Recent Advances in Pharmacotherapy

Anorexia nervosa and bulimia nervosa

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No definitive therapy exists for anorexia nervosa (AN) or bulimia nervosa (BN). Nevertheless, biologic and psychologic research into these disorders has increased over the last decade. We examine the various drugs available for treatment. Advances in pharmacotherapy for AN have been modest and have reflected efforts either to stimulate hunger and weight gain or to control complications of the starvation process. Food remains the "drug" of choice. Antidepressants have been found to be beneficial in the treatment of BN. The meaning of this in the context of a relation between BN and mood disorders remains unclear, since coexistent depression does not predict a positive response to these drugs. Pharmacotherapy represents a single but important dimension of the management of patients with eating disorders. The optimal integration of drug therapy and psychotherapy and the identification of predictors of a positive response to drugs have yet to be addressed by clinical research.

Si le traitement de l'anorexie mentale et de la boulimie n'est pas encore définitivement arrêté, ces troubles font de plus en plus, depuis 10 ans, l'objet de recherches biologiques et psychologiques. Revue de leur pharmacothérapie actuelle. Les acquisitions dans celle de l'anorexie sont maigres; elles visent soit à stimuler la faim et la prise de poids, soit à contrer les complications de l'inanition. La nourriture reste le traitement de choix. Dans la boulimie on se trouve bien des antidépresseurs; mais comme la réponse à ceux-ci n'est pas en corrélation avec la présence de dépression, on s'interroge sur le rapport pouvant exister entre la boulimie et les modifications de l'affect. Si la pharmacothérapie n'est qu'un volet du traitement des troubles de l'alimentation, elle garde son importance. La recherche clinique devra porter sur son intégration à la psychothérapie et sur la découverte de facteurs de prédiction de son efficacité.

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The last decade has witnessed a heightened public and scientific awareness of anorexia nervosa (AN) and bulimia nervosa (BN). The former features self-imposed starvation in the relentless pursuit of thinness and leads to various degrees of emaciation and associated physiologic and psychologic sequelae;[1] despite recent attention to this disorder, its predominant features were well described over 100 years ago.[2] BN is characterized by episodes of binge eating, a morbid fear of fatness and the use of various techniques to counteract the effect of overingestion; it can occur together with AN or as an autonomous disorder in people of normal or excessive body weight.[3] Current diagnostic criteria for these disorders are provided in Table I.[4]

AN affects about 1% and clinically significant BN 2% to 4% of the female adolescent and young adult population.[5,6] These disorders feature significant chronicity, morbidity and mortality; between 5% and 22% of the subjects in long-term outcome studies have died as a result of these disorders.[7] The causes remain unknown, and most clinicians and researchers believe that a combination of psychologic, biologic, familial and cultural varia-

bles and vulnerabilities plays a role.[1,3] New understandings of the psychophysiologic features may ultimately enhance treatment.[8,9]

Because of the refractory nature of AN and BN and the renewed interest in their biologic features, virtually every class of psychotropic drug has been tested. Studies have varied in concept and design, but some significant findings have emerged. How pharmacotherapy compares with psychosocial interventions is an unanswered research question; clinically, we believe that optimal treatment will involve the integration of psychotherapy, pharmacotherapy, education and nutrition.

Drug therapy

Anorexia nervosa

In 1874 Sir William Gull wrote: "I do not at present prescribe medicines, because the nursing and the food are more important than anything else";[2] 115 years later food remains the "drug" of choice. Nevertheless, anxiety and delayed gastric emptying may hinder refeeding and necessitate pharmacotherapy.

Antipsychotic agents: The use of chlorpromazine has been advocated for almost 30 years[10] despite limited evidence of its efficacy in promoting weight gain. Doses of 25 to 100 mg 1 hour before meals are commonly prescribed to diminish anxiety about eating.[1] Chlorpromazine therapy may be successful, particularly among patients in hospital, when other pharmacologic and nonpharmacologic means have failed. Careful monitoring is required, because the drug may aggravate orthostatic hypotension and constipation, which commonly occur in the anorexic population.[11] Other side effects include acute dystonias, parkinsonism, irreversible tardive dyskinesia[12] and, rarely, leukopenia, hepatic dysfunction and a decreased seizure threshold. Because there is no evidence to suggest that chlorpromazine is more efficacious than other treatments in reducing anxiety, its use is limited to a minority of patients with AN. In addition, there is no evidence that its antipsychotic properties help to alter the characteristic beliefs and attitudes of such patients.

