalamus, causing neuroendocrine changes, and indirectly influencing peripheral metabolism [43].

Jespersen and Scheel-Kruger, in 1973, looked at drugs that affect serotonin and studied their effects on the anorexia produced by fenfluramine. The serotonin-blockers methergoline and methysergide and the serotonin-reuptake inhibitor chlorimipramine were used. Methergoline antagonized the anorectic effect of fenfluramine, but methysergide did not antagonize the anorexia significantly. The authors felt this may be due to a difference in antiserotoninergic potency (10 to 30 times) between methergoline and methysergide. Chlorimipramine produced dose-related antagonism to femfluramine's anorexia-inducing activity [44].

Wurtman et al (1981) studied 24 obese people who stated that they had excessive appetite for carbohydrates. They were given fenfluramine, tryptophan (serotonin percursor), or placebo. Fenfluramine significantly reduced carbohydrate snacking in six of nine tested as well as for the entire group. The authors concluded that carbohbydrate snacking can sometimes be diminished by treatments, which are thought to enhance serotonin neurotransmission. The timing of the snacks was not changed by the drug and there was no significant weight loss. The doses used in this study are below those generally used to produce anorexia [45].

Fenfluramine and its main metabolite inhibit glyceride synthesis and increase glucose utilization. The drug may promote a wasting of calories leading to weight loss by a peripheral mechanism [43]. Fenfluramine hastens the end of an initial episode of eating, thereby decreasing food intake. It could be involved in the satiety mechanism via its effects on serotonergic pathways. Decreasing serotonin seems to increase food intake and, as shown by fenfluramine, increasing serotonin decreases food intake. Other studies suggest that Pondimin works by enhancing lipolysis or causing the release of hormones. Fenfluramine effects the size of the meal and the rate of intake.

Phenytoin

Green and Rau studied phenytoin (Dilantin) and its effect in eating disorders. In 1974, ten patients with compulsive eating were treated with phenytoin. All but one had an abnormal EEG, suggesting a possible neurological dysfunction. Nine of these ten were treated successfully. The authors suggested that compulsive eating may be a neurological disturbance with psychodynamic factors determining whether patients become anoretic, obese, or maintain normal weight. All the patients believed they were fat and had used amphetamine unsuccessfully in the past in attempting to overcome their compulsive eating [47].

In 1977 Green and Rau reported on 31 patients. They defined compulsive eating as eating episodes that were irregular, unpredictable, ego-dystonic, involving large amounts of food eaten "against the eater's will," accompanied by guilt, an aura at times, and mild depersonalization. Fourteen of these 31 had abnormal EEGs, and the authors noted the similarity between these episodes and some types of seizure activity, insofar as symptom complex. Twenty-six of the 31 were given phenytoin. Nine patients responded positively with reduced eating, while 17 didn't respond or had an inadequate trial. It is noteworthy that of 12 patients with abnormal EEGs, six had a positive response and only three of 14 with normal EEGs had a positive response. Four who had responded to phenytoin, including one with a normal EEG, were then put on a double-blind study of phenytoin versus placebo with a crossover for four months. All responded to the drug [48].

Wermuth et al in 1977 reported on 19 people in a 12-week, double-blind, crossover study comparing placebo and phenytoin in treating severe binge eating. When subjects were given placebo and then the drug, the number of binges decreased while on the drug compared with pretreatment and on placebo. However, when patients were given the drug first, the number of binges decreased from the pretreatment period but this pattern was not reversed when the subjects were switched to placebo. The EEG was abnormal in 7 of 19. There was no consistent change in weight or the intensity of the

binges. EEG abnormalities did not correlate with treatment response, and the same was true for phenytoin levels, weight, frequency of binges, night eating, frequent snacking, eating continuously during the day, eating at regular meals, and postbinge vomiting. Binges of one hour or less were associated with a good response, but a history of anorexia was associated with no improvement. The action of the drug terminates soon after it is discontinued. The authors noted that the effect on binges is similar to the effect on seizures in that the frequency of the binges was decreased but not the intensity. Binge activity was lowered even at low serum levels of phenytoin [49].

Weiss and Levitz (1976) reported one case of unsuccessful treatment with phenytoin in bulimia [50].

