Editorial: New Horizons in the Classification, Biology and Management of Eating Disorders

INTRODUCTION

Over the past decade there has been a significant change in the mix of people seeking help in eating disorders (ED) centers in Israel. Populations that were previously relatively protected and observed with reduced morbidity joined the circle of patients. The penetration of Western culture into traditional cultures of minorities such as ultraorthodox religious Jews, Arabs, Bedouin and Druze has led to an increase in ED-related morbidity in these minorities, as has been observed in similar places in the world. The spread of EDs to new immigrants from Ethiopia and Russia resembles similar processes in other immigrant populations elsewhere. The recent increase in young female patients suffering from active EDs and getting pregnant is another challenge. These young women often lack adaptive coping strategies during pregnancy and, after the delivery, potentially showing worsening of their ED, alongside considerable difficulties in their experience of motherhood.

Nonetheless, major difficulties may be encountered in the study of EDs, first and foremost in the establishment of the diagnosis. As is the case with the general psychiatric taxonomy, the diagnosis of EDs is based mainly on subjective clinical symptoms reported the patients, who often may deny and hide their symptoms, and there are only a few objective signs (e.g., measured reduction in weight) that can confirm it. Second, the criteria of ED diagnoses have changed dramatically along the different versions of the DSM. Last, ED diagnoses are unstable over time, and patients may shift from one diagnostic entity to another, particularly from restrictive to binge/purge EDs. All these intricacies make the study of the clinical course and the treatment of EDs highly complex and challenging.

DSM-5: FROM EVOLUTION TO REVOLUTION

Major changes in the diagnosis of EDs have occurred with the publication of the new version of the DSM-5 (2013). Thus, the task force working on the diagnostic criteria of EDs has created an entirely new diagnostic entity, the avoidant/restrictive food intake disorder (ARFID), to describe restrictive childhood EDs that do not include symptoms of wanting to lose weight or body image disturbances characterizing the "classical" EDs. The ARFID diagnosis has replaced the DSM-IV "feeding disorder of infancy or early childhood," restricted to children six years of age or younger only. ARFID has no age limitations and can theoretically be applied also to adolescent and adult populations.

Nonetheless, the most important change from the DSM-IV to the DSM-5 is the reshaping of the DSM-IV waste basket category of eating disorder not otherwise specified (EDNOS), including up to 50% of all ED patients, and transforming it into two major specific diagnoses. One is the other specified feeding or eating disorder (OSFED), including ED patients who do not fit in the main clinical diagnoses, but who can be classified to subthreshold AN, BN and BED. The other is formation of new specific diagnoses such as binge-eating disorder (BED; patients who binge but do not purge, a provisional diagnosis in the DSM-IV), purging disorder (PD; normal weight patients who purge but do not binge), and night eating syndrome (NES; normal-weight patients whose ED symptoms occur in the late evening or at night). A relatively small waste basket diagnosis, the unspecified feeding or eating disorder, replaces the much larger DSM-IV EDNOS.

The recent change in the diagnostic criteria of EDs from the DSM-IV to the DSM-5 has resulted in a major change in the diagnostic criteria of AN. In the previous DSM editions (DSM-3, DSM-3R and DSM-IV), a precise reduction in weight has been specified (i.e., reduction of 75% of required weight in the DSM-3/DSM-3R, and 85% in the DSM-IV). By contrast, in the DSM-5, a clinically significant reduction in weight is sufficient (the increase from 75% to 85% of required weight has been found to have no effect on outcome). In addition, behaviors interfering with weight gain despite objective low weight suffice for another diagnostic criterion of AN, taking into consideration that these patients may often deny or hide their fear of gaining weight. Last, the amenorrhea criterion has been removed in the DSM-5 because in recent years a considerable proportion of patients may

develop AN before menarche, showing that the presence of amenorrhea does not largely affect outcome.

These changes have transitioned patients belonging in the DSM-IV to the NOS category to being diagnosed as AN in the DSM-5. As treatment is mainly investigated with respect to specific diagnoses, such a shift may have a favorable effect on the prognosis of the ED. Not surprisingly, these diagnostic changes have been accompanied by concomitant changes in the rates of several EDs in epidemiologic studies. Thus, the recent increase (1) in the rate of AN, alongside a concomitant decrease in the rate of EDNOS is associated, at least in part, with the broadening of the diagnostic criteria of AN from the DSM-IV to the DSM-5. This primary evidence supports the success in the aim of the DSM-5 task force to reduce and minimize the size of non-specific ED categories.

