## How to address the treatment gap for patients with eating disorders and help with their recovery?"

Introduction
The term Eating Disorders (ED) refers to a range of mental conditions in which there is persistent disturbance in eating behaviour and an associated impairment in physical or mental health. Six main ED are recognised in diagnostic systems including: anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BEN), avoidant-restrictive food intake disorder (ARFID), pica, and rumination disorder (Treasure, Duarte, et al., 2020a). Breaching the treatment gap for ED requires a multifaceted approach based on the stage of ED the patient is in. This encompasses methods to prevent their emergence, as well more effective secondary interventions that reduce the time course of the disease thereby reducing the demand on services at any given time and overall improving the availability of treatment. Underlying this is also the need to diagnose and treat those that delay seeking treatment with early intervention strategies.

Stage model of eating disorders and interventions
In order to effectively implement strategies to address the treatment gap in eating disorders it is important to have a framework to appreciate the different stages of the illness, as outlined in the diagram below.
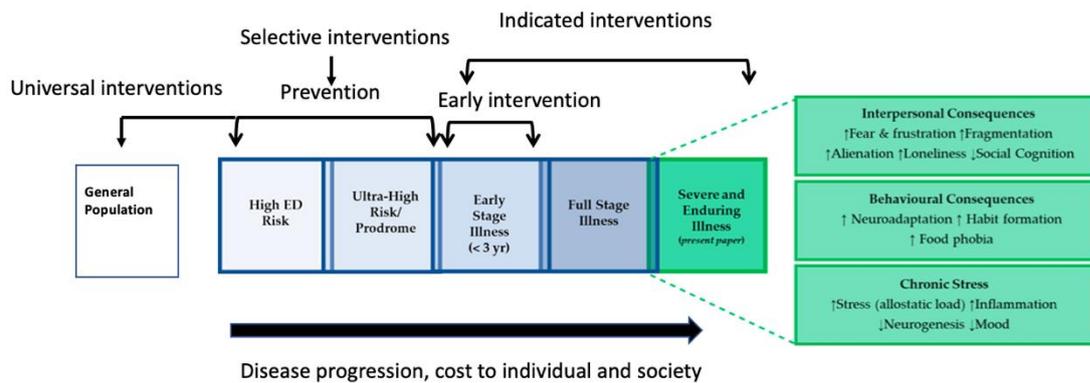
Diagram 1: the Stage model of illness, eating disorders: adapted from (Treasure, Willmott, et al., 2020) and (Treasure et al., 2015)

The development of an eating disorder is described as starting with a subpopulation of patients that are at high eating disorder risk. Several interrelated risk factors for eating disorders have been identified including biological factors (genetic predisposition, gastrointestinal microbiota), and psychosocial risk factors including body dissatisfaction, internalization of the thin ideal, elite sports, and childhood and early adolescent experiences (Varela et al., 2023). This then progresses to an ultrahigh prodrome with patients reporting subclinical symptoms (suitable for preventive interventions) after which they develop early stages of the illness (defined as symptoms for less than three years), the target population for early intervention. From the early stage of illness it can then progress on to full stage illness (symptoms for more) than three years and finally on to severe and enduring illness/eating disorder (SEED), characterised by their chronicity and treatment resistance thought to represent 20–30% of patients with AN or BN (Treasure, Duarte, et al., 2020b). As the disease progresses a complex sequalae of neurobiological changes occur including disturbances in the gut-brain axis, the release of neuropeptides and reductions in neuroplasticity that progress with disease duration.