Others

Other medications were suggested in the 1970s for treating eating disorders or were described to affect weight and/or appetite.

Johanson and Knorr (1977) suggested using L-Dopa for the treatment of anorexia nervosa. They noted similarities in behavior between anorectics and patients with Parkinson's disease, and they suggested that anorexia nervosa may have a dopaminergic component. Nine patients (eight females and one male) were given the drug and five of the nine gained weight while on the medication. The drug seemed well tolerated, though several had black urine and several noted significant hair loss [51].

Pizotifen is an antiserotonergic, antihistaminergic agent structurally similar to cyproheptadine and the tricyclic antidepressants. It has weak anticholinergic activity and is used for prophylactic treatment of vascular headaches (though it is of no value in acute attacks). With the usual dose of 1-1/2 to 3 mg daily, drowsiness, appetite increase, and weight gain have occurred, though in most, these effects are mild and tend to decrease with prolonged therapy. In one study of four anorectic patients, Pizotifen was helpful. It had a mild hypoglycemic effect, probably not due to a change in peripheral utilization of glucose, but perhaps to inhibition of glycogenolysis or gluconeogenesis in the liver. Other side-effects included bradycardia, hypotension, mydriasis, epileptiform seizures, muscle spasms, miosis, and hypotonia. Weight gain was 2 to 10 kg, mostly in the first few weeks. Appetite was described as voracious, and sweets were craved. Weight gain may be due to fluid retention or endocrine effects [52].

Rats injected intraventricularly with parachlorophenylalanine (PCPA) showed hyperphagia primarily in the daytime. This chemical decreases brain serotonin, thus supporting the concept that decreased brain serotonin leads to overeating and increased body weight. The effect was dose related. PCPA decreases serotonin by inhibiting tryptophan hydroxylase [53].

Zimelidine was developed as an antidepressant that inhibited serotonin reuptake (therefore increasing the effect of serotonin). A placebo-controlled, double-blind, crossover study on overweight nondepressed people was done. Of 18 women who completed the study, more weight was lost with the medication than with placebo and, according to self-rating, appetite was also reduced. Sleep disturbance occurred with the drug. Weight loss averaged 2.5 kg, which is comparable to marketed appetite suppressants [54]. Another study of the antidepressant efficacy of Zimelidine showed that of 15 patients, 13 lost weight and two gained. The average loss was less than 1 kg but was significant [55].

SECTION III: MEDICATIONS USED AFTER THE 1970s

Monoamine-Oxidase Inhibitors (MAOI)

As with other antidepressants, early reports suggested that MAOI, in combination with amitriptyline, increased hunger and cravings for sweet foods. This combination of drugs increases norepinephrine levels, intensifies beta-adrenergic effects, increasing insulin release, causing hypoglycemia, and leads to hunger.

More recently, studies have been done with the MAOI isocarboxazid and phenelzine. One study was done on depressed patients, some of whom exhibited hyperphagia and weight gain (at least 5 lb) as symptoms of their depression before treatment. These patients had rapid, early, and virtually complete cessation of overeating and weight loss on isocarboxazid. Other patients in the same trial who initially had poor appetite and weight loss as presenting symptoms, showed a tendency to increased appetite, but the change was gradual, not rapid as above, and was not significant [56].

Two reports appeared concerning the use of phenelzine and its effect on appetite. One patient with agoraphobia had increased appetite within two weeks after initiation of treatment and increased weight after six. When the phenelzine was discontinued, appetite returned to normal shortly thereafter [57]. Another patient gained 20 kg in four months. Weight gain terminated when the drug was discontinued [58].

Cholecystokinin (CCK)

Cholecystokinin (CCK) is normally released when food enters the duodenum and causes animals to stop eating. In man, slow infusion increases food intake but rapid infusion,as shown in one study, decreases it by 12%, with 96% of the decrease occurring in the first

eight minutes. With the slow infusion, food intake was increased by 22%. The CCK used in this study was only 20% pure [59].

Genetically obese mice have increased beta-endorphin and decreased CCK. Food intake increases with morphine or beta-endorphin administration. Opiates play a role in regulating stress-induced feeding, and CCK blocks that action. Faris et al hypothesized that CCK directly antagonizes endogenous opiates. They tested this by observing the effect of CCK on shock-induced analgesia in the front paw of rats. They found CCK blocks the analgesia and suggested that it may block other opiate-mediated behaviors, such as feeding [60].

