

**A PILOT OPEN CASE SERIES OF ETHYL-EPA SUPPLEMENTATION IN THE
TREATMENT OF ANOREXIA NERVOSA**

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SUMMARY

Anorexia nervosa (AN) carries the highest risk of morbidity and mortality amongst psychiatric disorders. The efficacy of current treatment approaches is limited. Despite the fat-phobic nature of the disease, poly-unsaturated fatty acids (PUFAs) have not received much research attention. Patients who consume Western diet, which is rich in n-6 PUFAs and trans-fatty acids, are likely to develop severe n-3 PUFA deficiency during self-induced starvation. Re-feeding programmes do not take into consideration n-3 EFA intake, possibly leading to further n-3 PUFA deficiency during weight restoration, and this might contribute to the maintenance of the disorder. To test this hypothesis, we carried out a systematic case series of E-EPA supplementation in the treatment of AN. Seven young patients received 1g/day E-EPA in addition to standard treatment, and were followed up for three months. Three of them recovered and four improved. Randomised controlled trials are warranted to examine the effectiveness of E-EPA in AN further.

BACKGROUND

Anorexia nervosa (AN) carries the highest risk of morbidity and mortality amongst psychiatric disorders. It is a difficult to treat condition. A recent systematic review found no improvement in the outcome of AN during the 20th century¹, and a large population-based follow-up study found no association between treatment and outcome², highlighting the need for new approaches.

Despite the fat-phobic nature of the disease, surprisingly little work has been done on the details of fatty acid metabolism although serious deficits of essential fatty acids (EFAs), including n-3 EFAs, have been reported^{3,4}. A review of epidemiology, risk factors, consequences, co-morbidity, and mortality indicates that PUFA deficiencies are significant in anorexia nervosa (Ayton, 2003, in press). It is likely that prolonged dieting during anorexia affects PUFA reserves in the body and their availability for the brain, and consequently PUFA availability changes during the course of illness. Modern western diet is high in saturated fats, trans-fatty acids and n-6 PUFAs⁵, and restriction of these may correct the n-6: n-3 PUFA ratio at the early stages of the illness. However, if the dietary restriction continues, PUFA deficiencies are likely to develop, not only because of the reduced dietary intake of essential fatty acids, but also because of impaired conversion. Current re-feeding programmes do not take into consideration the n-3 fatty acid intake (the LA/LNA [n-6: n-3] ratio is 5-6: 1 in artificial feeds). It is possible that as a result of this patients develop further n-3 PUFA deficiency during weight restoration. This may contribute to deteriorating mood, which is a common feature of re-feeding, and increases the risk of relapse. We hypothesised that the n-3 fatty acid fatty acid supplementation might prevent the deterioration of mood during re-feeding, and it might improve the outcome of treatment. After a review of the literature, Ethyl-EPA was chosen, because it has been shown to be helpful in the treatment of affective disorders⁶⁻⁸, and possibly in schizophrenia^{9,10}, and AN shares some features with these conditions.

Aims and objectives:

The present study aimed to provide initial data regarding the use of E-EPA in AN, which can be used for the design of a future randomised controlled trial.

PATIENTS AND METHODS:

Consecutive cases of adolescent AN referred to the first author were asked to participate in the study. The design was approved by the local Ethics Committee.

Entry criteria:

ICD-10 diagnosis of AN in young people between 13-22 years old, and informed written consent by the parents and the patient. Ten patients were approached for participation. Exclusion criteria were kept to the minimum (risk of pregnancy), and patients with co-morbid disorders (such as depression) were included. All patients were offered treatment as usual. Participants were given 1 g/day E-EPA for three months in addition to standard treatment (provided by Laxdale Ltd). If the family and the patient wished to continue with the E-EPA beyond the three months, a prescription was provided on a named patient basis, and in some cases, the dose was increased during this time. None of the patients received any psychotropic medication during the study.

Assessment and treatment as usual:

All patients were offered the standard treatment that was available at the local district services. This included full psychiatric and physical assessment, regular monitoring of

physical parameters, including weight, full biochemical profile, full blood count and differential, liver function tests, serum proteins, lipid profile, thyroid functions, FSH, LH, oestrogen (or testosterone), progesterone, B12, folate, transferrin, Zinc and Selenium.