Two other antipsychotic drugs, sulpiride and pimozide, have been studied in double-blind placebo-controlled trials and have shown no advantage over placebo in the promotion of weight gain.[13,14]

Antidepressant drugs: Depression is common in patients with AN and may reflect a nonspecific complication of starvation; in addition, long-term outcome studies have revealed a high lifetime risk for depression among such patients, whether or not the eating disorder has resolved.[15,16] Double-blind placebo-controlled trials have failed to show that relatively low doses of amitriptyline and clomipramine induce weight gain.[17,18] Food must be considered first-line antidepressant therapy when starvation is present. Use of antidepressant drugs should be restricted to patients who continue to be depressed after emaciation has been eliminated. As with antipsychotic agents the added ability of antidepressant drugs to induce weight gain is of limited use in the global treatment of these patients. Furthermore, tricyclic antidepressant agents may exacerbate constipation, which can sometimes interfere with refeeding.

Anxiolytic agents: There have been no rigorous studies of benzodiazepines or other anxiolytic drugs for AN. Nevertheless, anxiety, particularly before meals, is common and may thwart refeeding.[1] Furthermore, as with depression, there is a high lifetime risk for anxiety disorders even after the resolution of AN.[15,16]

Such short-acting benzodiazepines as lorazepam (0.5 to 1.0 mg) and oxazepam (15 mg) that do not rely on hepatic metabolism may be helpful when given 1 hour before meals. In addition to reducing anxiety, these drugs may counter the occasional frantic urge to pace or exercise. However, the risks of tolerance and dependence may complicate their use. Controlled studies are needed to confirm their efficacy.

Prokinetic agents: Delayed gastric emptying and the associated symptoms of bloating and early satiety have been well documented through radionuclide studies in patients with AN.[19,20] This physiologic complication may heighten food

Table I — Diagnostic criteria for anorexia nervosa and bulimia nervosa[4]

Anorexia nervosa
Refusal to maintain body weight over a minimum normal weight for age and height (e.g., weight loss leading to maintenance of body weight 15% below that expected or failure to make expected weight gain during period of growth, leading to body weight 15% below that expected)
Intense fear of gaining weight or becoming fat, even though underweight
Disturbance in the way in which one's body weight, size or shape is experienced (e.g., the person claims to "feel fat" even when emaciated or believes that one area of the body is "too fat" even when obviously underweight)
In females, absence of at least three consecutive menstrual cycles when otherwise expected to occur (primary or secondary amenorrhea) (A woman is considered to have amenorrhea if her periods occur only following hormone [e.g., estrogen] administration.)
Bulimia nervosa
Recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period)
A feeling of lack of control over eating behaviour during eating binges
Regular engagement in self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise to prevent weight gain
A minimum average of two binge eating episodes a week for at least 3 months
Persistent overconcern with body shape and weight

avoidance and limit compliance with refeeding. The effects of antidopaminergic agents (e.g., metoclopramide and domperidone) and of procholinergic agents (e.g., cisapride and bethanechol) have been examined in well-designed, usually acute-challenge studies.[19,21-23] It has not been established that these drugs provide sustained benefit through weeks of refeeding, and the use of antidopaminergic agents may result in central dopamine blockade, which can lead to parkinsonism and even tardive dyskinesia.[24] Furthermore, refeeding alone has been found to enhance the rate of gastric emptying for most anorexic patients.[25] Nevertheless, domperidone, 10 to 20 mg half an hour before meals, may diminish postprandial bloating and early satiety in the initial weeks of refeeding.

Appetite stimulants: The term anorexia nervosa is a misnomer; until the final stages of emaciation there is no true loss of appetite. Rather, the anorexic patient struggles to resist appetitive drives. The use of appetite stimulants has nevertheless been the subject of several controlled trials. Cyproheptadine, a serotonin antagonist, has been proven to be ineffective in the promotion of clinically significant weight gain, and thus its use cannot be advocated.[26]

Other agents: Similarities between the symptoms of AN and of zinc deficiency, as well as decreased urine zinc levels in anorexic subjects, have led to trials of zinc sulfate supplements. In the only double-blind placebo-controlled trial zinc was found to improve mood but not weight gain or even taste function.[27] To advocate its use on the basis that it can do no harm is unacceptable.

Evidence of markedly elevated opioid activity in the cerebrospinal fluid of anorexic patients has led to trials of opiate antagonists, such as naloxone and naltrexone.[28] However, the investigation has been limited to case reports and studies of multimodal therapy, and as yet these drugs have no clinical role.

Recognition of the appetite-stimulating effects of such drugs as tetrahydrocannabinol, the most prominent psychoactive ingredient in marijuana, and clonidine, an α_2-adrenergic agonist, has led to further clinical trials.[29,30] There has been no evidence to recommend the use of either drug.