ATTEMPTS TO IMPROVE OUTCOME AND TREATMENT

AN is the most severe clinical entity in the ED category. Over the years, many attempts have been made to plan treatment protocols that would increase the chances for recovery and reduce the risk of mortality and chronicity. An illness staging model for AN seeking to find the right treatment along the developmental continuum of the illness has received increased attention in recent years. The overall concept is that psychiatric illnesses, including EDs, may follow a trajectory across the life course. High risk markers and prodromal features may already be present in childhood and adolescence. Partial subsyndromal disorders may develop during adolescence and can later transition to the full manifestation of the illness in early adulthood. Over time, the illness may become severe and enduring, resistant to treatment and associated with significant physical and psychiatric co-morbidity.

The use of the empirical Clinician Administered Staging Instrument for Anorexia Nervosa (CASIAN) has been recently found significantly to distinguish between earlier and milder clinical stages of AN vs. more severe and enduring stages of the illness. There is, however, currently only a preliminary support for a staging model in AN. Larger longitudinal studies with longer follow-up periods from the premorbid stage to recovery or chronicity are needed to evaluate the overall utility of the staging model in EDs (2).

Nonetheless, the staging model may have a specific importance in the study of severe and enduring (chronic) AN. The pattern of symptoms in the early phases of the illness (e.g., fasting, bingeing and/or purging) and the nutritional sequelae associated with protracted starvation may impact on brain plasticity and neuroadaptation in later stages. There is still uncertainty about how to manage patients with severe and enduring AN. A consensus, though, is emerging toward changing treatment priorities. Accordingly, obtaining the best quality of life for patients with severe and enduring AN and their families and minimizing discomfort may be prioritized to achieving significant restoration of weight and eating behaviors.

Last, severity specifiers were added in the DSM-5 to AN, BN and BED. Specifying the severity of the ED may have great impact on medical decisions and treatment priorities and facilities. Recent studies show limited support for the DSM-5 severity specifiers for BN and modest support for the DSM-5 severity specifiers for AN and BED (3-5). To conclude, the DSM-5 version seems to be a better diagnostic system for EDs than the earlier DSM editions, although the real test awaits its durability over time

THE ROLE OF DIETING IN PSYCHIATRY

A growing body of evidence suggests that the human diet is an important contributing factor in the development, management and prevention of several psychiatric illnesses. Tryptophan, an essential amino acid, is the sole precursor of 5-hydroxytryptamine (5-HT; serotonin). Administration of tryptophan can boost serotonin neurotransmission to produce therapeutically important effects in serotonin deficiency disorders, for example depression. Evidence suggests that excessive dieting and food restriction can decrease brain tryptophan and serotonin in patients with AN to precipitate depression, psychosis and hyperactivity.

NEUROIMAGING, NEUROMODULATORS AND NEUROSTIMULATION IN EATING DISORDERS

Anatomical and functional neuroimaging research in EDs has recently gained considerable momentum. Although important structural magnetic resonance imaging studies have been carried out in recent years, there are still no definite conclusions about the exact brain areas involved in ED-related pathology.

New functional MRI (fMRI) studies investigate network alterations potentially shared across different ED types. Findings on reward processing across both AN and BN point to the presence of altered sensitivity to salient food stimuli in striatal regions, and to the possibility of hypothalamic inputs being overridden by top-down cognitive control regions. Nevertheless, findings from functional network connectivity studies are still equivocal (6).

While the number of brain imaging studies in EDs has dramatically increased, there has been recent criticism that many of these studies have been too lenient in the control of statistical thresholds. Another major problem in human brain imaging research, including in the field of EDs, is the poor reproducibility of the results. It has been suggested recently that important factors should be considered when grouping together patients with EDs in neuroimaging studies to refine the findings. These include the development history, demographic details, illness condition, and effects of exercise, hydration, binge/purge behavior, malnutrition, hormone levels, psychiatric comorbidity and use of medications (7).