Benzodiazepines

Early studies on benzobiazephine (BZDZ) showed that it induces eating behavior. Thus, high doses of Librium and Valium countered amphetamine-induced anorexia in humans. Increases in weight have been reported in animals as well. Even satiated animals will increase food intake when given BZDZ, suggesting they may be able to override the normal control of feeding. It may be that BZDZ- induced hyperphagia is controlled by endogenous opiates as recent evidence suggests that naloxone decreases diazepam-induced hyperphagia in satiated animals, even at low doses [61].

Endogenous Opiates and Opiate Antagonists

Opiates have been reported to both increase and decrease feeding behavior. The research is in its early stages, but most of the evidence suggests that endogenous opioids induce obesity in animals by increasing appetite.

Naloxone and naltrexone are the opiate antagonists studied. Naloxone decreases diazepam-induced hyperphagia in satiated animals, possibly by inducing early satiety so feeding terminates sooner, by decreasing incentives to eating (visual, gustatory, olfactory, thermal stimuli) or the rewards of food and/or palatability of food. It reduces food intake in food-deprived rats as well. Mild pinching of rats (stress) promotes eating, and naloxone can reverse this effect, suggesting that the eating is mediated by endogenous opiates. It is possible that opiates are released strictly for analgesia and the increased food intake is an ancillary effect. Less likely, the animals may eat to obtain analgesia from some element of the food (Zioudrou et al found "exorphins" in casein and gluten, which bind to opiate receptors [72]).

McCarthy et al in 1981 studied the effect of naloxone on food intake in rats, rabbits, and cats and compared it with the known anorectic agents fenfluramine and diethylproprion. Naloxone produced dose-related decreases in food consumption in all three species [46].

Moore et al found that when naloxone was administered intravenously over a five-week period to anorectics who were also on an antidepressant, weight gain occurred [62].

Lowy and Yim (1981) studied the effect of naltrexone in food-deprived rats and found that it decreased the feeding that normally follows food deprivation by 47% compared with control. This effect occurred independently of suppression of water intake [63].

Sternbach and co-workers, in 1982, gave naltrexone to clonidine-detoxified opiate addicts as part of their drug treatment program. Several had decreased appetite and weight loss, with the loss regained after the drug was stopped [64]. They indicated that Hollister reported decreased food intake in six of ten nonaddicted, normal subjects given the medication [73]. Naltrexone has few side-effects and no known abuse potential compared with amphetamines [64].

Others

Apomorphine stimulates dopamine receptors. Intraperitoneal administration of apomorphine to food-deprived rats decreased food consumption during the first half hour. Pimozide, a dopamine blocker, reversed this effect, reportedly without affecting food intake itself. These findings suggest that dopaminergic neurons mediate the effect of apomorphine on food intake in rats and that dopamine inhibits feeding behavior [65]. Morphine is reported to increase feeding at times and decrease it at other times.

Antelman and Szechtman in 1975, investigated the effect of dopamine blockers on eating induced by tail pinching in rats. Haldol and spiroperidol significantly blocked about 50% of the behaviors at various doses, and pimozide about 60%. Each produced moderate ptosis in most and discontinuous lurching movements (more with spiroperidol), which may be similar to human extrapyramidal symptoms [66].

One preliminary report exists on the effect of dopamine blockers on eating behavior in humans. A male anorectic who was taking pimozide for a month gained weight, and his obsession with weight disappeared, as did his bradycardia and overactivity [67].

Tryptophan is a precursor of serotonin. When tryptophan is administered to rats, both food intake and meal size decrease. These phenomena occur even in food-deprived animals, in whom there was more time between meals, with little effect on the rate of eating. The action on meal size occurs only in the first few hours after administration and the latency (time beween administration and start of meal) was not affected. Also, reduction of meal frequency is absent. These results resemble those that occur with other drugs believed to affect serotonin metabolism, but do not suggest whether

the mechanism is central or peripheral (influence on gastric emptying or gut motility) [68].