The different types of interventions for ED can be subdivided based on their target population and correspond to the stage of disease model as outlined above(Koreshe et al., 2023). Universal interventions indiscriminately target the entire population, including all the stages of disease as well as the general population (Koreshe et al., 2023). Selective interventions are used for those at risk of developing the disease, including those with high ED risk as well as those in an ultrahigh risk prodrome (Koreshe et al., 2023). Universal and selective interventions together are the basis of a preventive approach to ED. Most current preventive approaches focus on key modifiable psychosocial risk factors namely body dissatisfaction and the related internalization of the thin ideal. Indicated interventions are used for those already presenting with symptoms of disease, with early intervention being used for those with symptoms lasting less than three years (Treasure et al., 2015). A number of novel, indicated interventions that aim to modify the pathophysiological changes seen in ED are being researched and will be discussed below. Currently these approaches are being studied in more enduring forms of the disorder but have potential to be integrated further, earlier on in the illness, including in prevention and early intervention.

Preventing the emergence of eating disorders
Key preventive psychosocial interventions include cognitive dissonance training, cognitive behavioural therapy and media literacy training (Le et al., 2017). Universal interventions are less studied and thought to be less effective, then selective or indicative approaches, however meta-analyses have shown they can be effective in modifying ED risk factors. (Chua et al., 2020). Studies suggest the most effective approach for universal interventions is media literacy training which involves teaching individuals to critically analyse media content across various platforms (Koreshe et al., 2023). When applied to ED, media literacy training focuses on idealisation of the thin ideal/ideal masculinity and body satisfaction, with media literacy programmes such as Media Smart, showing positive changes in these parameters at 12 month follow up (Wilksch et al., 2017).

Selective interventions focus on those at higher risk of the disease, namely adolescent females with body dissatisfaction and internalization of the thin ideal. Multiple systematic reviews have found cognitive dissonance training has the strongest evidence for this population, causing an almost 60 percent reduction in future ED risk compared to controls (Koreshe et al., 2023). Cognitive dissonance training aims to increase cognitive dissonance, so that the participants understand that pursuit of the unattainable thin ideal is contradictory to core beliefs, values, and desired future actions (Dakanalis et al., 2019). One of the most studied programmes is the Body Project, developed by (Stice et al., 2015) which showed reductions in ED symptoms at a one year follow up. The intervention is delivered in a group format and usually given in person, with a virtual form to aid wider application being developed (Wisting et al., 2023).

In addition to the established psychosocial risk factors mentioned above, a key paradigm shift faced by todays adolescents is the ubiquitous nature of social media, which has been shown to negatively impact on body image, and is relevant to all patient demographics. A recent randomized control trial by (Thai et al., 2023), demonstrated that reducing social media use to one hour a day, in a selective population - youth with anxiety and depressive symptoms aged 17-25-, produced a robust improvement in appearance and weight esteem over a period of four weeks compared to no intervention. This study is limited by the lack of longer term follow up and application to ED risk but does highlight several potential interventions including policy initiatives and working with social media companies to reduce problematic use.

Early detection of eating disorders
The indicated population refers to patients that are already experiencing the symptoms of an ED, that meet the threshold for diagnosis. They are the target for early intervention, with studies showing this population most likely to benefit from evidence based psychological therapy interventions (Koreshe et al., 2023). Early detection of ED is key for improving longer term morbidity and mortality, with poorer outcomes being associated with delayed intervention. This is reflected in the Royal College of Psychiatrists Position Statement on early intervention in ED, which highlights the importance of early detection and reducing the duration of untreated ED (DUED) to improve longer term outcomes in patients. An example of an innovative NHS service model implementing this approach is the First Episode Rapid Early Intervention for Eating Disorders (FREED) (Brown et al., 2018). This project is for young people (aged 18-25) who have had ED (AN, BN ,BEN or other ED) for three years or less. The service aims to reduce DUED via improving recognition of ED and increasing access to treatment, with key targets including: engagement calls within 48 hours of referral, two weeks from referral to assessment and four weeks from referral to treatment (Potterton et al., 2021). During the assessment it emphasizes psychoeducation using personal feedback and information on the malleable changes to body and brain, as well as the importance of instilling a sense of hope for recovery (Potterton et al., 2021). A key concept of the service is emerging adulthood, defined as the interval between adolescent and adulthood, with this period being identified as being distinct in terms of demographic characteristics, subjective experiences, and identity formation/exploration. It proposes this group of ED patients may need extra care and attention to help them navigate key transitions (e.g education, relationships) so that they can create an identity separate from the ED (Hyam et al., 2024). The importance of transitions in all stages of an ED, is reflected in the Royal college of psychiatrist report, Managing Transitions When the Patient Has an Eating Disorder (CR208 Nov 2017) with life transitions as well as service transitions (such as from CAHMS to adult services) being highlighted as important points of care that require added attention and personalized care.