Bulimia nervosa

Pharmacotherapy offers greater hope for BN than for AN. In the absence of emaciation numerous studies have documented neuroendocrine and neurotransmitter dysregulation similar to that in affective disorders.[9]

Antidepressant drugs: All but 2 of the 12 placebo-controlled double-blind studies have shown that antidepressant drugs significantly reduce binge frequency. Two studies each of desipramine[31,32] and imipramine[33,34] have shown that these drugs can be used effectively in doses similar to those used to treat depression. However, this does not mean that these drugs are treating a forme fruste of affective disorder. Indeed, the first desipramine study specifically excluded bulimic subjects with depression.[31] The monoamine oxidase inhibitors phenelzine[35] and isocarboxazid[36] have also been found to diminish bulimic behaviour; however, the patient must adhere to a tyramine-free diet. Side effects such as hypotension may limit the use of these drugs in this potentially fluid-compromised population. In addition, studies of monoamine oxidase inhibitors have been hampered by high drop-out rates.

Positive results have been reported from studies of new and experimental antidepressant drugs, such as trazodone[37] and fluoxetine,[38] both of which enhance brain serotonin activity. Fluoxetine, recently licensed in Canada, has been studied among 382 people with BN in the largest double-blind placebo-controlled trial to date;[39] the drug was found to be significantly better than the placebo in reducing the frequency of binging and vomiting. These studies are tantalizing because of evidence suggesting an underlying serotoninergic dysregulation in patients with BN.[26]

There has been no evidence to suggest the relative superiority of any particular antidepressant drug; therefore, clinicians must consider tolerability and compliance in selecting a drug with proven efficacy. We usually start with desipramine because of the few anticholinergic toxic effects (Fig. 1).

In two studies the traditional agent amitriptyline[40] and the experimental drug mianserin[41] (long available in Britain) were found to be ineffective. However, subtherapeutic doses had been used.

The mechanism of action of antidepressant drugs in BN is unknown, but it neither requires nor correlates with coexistent depression. The benefits of these drugs are reflected in fewer urges to binge, decreased binge frequency and increased satiety during feeding.

Anticonvulsant drugs: In the last decade carbamazepine has been used primarily as an alternative to lithium for stabilizing the mood in bipolar affective disorder. Its study reflects both a hypothesized relation between BN and affective disorder and evidence that compulsive eating behaviour is associated with neurophysiologic disturbance. A double-blind placebo-controlled trial revealed carbamazepine's benefit to be limited to a patient with cyclothymia.[42] Although phenytoin enjoyed a brief vogue in the 1970s[43] it is no longer used to treat ill-defined compulsive eating behaviour.

Anxiolytic agents: Although anxiety may trigger binging behaviour, there have been no rigorous trials of anxiolytic drugs. Patients with BN are vulnerable to mixed substance abuse, which may include benzodiazepines.

Lithium: An uncontrolled clinical trial of lithium and cognitive-behaviour therapy has suggested that the drug is potentially beneficial;[44] however, a double-blind placebo-controlled trial is necessary

to confirm its efficacy. Serious toxic effects may occur in patients who have a threatened fluid and electrolyte balance and who may be at risk for overdose.

Other agents: Understanding of the role of endogenous opiates in controlling food intake and the role of serotonin in regulating satiety and macronutrient selection has generated new treatments. The preliminary results of studies have suggested a role for naloxone and naltrexone in treatment-resistant patients,[45,46] but the general use of these drugs cannot be advocated yet. Fenfluramine is an anorexiant that increases serotonin activity and, in animals, promotes satiety and diverts food choice from carbohydrates; in acute-challenge and placebo-controlled double-blind trials the drug has helped to control bulimic behaviour.[47,48] These results must be confirmed through larger studies, but they do support the hypothesis that patients with BN have serotoninergic dysfunction.[26]

Psychosocial therapy

We chose not to enumerate and evaluate the broad range of psychosocial interventions in eating disorders[49] in this article. Surprisingly, there have been no completed clinical trials that compare pharmacotherapy with psychotherapy. Only recently have research data confirmed the value of family therapy for AN[50] and of cognitive-behaviour therapy for BN.[51] We continue to advocate the combination of such interventions with drug therapy in certain patients and recognize that nutritional rehabilitation and a trusting doctor–patient relationship are critical cornerstones of the global treatment of AN and BN.