Whereas multimodal treatment is still considered the main approach for the management of patients with EDs, advances in etiological research call for the development of more targeted, brain-focused treatments. A range of neuro-stimulation approaches, most prominently repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS), are rapidly emerging as potential novel interventions for refractory patients. Indeed, new basic science research has looked for novel approaches to stimulate target areas in the brain that might be connected to EDs. Thus, investigation of DBS in the rat brain suggests that low-frequency prelimbic cortex stimulation might be useful for correcting prefrontal hypofunction, likely associated with bingeing and ED- and non-ED related addiction pathogenesis (8).

Additionally, brain circuits hypothesized to drive AN symptoms can be accessed using DBS. Initial results suggest that DBS of the subcallosal cingulate is safe, potentially associated with improvement in mood and anxiety. In patients with treatment-refractory AN, DBS has been found to be well tolerated and associated with significant and sustained improvement in affective symptoms, body mass index (BMI), and changes in neural circuitry, at 12 months post-treatment (9).

A meta-analysis of a total of 32 studies (526 participants) of brain stimulation was published recently (10). Whereas the findings are somewhat mixed for BN, neuro-stimulation techniques have shown favorable potential in the treatment of other EDs, in terms of reduction of ED and associated symptoms. Studies exploring cognitive, neural and hormonal correlates of these techniques have also been appearing recently. Nonetheless, despite the promise of neuro-stimulation approaches as potential treatment for EDs, large, well-conducted randomized controlled trials are required to assess treatment targets, stimulation parameters and mechanisms of action (10).

In contrast to DBS, rTMS is a less invasive technique, with less associated risk, and thus has greater potential to become a more widespread augmentation or add-on therapy for patients with refractory AN. The improvement of core ED symptoms with rTMS, however, is as yet only modest and limited (11). As the CNS-related pathophysiology of AN is still unclear, and since brain reactivity can be diminished overtime because of prolonged starvation, it is challenging to find the stimulation target area(s) and stimulation parameters proven beneficial for patients with severe and enduring AN.

NEW MEDICATIONS IN THE TREATMENT OF EATING DISORDERS

Drug therapy is a major component of integrated treatment for patients with EDs. Despite the extensive use of medications in these patients treatment options are relatively few, and limited mainly to symptomatic alleviation.

NEW MEDICATIONS IN ANOREXIA NERVOSA

There are currently no FDA approved pharmacological treatments for AN. In addition, APA and NICE guidelines state that currently there is a very limited evidence base for any pharmacological treatment in AN.

Antidepressant and antipsychotic medications are used in patients with AN mainly to treat associated psychiatric comorbidities such as depression, anxiety and obsessionality, and are not effective in increasing the patients' weight. This is despite the obesogenic effect of these medications in other psychiatric disorders. SSRIs may be ineffective in acutely-ill AN patients because of reduced absorption of tryptophan, the precursor of serotonin, compared to other essential amino acids, in malnourished conditions. Along these lines, tryptophan supplementation may enhance the therapeutic effect of SSRIs in AN patients (12). Last, some studies, although not all, suggest that antidepressants may reduce the risk of relapse in recovered weight-restored patients with AN.

The use of the atypical antipsychotic medication Olanzapine, a dopamine (D2), serotonin (5-HT2) and histamine antagonist, is associated with significant weight increase owing to its dopamine, serotonin and histamine blocking effects. This has led to the investigation of its weight enhancing effects in AN. Indeed, several open studies and four randomized control studies conducted in the past decade found that, in comparison to placebo, the use of Olanzapine may increase weight and reduce the severity of ED-related and obsessional symptomatology, anxiety and depression.

Lately, a randomized, double-blind, placebo-controlled design assessed the effect of the ghrelin agonist Relamorelin in AN. Indeed, treatment with a ghrelin agonist, significantly decreasing gastric emptying time, has been found to lead to a trend in weight gain after four weeks (13).

Additionally, since dopamine D2 receptor agonists may reduce anxiety, improve perceptual distortion, and increase appetite and weight gain, they may have a role in the treatment of AN. Thus, the use of the D2 receptor partial agonist Aripiprazole in patients with AN has been associated with an increase in BMI. Current knowledge is limited, though, and the effect of Aripiprazole in AN awaits further investigation (14).

Last, the endocannabinoid system may influence feeding behavior by acting on circuits located in the hypothalamus, on reward systems regulating and controlling feeding behavior by inducing pleasurable effects, and on the brain stem. Thus, the overall effect of the endocannabinoid tetra-hydro-cannabinol (THC) is anabolic, owing to an overall enhancement of food consumption. THC derivatives are FDA-approved for inducing appetite in cancer and HIV patients. Moreover, the cannabinoid receptor-1 antagonist Rimonabant has been studied for weight reduction in complicated obesity (although being associated with weight reduction, it had to be stopped because of significant adverse effects).