Optimizing current treatment and finding new treatments for eating disorders:
Reducing the treatment gap faced by the indicated ED population will involve optimizing existing care in addition to finding and integrating novel approaches. The current best practice for ED is the provision of evidence-based psychotherapies, namely family based therapy (FBT) for AN/ BN/Maudsley model, or CBT for BN, BN, BED (Keeler et al 2023). These are performed in the context of a multidisciplinary team that can be involved in weight monitoring and addressing the physical and mental health of patients (Heruc et al., 2020). A comprehensive overview of the latest evidence for providing optimal care for ED, was carried out by the Royal College of psychiatrists in 2022, culminating in the Managing Medical Emergencies in ED guidelines. Improving outcomes in the UK will involve widespread dissemination and adoption of these guidelines, such as with FREED project named above. A key component of providing optimal care is the personalization of treatment, including modifying care to account for neurodivergence and co-morbidity, (Byrne & Fursland, 2024), this is particularly pertinent for patients with ARFID for which established guidelines are lacking but early research has suggested existing psychotherapies can be successfully adapted (Di Cara et al., 2023).

The importance of finding novel treatments is highlighted by the fact that despite best practice, a significant cohort of patients - an estimated 20–30% of patients with AN or BN- fail to recover with current treatments. Recent research has started to delineate the pathophysiological sequelae for ED, with neuroplasticity/neuromodulation being promising avenues for novel psychopharmacological interventions, of which to date there are no approved therapies (Keeler et al., 2023). The majority of these therapies are currently being researched into those more enduring forms of the disorder, but there is potential for them to be integrated earlier on in the disease process. Novel psychopharmaceutical agents that aim to ameliorate deficiencies in neuroplasticity that occur with prolonged disease include ketamine, psilocybin, MDMA and human recombinant leptin, as outlined in the table below (Keeler et al., 2023).

	Psilocybin	Ketamine	MDMA	Human recombinant leptin / metreleptin)
Target	Psychoactive component of magic mushrooms, that acts on serotonin 2A (5-HT_{2A}) receptors directly with indirect modulation dopaminergic and glutamatergic systems (Peck et al., 2023).	Glutamatergic system, NMDA receptor agonist (Mills et al., 1998).	Potent monoamine releaser and reuptake inhibitor with indirect effects on neurohormone release (oxytocin) (Brewerton et al., 2022).	Analogue of leptin hormone secreted by adipose cells. Hypoleptinemia thought to trigger adaptation to starving including changes in reward pathways and disruption of hypothalamic pituitary axis (Milos et al., 2020).
Current evidence	A phase 1, open-label feasibility study in 10 female patients with AN showing significant decreases in symptoms at three month follow up, after one dose of 25 mg psilocybin with psychological support. In half of the patients there was an associated increase in weight and BMI with a range of 0.4–1.2 kilograms. No significant side effects aside from transient hypoglycaemia were noted, although medically compromised patients and those with a BMI under 16 were excluded	A number of case studies and reports exist, with a study (Mills et al., 1998) looking to see if intermittent ketamine infusions could reduce compulsive behaviour (defined as compulsive eating, Compulsive starving, alcohol use) in patients with chronic treatment resistant eating disorders (anorexia nervosa or bulimia). The study involved 15 patients, 9 of which responded to the infusions, with reductions in complicity and associated increase in weight in anorexia and decrease in bulimia.	Encouraging results in treating PTSD. A trial of MDMA-assisted therapy for PTSD included 89 participants with PTSD, of whom 13 had clinical eating disorder symptoms and 28 were observed to be at risk of an eating disorder. There was a significant improvement in eating disorder symptoms for those participants who received MDMA-assisted psychotherapy compared with a placebo (Brewerton et al., 2022).	Four case studies suggest to date, showed improved mood, ED symptoms and ED cognition during and after dosing period, in patients with eating disorders (Milos et al., 2020).
Future trials	Further clinical trials are on-going (NCT05481736, NCT04505189, NCT04052568), with one taking place at Imperial college London, and one international study using Kings college London as a study site. Further trials looking at the use of psilocybin for binge eating disorder are also planned.	A trial at Kings College London exploring ketamine for depression with anorexia nervosa, termed the EDEN project (kEtamine for DEpression with anorexia Nervosa), has also recently been given funding. Participants in the will randomly receive either ketamine, or a placebo, twice a week across a period of six months, it will also measure the serum ketamine and brain-derived neurotrophic factor (BDNF).	Further clinical trials in patients with an ED as a primary diagnoses are also planned, with a phase 2 study (NCT04454684) of MDMA assisted therapy for patient with an ED (using MDMA therapy in patients with a primary diagnosis of anorexia nervosa restricting subtype and binge eating disorder due to start in 2026).	RCTs assessing efficacy of meleptin are lacking (Keeler et al., 2023).