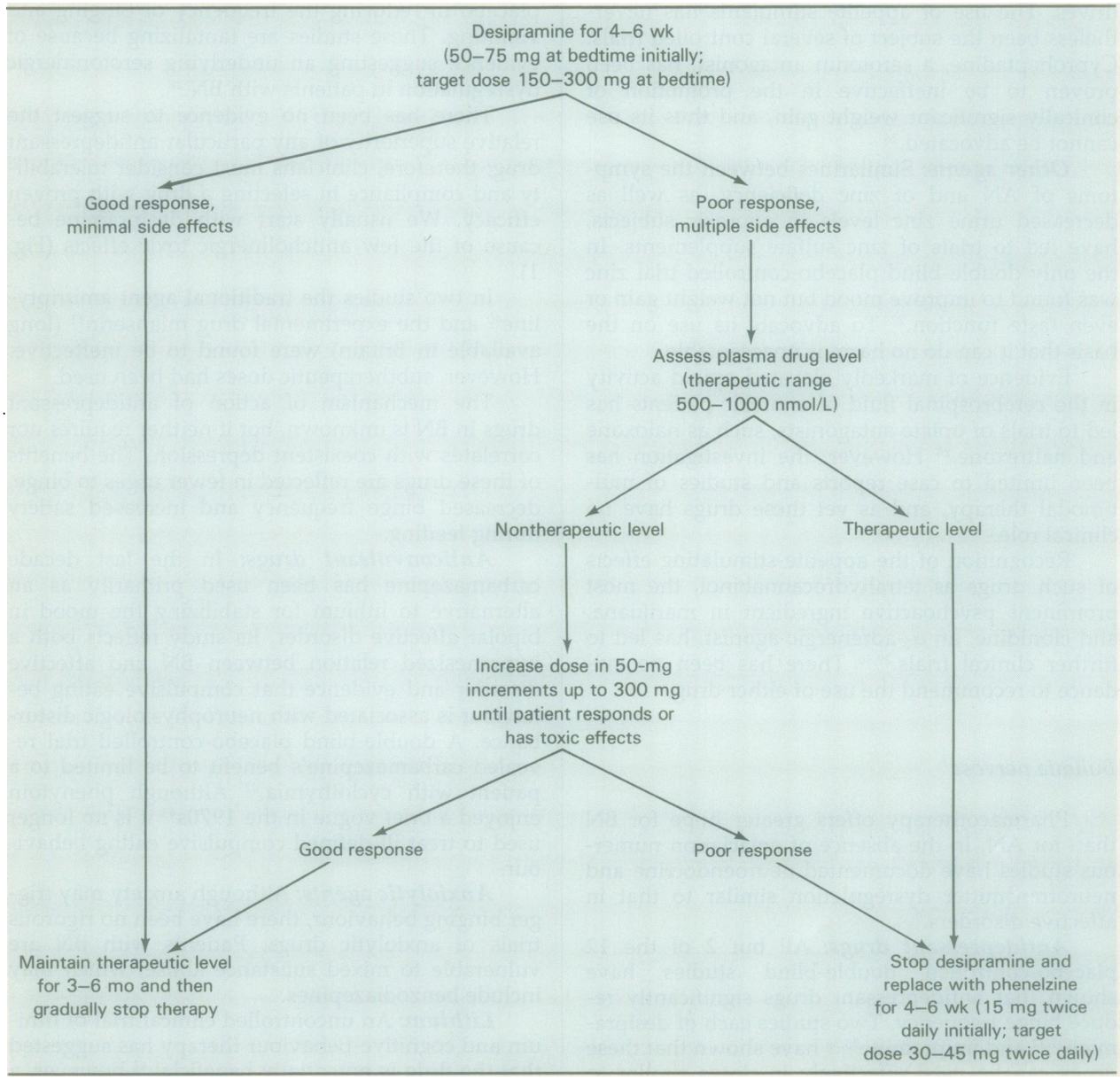

Fig. 1 — Clinical strategy for treatment of bulimia nervosa with desipramine.

Conclusions

Although research in the last decade has identified the multiple perturbations associated with emaciation due to AN, no definitive drug therapy or primary biologic markers have been found. The biologic disturbances are usually reversed by the regular intake of enough food to re-establish normal weight.

Pharmacotherapy for BN points to an unequivocal role for various antidepressants to act as antibulimic agents. However, a number of clinical concerns remain unanswered: What are the characteristics of the subset of BN patients who will respond to these drugs? What are the appropriate durations and mechanisms of action of pharmacotherapy? What are the long-term benefits of short-term drug treatment? and How does the relative efficacy of pharmacotherapy compare with that of other proven forms of BN treatment? The clinician is left to balance the precept of *primum non nocere* against the real benefits that may emanate from drug treatment of this chronic and often refractory disorder.

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Additional comments on anorexia nervosa and bulimia nervosa

The article by Goldbloom and associates indicates that numerous attempts to treat eating disorders with various drugs have rarely succeeded. However, the drug trials have seldom been based on a well-developed rationale linking the mechanism of action of the drug with a known hypothesis regarding cause. Moreover, the mechanisms of action of the few agents known to be effective are still not fully understood.

Because of the limited success of pharmacotherapy a multimodal treatment strategy is recommended. However, a broad, general approach is not a substitute for carefully developing an understanding of each potential precipitating and perpetuating factor. Breakthroughs in treatment will occur only after the mechanism of action of the treatment is closely linked to our understanding of these factors.

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