According to local service arrangements, young people, who were physically unstable or severely malnourished (less than 0.04 centile on the 1990 UK BMI chart), were first admitted to the paediatric ward for naso-gastric feeding (NG) for a few weeks (Nutrason Energy containing LA/LNA 4.86:1 ratio). When their medical status stabilised and they reached around 80-85% of average body weight for age and height (ABW), they were offered a transferral to the local general adolescent mental health unit, as either 5 day/week residents or day-attenders according to the family's wishes. All patients were offered psycho-education, dietary advice, some form of individual therapy (art-therapy, motivational counselling), and systemic family therapy. Cognitive behavioural therapy or cognitive-analytic therapy was not available locally.

Measures:

All parameters were monitored on a monthly basis. These included the patients' weight and height. BMI, and average body weight for age and height ratio (ABW) were calculated by using Weight 4 Height software (based on 1990 British reference data by the Child Growth Foundation). The following psychometric measures were used: EDI-2, BDI-2, CGAS, CGI-S, the modified Morgan-Russell Scale.

RESULTS:

Adherence to the study:

Seven patients completed the three months. Compliance was generally good in these patients, all of whom suffered from AN restrictive subtype. In three of them, six-months' follow-up information was available, and in further three cases, one year follow-up information was also available.

From the remaining three, one patient stopped E-EPA after the first capsule because it was too big. This patient's illness became chronic during the following year; her ABW remained around 82%, and there was evidence of growth retardation. One patient stopped after two weeks: she had a general poor compliance to treatment, and her family background was chaotic. She had AN (purging subtype) with co-morbid PTSD and depression. She was lost to follow-up. One patient, who took about 6 months to consent to the study, deteriorated during this time, and had to be admitted to the paediatric ward for NG feeding.

Side effects and beneficial effects:

One patient developed acne, but this was attributed to Polycystic Ovary Syndrome (POS). (This diagnosis was supported by high free androgen index, and abnormal abdominal ultrasound). There were no other side effects. All laboratory tests normalised during the treatment. In some cases, there was a clear reduction in triglyceride levels as a consequence of treatment.

There was a general improvement in dry skin, sleep, mood and constipation was alleviated. No patient needed any additional treatment for constipation or poor gastric motility.

The summary of the results are presented on Table 1.

Patient 1

Patient No 1 was 15.6 years old when she presented with 18 months history of restrictive anorexia. There was a family history of POS, obesity and depression. During the last 4

months of her illness, she lost about one third of her body weight (pre-morbid BMI was around 24). She had secondary amenorrhoea, poor circulation, and lanugo. Blood tests revealed hypoglycaemia, leucopenia, and abnormal liver function tests. On admission to hospital, her BMI was 16.9 (ABW 83.6%). Her mental state was severely impaired, she was hardly accessible, she was overwhelmingly anxious around food, and had severe body image distortion. She was started on 1 g E-EPA a few weeks after commencing nasogastric re-feeding (Nutracon Energy). In addition, she also received Forceval 2 caps/day and Solvazinc, to correct micronutrient deficiencies. The NG feeding stopped after three weeks, because she was prematurely discharged from hospital. She continued to lose weight rapidly, and as it was not possible to ensure treatment on a voluntary basis, she had to be detained. Afterwards, her treatment continued on the adolescent mental health unit, where she received oral re-feeding and milieu therapy. She was unwilling to engage in individual psychotherapy, and repeated attempts of family therapy failed. Despite the lack of engagement, there was a remarkable improvement after 2 months of treatment, which included improved appetite, mood, self-esteem, interest in the future, and normalisation of all psychometric measures. She developed acne, which later was found to be the consequence of Polycystic Ovary Syndrome (POS). The patient completed three months of E-EPA treatment, but decided to stop afterwards, as she was concerned about ongoing weight gain (BMI 22.8, ABW 111%). She enrolled onto a college course, and her level of functioning became higher than pre-morbidly for about further three months after the completion of the E-EPA. However, after about 6 months, her mood deteriorated and she experienced significant mood swings. This was related to family and relationship difficulties. At one-year follow-up, she was approximately her pre-morbid weight; there was no return of her anorexia, and she did not develop bulimic symptoms. Her sexual functions normalised.