The research for these compounds is still in its infancy, but due their established prior medical use, ketamine and human recombinant leptin may be more readily translatable with ketamine also having the advantage of being evidence based for the treatment of depression, a common co-morbidity in many eating disorders (Ragnhildstveit et al., 2022). Conversely, MDMA is likely to be less translatable due to its profound cardiovascular effects on blood pressure and heart rate, which may contraindicate its use in a significant subset of ED patients (Fonseca et al., 2021).

Other non-pharmacological approaches to treating ED could include deep brain stimulation (DBS). A meta-analysis by (Karaszewska et al., 2022) found deep brain stimulation to have large effects on weight restoration, quality of life, and reduction of psychiatric symptoms in patients with treatment-refractory AN. Several potential targets have been identified as promising for AN (Shaffer et al., 2023), with the subcallosal cingulate cortex (SCC) as the most supported region for BMI change. Research into DBS for ED is still in its infancy and future research is indicated, as it could be a viable option for select patients; it may however be less likely to be widely adopted or integrated into early stages of treatment due to its cost and invasiveness.

Summary:
Addressing the treatment gap in ED requires a multifaceted approach including prevention, early intervention, and improving treatment efficacy. Prevention can include universal interventions that target psychosocial risk factors for ED, with media literacy training being an evidence based, widely accepted form of treatment, as well as selective interventions that look at individuals at high risk of the disorder, with cognitive dissonance training being shown to be one of the most effective and scalable interventions.

Early intervention is also key to reduce the time of untreated ED and improve longer term outcomes, with the further support of programs such as the FREED project being vital for this goal. The search for novel psychopharmacological approaches to treat more enduring and resistant forms of ED is ongoing, with agents such as psilocybin and ketamine being potential promising treatment avenues that are being actively studied in the United Kingdom at the time of writing. These novel treatments are currently studied in the context of treatment resistant ED, but if proven safe and efficacious may be integrated earlier on in the treatment.

Word count excluding diagrams and bibliography - 1900

Bibliography

- Brewerton, T. D., Wang, J. B., Lafrance, A., Pamplin, C., Mithoefer, M., Yazar-Klosinki, B., Emerson, A., & Doblin, R. (2022). MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. Journal of Psychiatric Research, 149, 128–135. https://doi.org/10.1016/J.JPSYCHIRES.2022.03.008

- Brown, A., McClelland, J., Boysen, E., Mountford, V., Glennon, D., & Schmidt, U. (2018). The FREED Project (first episode and rapid early intervention in eating disorders): service model, feasibility and acceptability. Early Intervention in Psychiatry, 12(2), 250–257. https://doi.org/10.1111/EIP.12382