These findings have led to the investigation of the potential of THC to increase weight in patients with AN. However, two small scales studies have not found increase in weight in AN patients treated with THC vs. placebo/other medications. The patients treated in these studies, on the other hand, were chronic, perhaps resistant to any treatment. By contrast, Drobnabinol, a synthetic form of THC, showed greater weight gain vs. placebo in 25 patients with AN.

NEW MEDICATIONS IN BULIMIA NERVOSA AND BINGE EATING DISORDER

The use of Methylphenidate (MPH), particularly its long acting compounds, has been found useful in reducing bingeing behavior in case reports of patients with concomitant BN/BED and attention deficit hyperactivity disorder (ADHD). The rationale of MPH treatment in these patients is related to its potential to regulate reward-related activity, to reduce hyperactivity, impulsivity, affective instability, reactivity to food and stress, and obsessionality, and to enhance the organization of maladaptive eating behaviors. Nonetheless, the use of MPH in these patients has not been FDA approved yet, and is limited to BN/BED patients not responding to other treatments.

In 2015, McElroy and her associates published the first study showing the positive effect of another psychostimulant, Lisdexamfetamine, in reducing bingeing behavior in patients with BED (15). In later clinical trials, Lisdexamfetamine demonstrated statistical and clinical superiority over placebo in reducing binge eating (16, 17). These findings led the FDA to approve the use Lisdexamfetamine in the treatment of moderate to severe BED.

Altogether these studies suggest that although there are promising preliminary findings in EDs with the use of several new medications working on new mechanisms, their efficacy is mostly modest and limited. Future large-scale multicenter studies are required to support the effectiveness of these medications in the treatment of EDs and establish their indications and long-term safety.

THE CURRENT ISSUE

The aim of the current issue, the first of two publications, is to deepen our knowledge and broaden our understanding about clinical and biological aspects of EDs, to improve diagnostic methodology and to develop innovative treatments. We hereby present the summary of the seven studies included in this issue.

In the first study, Kreitler concludes that eating habits characterized by deviances from the common eating behaviors in one's family and culture that are not concerned with weight and physical appearance are not akin to classical EDs, but rather represent an independent manifestation of disordered eating

In the second study, Zohar and her associates show that the Hebrew translation of the Eating Disorders Examination Questionnaire (EDE-Q), the golden screening tool for EDs, has adequate structural validity, convergent validity, and screening properties and can safely be used in Israeli ED populations.

In the third study, Zohar and her associates show that the Hebrew translation of the Dresdner Körperbildfragebogen (DKB-35), a comprehensive self-report measure of the relationship with the body, has adequate structural validity, convergent validity, and screening properties, and can be used in the assessment of attitudes toward the body in Israeli patients with EDs.

In the fourth article, Hetman and her associates show that the percentage of the discharge weight relative to the recommended weight following inpatient treatment

may predict re-hospitalization in adolescents with AN. Accordingly, the recommendation to discharge adolescents with AN close to their recommended weight is of merit in reducing the risk for re-hospitalization.

In the fifth study, Nachum and his associates show that the neurocognitive search activity (SA) problem-solving ability – potentially related to the core ED-trait of ineffectiveness - is variously represented in different ED types. Thus, less adaptive SA strategies are found in acutely-ill patients with binge/purge EDs vs. controls but not in patients with restrictive-type AN (AN-R). Binge/purge, but not AN-R patients, show improvement in SA upon symptomatic stabilization.

In the sixth study, Avraham and her associates show that chronic patients with AN treated with low doses of oral Δ9-Tetrahydrocannabinol (Δ9-THC), the active compound of Cannabis Sativa with appetite-stimulating properties, show improvement in body care, ineffectiveness, asceticism and depression, but no increase in weight.

Last, in the seventh study, Israely and her associates show that adding Tyrosine, an essential amino acid that is the precursor of catecholamines to the diet of patients with AN, may shorten reaction time and test duration in memory tasks, and improve depressive mood.

We hope that the readers of the IJP will find this special issue a valuable and interesting read. We certainly do.

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