Patient 2

Patient 2 was 14.5 years old when she enrolled onto the study, with two years history of restrictive diet, excessive exercise, and primary amenorrhoea. She suffered from chronic low self-esteem and low mood. There was a family history of depression. She was admitted to the paediatric intensive care unit as a medical emergency and had to be resuscitated on arrival to hospital due to hypoglycaemia and cardiovascular collapse. On admission, her BMI was 14.4, (ABW: 76.3%). She demonstrated a high level of psychopathology, including severe body image distortion, extreme fear of food, a desire to lose further weight even if it meant losing her life, and obsessive symptoms. Initial blood tests showed mildly increased cholesterol, bilirubin, increased amino transferase, low levels of zinc, and selenium. (This patient had consistently low Zinc levels despite supplementation.) She was NG fed on parental consent until her physical parameters stabilised, and she reached BMI 16.1 (ABW 84.4%). The E-EPA treatment started a few weeks after the NG feed. Following the discharge from paediatric ward, her parents only consented to day hospital treatment on the adolescent mental health unit. They refused family therapy, but she accepted individual psychotherapy, which was based on motivational and psycho-educational principles. She had partially improved by three months of E-EPA treatment (ABW 86.34 %, and there was only small improvement in her psychometric measures). She was discharged from the adolescent unit by her parents prematurely, but maintained weight for further three months as an outpatient. She stopped the E-EPA after 6 months, and this resulted in a significant downturn a few weeks later, both in terms of weight (lowest ABW 73%), and psychopathology. The parents refused re-admission to hospital, but agreed to re-start the E-EPA and Zinc. This was followed by significant improvement. At 1-year follow-up her BMI was 17.74 (ABW: 88.3%), she had much improved psychosocial functioning, improved social life, but remained amenorrhoeic.

Patient 3

This 13.3 years old female patient was referred to the adolescent unit with three years history of restrictive diet, primary amenorrhoea, growth retardation, and delay in sexual development.

She was pre-pubertal. The patient denied body- image distortion, and there were significant emotional problems and low mood. Food Avoidance Emotional Disorder diagnosis was made (atypical AN). Her BMI was 13.3 (ABW 74.4%). Despite her low body weight, she had been physically stable, and she was managed as a 5-day/week inpatient on the adolescent mental health unit. She received oral re-feeding, milieu therapy, psycho-education, and supportive counselling. She had low ferritin and folate level, which were corrected. She did not engage in psychotherapy, and the family did not participate in family therapy due to difficulties with transport. After 3 months of E-EPA treatment, she grew 3 cm in three months, her BMI became 15.5 (ABW: 81%) and her puberty began. Her mental state significantly improved. She had no abnormal preoccupation with food, and was able to consume a wide range of high calorie foods. After her discharge from the adolescent mental health unit, the parents did not continue with follow-up, and she discontinued E-EPA. At 6 months, she was at the same weight as at discharge, and there was no further growth. She was lost to follow-up after 6 months.

Patient 4

This 14.5-year-old female was referred urgently with 6-months history of restrictive diet and rapid weight loss, in the context of bullying and family problems. She had three months history of secondary amenorrhoea. On physical examination, her BMI was 14.8 (ABW 74.7 %). She had bradycardia, low blood pressure, and poor peripheral circulation. She was cachectic; she had dry skin and she was constipated. Mental state examination revealed low mood, severe body image distortion, preoccupation with weight and shape, and obsessional behaviour around food. On the paediatric ward, she was NG-fed, and received Solvazinc to correct Zinc deficiency. Following her discharge from the paediatric hospital a few weeks later (at ABW 83.9%), the family only agreed to minimal mental health input. However, she was willing to continue with the E-EPA (in total for 6 months). There was a dramatic improvement in her mood after 2 months, and a marked improvement on the psychometric measures. She resumed an active social life, and became interested in boys. Her weight stabilised around 85.5% ABW. However, her weight deteriorated within three months after she stopped taking E-EPA (80% ABW). Her periods had not returned by the end of the year.

Patient 5

Patient 5 was 22 years old with 7-years history of AN with bulimic symptoms. There was a family history of depression. She had no previous admission despite the fact that her lowest BMI was around 14-15 due to lack of services. She had secondary amenorrhoea, but was sexually active. She had low self-esteem, poor impulse control, and significant co-morbid anxiety with panic attacks. As she was not under the care of local services, she received no psychological treatment, apart from one psycho-educational session. Her BMI before starting the E-EPA was 17.15 (ABW: 77%). There was a dramatic improvement after three months in terms of her weight (BMI 20, ABW 90%), eating habits, and mood, but her anxiety did not improve. The E-EPA was increased to 4 g/day – and this helped with her panic attacks. She was sexually active and happy at 6 months follow-up.