- Byrne, S. M., & Fursland, A. (2024). New understandings meet old treatments: putting a contemporary face on established protocols. Journal of Eating Disorders 2024 12:1, 12(1), 1–11. https://doi.org/10.1186/S40337-024-00983-4

- Chua, J. Y. X., Tam, W., & Shorey, S. (2020). Research Review: Effectiveness of universal eating disorder prevention interventions in improving body image among children: a systematic review and meta-analysis. Journal of Child Psychology and Psychiatry, 61(5), 522–535. https://doi.org/10.1111/JCPP.13164

- Dakanalis, A., Clerici, M., & Stice, E. (2019). Prevention of eating disorders: current evidence-base for dissonance-based programmes and future directions. Eating and Weight Disorders, 24(4), 597–603. https://doi.org/10.1007/S40519-019-00719-3/METRICS

- Di Cara, M., Rizzo, C., Corallo, F., Cardile, D., Calabrò, R. S., Quartarone, A., Buda, M., & Cucinotta, F. (2023). Avoidant Restrictive Food Intake Disorder: A Narrative Review of Types and Characteristics of Therapeutic Interventions. Children 2023, Vol. 10, Page 1297, 10(8), 1297. https://doi.org/10.3390/CHILDREN10081297

- Heruc, G., Hurst, K., Casey, A., Fleming, K., Freeman, J., Fursland, A., Hart, S., Jeffrey, S., Knight, R., Roberton, M., Roberts, M., Shelton, B., Stiles, G., Sutherland, F., Thornton, C., Wallis, A., & Wade, T. (2020). ANZAED eating disorder treatment principles and general clinical practice and training standards. Journal of Eating Disorders 2020 8:1, 8(1), 1–9. https://doi.org/10.1186/S40337-020-00341-0

- Karaszewska, D., Cleintuar, P., Oudijn, M., Lok, A., van Elburg, A., Denys, D., & Mocking, R. (2022). Efficacy and safety of deep brain stimulation for treatment-refractory anorexia nervosa: a systematic review and meta-analysis. Translational Psychiatry, 12(1). https://doi.org/10.1038/S41398-022-02102-W

- Keeler, J. L., Kan, C., Treasure, J., & Himmerich, H. (2023). Novel treatments for anorexia nervosa: Insights from neuroplasticity research. European Eating Disorders Review : The Journal of the Eating Disorders Association. https://doi.org/10.1002/ERV.3039

- Koreshe, E., Paxton, S., Miskovic-Wheatley, J., Bryant, E., Le, A., Maloney, D., Touyz, S., Maguire, S., Aouad, P., Barakat, S., Boakes, R., Brennan, L., Byrne, S., Caldwell, B., Calvert, S., Carroll, B., Castle, D., Caterson, I., Chelius, B., … Hobart, R. (2023). Prevention and early intervention in eating disorders: findings from a rapid review. Journal of Eating Disorders 2023 11:1, 11(1), 1–20. https://doi.org/10.1186/S40337-023-00758-3

- Le, L. K. D., Barendregt, J. J., Hay, P., & Mihalopoulos, C. (2017). Prevention of eating disorders: A systematic review and meta-analysis. Clinical Psychology Review, 53, 46–58. https://doi.org/10.1016/J.CPR.2017.02.001

- Mills, I. H., Park, G. R., Manara, A. R., & Merriman, R. J. (1998). Treatment of compulsive behaviour in eating disorders with intermittent ketamine infusions. QJM: An International Journal of Medicine, 91(7), 493–503. https://doi.org/10.1093/QJMED/91.7.493

- Peck, S. K., Shao, S., Gruen, T., Yang, K., Babakanian, A., Trim, J., Finn, D. M., & Kaye, W. H. (2023). Psilocybin therapy for females with anorexia nervosa: a phase 1, open-label feasibility study. Nature Medicine 2023 29:8, 29(8), 1947–1953. https://doi.org/10.1038/s41591-023-02455-9