Wurtman et al administered fenfluramine, tryptophan, and placebo to 24 obese subjects with carbohydrate craving. Tryptophan did not significantly modify eating patterns for the group as a whole. Brain uptake of tryptophan is increased when given before meals and with some carbohydrates, and its uptake is suppressed by high-protein meals. However, neither of the conditions for increasing tryptophan uptake into the brain were met in this study [45].

Methysergide (Sansert) is used to prevent migraine headaches, possibly through serotonin antagonism. Weight gain and fluid retention are associated with the commonly used dosage [69]. Sansert may influence serotonin in the gut, and serotonin may influence satiety by a peripheral mechanism. Ninety-eight percent of the body's serotonin is in the gut, not the brain [70].

Clonidine, an alpha-adrenergic agonist, was given intramuscularly to monkeys. Food intake increased significantly, and all but two gained weight by the end of one week. Substantial decreases in food intake occurrred in most during drug withdrawal, and there was weight loss back to baseline by the seventh day after withdrawal. Previous reports have stated that the injection of the drug into the lateral hypothalamus of satiated rats greatly increased food intake [71].

Gamma-aminobutyric acid (GABA) has been implicated in the mechanism of action of benzodiazephines, and bicuculline is a GABA antagonist. GABA may be involved in the feeding induced by norepinephrine and beta-endorphins, since these effects are partially blocked by bicuculline, which also decreases benzodiazepine-induced hyperphagia. Bicuculline itself has been reported to both increase and decrease food intake. Benzodiazepine, opiate, CCK, GABA, and bicuculline effects on eating may be linked.

Since the original writing of this chapter, more literature has appeared on medications in the treatment of the eating disorders. The field is getting even more specific as these papers deal with trials of the drugs in the eating disorders, not just descriptions of effects on weight and/or appetite as the early literature did.

Some case reports on the use of imipramine, carbamazepine, sodium valproate, alprazolam and nomifensine have been published. Additionally, further case reports can be added to the review above for medications such as lithium, phenytoin, phenelzine, tranylcypromine, methylamphetamine, fenfluramine and isocarboxazid.

We have also reached the stage where double-blind, placebo-controlled studies are being done. Mianserin has been studied for treatment of bulimia nervosa and lithium for anorexia nervosa.

Hughes et al showed a 91% decrease in binge frequency with desipramine compared with a 19% increase with placebo. Crossover yielded 84% decrease for those originally on placebo. 69% of the 22 patients had complete abstinence. Results persisted at one month follow-up [74].

Pope and Hudson also studied 22 bulimics with imipramine versus placebo. The medication significantly reduced binge frequency and 90% at follow-up continued doing well [75].

Mitchell and Groat used amitriptyline in 32 female, bulimic outpatients and compared it to placebo in double-blind conditions. 150 mg at bedtime was associated with considerable improvement in eating behavior as well as a significant antidepressant effect. There was a minimal, concurrent behavior modification program as well [76].

Walsh and his group studied 20 normal weight bulimics. Nine were treated with phenelzine and eleven were given placebo in a double-blind trial. Phenelzine significantly reduced the number of binges per week. Five of the nine with medication stopped beinging completely and the other four decreased by at least 50%. No one on placebo stopped completely and only two of eleven reduced by 50% or more [77].

Halmi randomly assigned 72 anorectics in a double-blind study to receive cyproheptadine, amitriptyline or placebo. Those with bulimia had worse results with cyproheptadine than placebo or amitriptyline where as the nonbulimics did significantly better with cyproheptadine [78].

CONCLUSION

Many medications are available with side-effects that include influence on weight and/or appetite. Those that increase appetite could be helpful in treating anorexia nervosa, and some have been tested to that end. Others decrease appetite and may be helpful in alleviating bulimic symptoms. Research has begun in that direction. Thus far, no single medication, nor any combination of drugs, has been definitively successful in treating the eating disorders.

Some medications have been tried to no avail. Others await their turn. A look to the immediate future indicates that opiate antagonists and agonists, MAOI, CCK, and benzodiazepines may give some hope for treatment of these illnesses. Further, these compounds may provide more knowledge of the basics of appetite and weight regulation, that could lead to medications for amelioration of the eating disorders some time in the distant future.

Work in this area is extremely important, since even temporary relief of symptoms can produce improved health for the patient, more effective psychotherapeutic work, and possibly a cure for the eating disorders.

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