Patient 6

A 17 years old male presented with 9-years history of dietary restriction, preoccupation with weight and shape. He became highly obsessional around food, which caused significant arguments at home and impacted on his social life. On the first presentation, his BMI was 17.57 (ABW 87%). His height was on the 0.01 centile, suggesting severe growth retardation (there was no growth hormone deficiency). There was little evidence of puberty, and he had an appearance of a much younger child. He had low blood pressure, mild bradycardia, and poor peripheral circulation. There was a lack of libido. The patient and the family wanted

outpatient treatment. As he did not consent to family therapy, he received psycho-education and dietary counselling. He improved dramatically within the first 4-6 weeks of E-EPA treatment. By the end of the three months, his BMI was 19.1 (ABW: 93.6 %), he grew 3 cm, there was a complete resolution of his anorexic symptoms, and his libido returned. The only residual symptom at 6 months was mild anxiety.

Patient 7

This 13.5 years old female patient presented with 18 months history of dietary restraint and excessive exercise, growth and developmental delay. She was pre-pubertal. There was a family history of AN and depression, and major parental discord. She had low mood, preoccupation with weight and shape and body image distortion. As she was physically stable, she was admitted to the adolescent mental health unit as a 5-day/week inpatient. She received oral re-feeding, milieu therapy, family therapy and individual therapy. Her BMI before starting E-EPA was 14.8 (ABW: 78.21), and at the end of three months it was 16.21 (ABW: 84.5%). She grew 1.5 cm during the three months. She had an emotional downturn at about 6 weeks. This was related to parental separation, impending divorce and moving house.

DISCUSSION:

N-3 fatty acids (particularly eicosapentaenoic acid and docosahexaenoic acid) have been shown to be helpful in a number of diseases,¹¹ including cancer cachexia,^{12;13} and they are essential for normal development and growth in childhood.^{14;15} Most recently, ethyl-eicosapentaenoate has been found effective in treatment-resistant depression.^{8;16} Considering that cachexia and depression are characteristic features of AN, and that patients usually avoid dietary fats, we hypothesised that n-3 fatty acid supplementation might be beneficial for this patient group. To our knowledge, this is the first case series in the literature using ethyl-eicosapentaenoate as an adjunct in the treatment of AN. This was an exploratory study and had many limitations such as the small sample size, the lack of a comparison group, the short follow-up, and the heterogeneous standard treatment. The seven patients participating in this study represented the whole range of AN in young people, from those who needed nasogastric re-feeding on a paediatric ward, to those who could be managed as outpatients.

It is remarkable that no patient deteriorated whilst receiving E-EPA treatment. (In contrast, one patient, who delayed participation in the study for about 6 months, deteriorated during this time despite receiving standard treatment.) There was partial improvement in four cases, and full recovery in three cases, which is unusual during such a short period of time. Those patients who had growth retardation, responded with significant growth during the time of the E-EPA supplementation. The recruitment and adherence to treatment was surprisingly good, particularly given that the majority of patients participating in this study were reluctant to engage in standard treatment. The E-EPA was well tolerated, and there were no significant side-effects. Generally, there was a significant increase in mood after the first 6-8 weeks of treatment, and this was accompanied by improved general functioning. In those patients who stopped the E-EPA treatment, there was a deterioration in mood, and in weight and growth at about 2-3 months after the cessation of the treatment, which is consistent with the rate of depletion of EPA from red cell membranes. This observation suggests that ongoing treatment and longer follow-up may be necessary in future studies.

We conclude that ethyl-eicosapentaenoate supplementation during re-feeding might be beneficial for AN sufferers, and this possibility needs to be tested further in randomised controlled trials.

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Table 1. Summary of the changes during E-EPA treatment between baseline (T-0) and 3 months (T-3)

Patient number	Age Years	Height (cm) T-0	Height (cm) T-3	Weight (kg) T-0	Weight (kg) T-3	ABW % T-0	ABW % T-3	BDI-2 T-0	BDI-2 T-3	EDI-2 T-0	EDI-2 T-3	CGAS T-0	CGAS T-3	Morgan-Russell outcome
1	15.8	163	163	45.5	60.6	84.6	111.9	20	7	33	7	11	85	Good
2	14.4	156	156	36.6	41.4	76.9	84.5	29	26	168	151	11	50	Intermediate
3	13.3	148	151	31.7	34.9	77.3	81	24	0	57	33	40	70	Intermediate
4	14.5	156.5	156.5	36.2	41.4	75.2	85.3	30	0	85	6	21	69	Intermediate
5	22	162	162	45	51.9	77.6	89.4	16	6		NA	55	75	Good
6	16.5	147	150	38.3	43	87.5	93.7	10	1	62	17	55	90	Good
7	13.5	151	152.5	33.9	38.7	78.2	84.6	10	14	35	71	31	45	Intermediate