- Potterton, R., Austin, A., Flynn, M., Allen, K., Lawrence, V., Mountford, V., Glennon, D., Grant, N., Brown, A., Franklin-Smith, M., Schelhase, M., Jones, W. R., Brady, G., Nunes, N., Connan, F., Mahony, K., Serpell, L., & Schmidt, U. (2021). "I'm truly free from my eating disorder": Emerging adults' experiences of FREED, an early intervention service model and care pathway for eating disorders. Journal of Eating Disorders, 9(1), 1–14. https://doi.org/10.1186/S40337-020-00354-9/FIGURES/1

- Shaffer, A., Naik, A., Bederson, M., Arnold, P. M., & Hassaneen, W. (2023). Efficacy of deep brain stimulation for the treatment of anorexia nervosa: a systematic review and network meta-analysis of patient-level data. Neurosurgical Focus, 54(2), E5. https://doi.org/10.3171/2022.11.FOCUS22616

- Stice, E., Yokum, S., & Waters, A. (2015). Dissonance-Based Eating Disorder Prevention Program Reduces Reward Region Response to Thin Models; How Actions Shape Valuation. PLOS ONE, 10(12), e0144530. https://doi.org/10.1371/JOURNAL.PONE.0144530
- Thai, H., Davis, C. G., Mahboob, W., Perry, S., Adams, A., Goldfield, G. S., & Goldfield, S. (2023). Reducing Social Media Use Improves Appearance and Weight Esteem in Youth With Emotional Distress Psychology of Popular Media. https://doi.org/10.1037/ppm0000460
- Treasure, J., Duarte, T. A., & Schmidt, U. (2020a). Eating disorders. The Lancet, 395(10227), 899–911. https://doi.org/10.1016/S0140-6736(20)30059-3
- Treasure, J., Duarte, T. A., & Schmidt, U. (2020b). Eating disorders. Lancet (London, England), 395(10227), 899–911. https://doi.org/10.1016/S0140-6736(20)30059-3
- Treasure, J., Stein, D., & Maguire, S. (2015). Has the time come for a staging model to map the course of eating disorders from high risk to severe enduring illness? An examination of the evidence. Early Intervention in Psychiatry, 9(3), 173–184. https://doi.org/10.1111/EIP.12170
- Treasure, J., Willmott, D., Ambwani, S., Cardi, V., Bryan, D. C., Rowlands, K., & Schmidt, U. (2020). Cognitive Interpersonal Model for Anorexia Nervosa Revisited: The Perpetuating Factors that Contribute to the Development of the Severe and Enduring Illness. Journal of Clinical Medicine, 9(3). https://doi.org/10.3390/JCM9030630
- Varela, C., Hoyo, Á., Tapia-Sanz, M. E., Jiménez-González, A. I., Moral, B. J., Rodríguez-Fernández, P., Vargas-Hernández, Y., & Ruiz-Sánchez, L. J. (2023). An update on the underlying risk factors of eating disorders onset during adolescence: a systematic review. Frontiers in Psychology, 14. https://doi.org/10.3389/FPSYG.2023.1221679/FULL
- Wilksch, S. M., Paxton, S. J., Byrne, S. M., Austin, S. B., O'Shea, A., & Wade, T. D. (2017). Outcomes of three universal eating disorder risk reduction programs by participants with higher and lower baseline shape and weight concern. International Journal of Eating Disorders, 50(1), 66–75. https://doi.org/10.1002/EAT.22642
- Wisting, L., Stice, E., Ghaderi, A., & Dahlgren, C. L. (2023). Effectiveness of virtually delivered Body Project groups to prevent eating disorders in young women at risk: a protocol for a randomized controlled trial. Journal of Eating Disorders, 11(1), 1–8. https://doi.org/10.1186/S40337-023-00932-7/METRICS