LONDON'S GLOBAL UNIVERSITY

Pharmacotherapy in Anorexia Nervosa

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UCL statement

I, Maedeh Yakhchi Beykloo, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature _____ Date _____

Abstract

There is currently no evidence base for prescribing antidepressants or antipsychotics in young people with eating disorders. There is a need for greater understanding of psychotropic prescribing in individuals with anorexia nervosa (AN) to provide guidance for their use in clinical practice. The aim of this PhD was to explore and describe the drug utilisation and effectiveness of psychopharmacotherapy in individuals with AN.

First, a systematic review was conducted to review the current literature. Next, pharmacotherapy in individuals with AN was explored by three means; 1) through self-reported questionnaires by child and adolescent eating disorder (CAED) psychiatrists on their prescribing practices in AN, 2) using The Health Improvement Network (THIN) database by reporting on AN patterns and describing prescribing patterns in AN in primary care, and 3) in multisite specialised child and young people eating disorder services (CYP EDS) within secondary healthcare settings by describing AN population and examining the effects of psychotropic treatment on weight change.

Findings from my review fail to provide strong evidence for any increase in weight associated with the use of psychotropic drugs in adolescents with AN and show some evidence of harmful effects associated with their use. Studies in this thesis have shown there is a high use of psychotropics in AN treatment, with around half of individuals in the primary and secondary care study having a record for psychotropic prescriptions, of which olanzapine and fluoxetine are the most common. No serious adverse events were found in any of the studies. After six months of pharmacotherapy, the mean BMI of those individuals on antipsychotics was greater than the mean BMI of those on antidepressants or no medication, despite having a lower starting BMI upon diagnosis. This thesis found that although a lack of strong

existing evidence, psychotropic medications are often prescribed for the treatment of young people with AN.

Impact statement

The studies presented in this thesis have the potential to be beneficial for both inside and outside academia. The ways in which these benefits could be brought about are discussed below.

Impact on clinical practice

With regards to the potential impact of this research outside academia, the main output was to raise awareness of the current practice of clinicians for the treatment of AN. The results can help to generate recommendations for clinical practice in the management of AN and further inform policy guidelines.

Impact within this research area

This study has created knowledge that may inform future research in this field. These include:

- The views and current practice of eating disorder psychiatrists on the requirements of guidelines
- The incidence and prevalence of AN in the UK
- The initiation and cessation of psychotropic medications prescribed for individuals with AN in primary care
- Current practice of eating disorder psychiatrists for medication treatment in individuals with AN in CYP EDS
- The effect of psychotropic medication treatment on weight change in adolescents with AN in CYP EDS

The results of this thesis can be used for implementation in the curriculum for degrees centred on eating disorders, mental health and pharmacy. It has also been decided by academic supervisors at UCL that the studies conducted in this thesis can be

expanded on a larger scale by commissioning a researcher, to include more CYP EDS in England and perhaps expand it to Europe in order to grasp the bigger picture.

Realisation of impact

The academic knowledge presented in this thesis has the potential to be used immediately for future studies, however further research will be required to ensure the results reflect into routine practice and prove effective for the treatment of AN. This will allow for the development of trials and higher quality of evidence studies and eventually, pharmacotherapy specific guidelines for the treatment and management of AN. Depending on the type of study design used and funding opportunities, the estimated time to complete these studies can take up to three years.

Thus far, the research presented in this thesis has partly been disseminated as publication in peer-reviewed journals, displayed at professional, academic and scientific conferences and presented in lectures and meetings. The intention is to present the studies completed as part of this thesis at relevant patient and public meetings at the specific study sites and work closely with patient and public members to develop a wider public dissemination strategy. After higher quality of evidence based studies are conducted, it would be a goal to work with key decision makers to collate the current evidence for medication use in AN and advise on evidence based practice for AN treatment.

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List of abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AFP-AN	Adolescent Focused Psychotherapy for Anorexia Nervosa
AHD	Additional Health Data
AN	Anorexia Nervosa
ANIS	Anorexia Nervosa Self Inventory
ASD	Autistic Spectrum Disorder
BED	Binge Eating Disorder
BIS	Body Image Software Program
BMA	British Medical Association
BMI	Body Mass Index
BMJ	British Medical Journal
BN	Bulimia Nervosa
BNF	British National Formulary
CAED	Child and Adolescent Eating Disorder
CAG	Confidentiality Advisory Group
CAMHS	Child and Adolescent Mental Health Services
CAPT	Color-A-Person Test
CBT	Cognitive Behavioural Therapy
CBT-ED	Cognitive Behavioural Therapy for Eating Disorders
CGAS	Children's Global Assessment Scale

CI	Confidence Interval
CPRD	Clinical Practice Research Database
CY-BOCS	Children's version of the Yale Brown obsessive-compulsive scale
CYP	Child and Young People
CYP EDS	Child and Young People Eating Disorder Service
DBS	Disclosure and Barring Service
DIKJ	German version of the child depression inventory
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5
EAT	Eating Attitudes Test
ECG	Electrocardiogram
ED	Eating Disorder
EDC	Eating Disorders Coalition
EDI 2	Eating Disorder Inventory 2
EDNOS	Eating Disorder Not Otherwise Specified
EMBASE	Excerpta Medica database
FT-AN	Family Therapy for Anorexia Nervosa
GP	General Practice
GPRD	General Practice Research Database
HEE	Health Education England

HES	Hospital Episode Statistics
HoNOSCA	Health of the Nation Outcome Scales for Children and Adolescents
HRA	Health Research Authority
IBW	Ideal Body Weight
ICD-10	International Classification of Diseases 10
ID	Identifier/identification
InPS	In Practice Systems ltd
IQR	Interquartile Range
IRAS	Integrated Research Application System
IRR	Incidence rate ratio
ITP	Intensive Treatment Day Programme
JRO	Joint Research Office
MANTRA	Maudsley Model of Treatment for Adults with Anorexia Nervosa
MASC	Multidimensional Anxiety Scale for Children
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
MDT	Multidisciplinary Team
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

NIMH	National Institute of Mental Health
NOS	Newcastle-Ottawa scale
OCD	Obsessive Compulsive Disorder
OSFED	Other Specified Feeding or Eating Disorder
PhD	Doctor of Philosophy
PICO	Population, Intervention, Comparison & Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCADS	Revised Children's Anxiety and Depression Scale
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
REE	Resting Energy Expenditure
SAS	Simpson-Angus Scale
SD	Standard Deviation
SIAB	Structured Interview of Anorexia & Bulimia nervosa
SMR	Standardised Mortality Ratio
SOHO	Schizophrenia Outpatient Health Outcomes
SPC	Summary of Product Characteristics
SRC	Scientific Review Committee
SSCM	Specialist Supportive Clinical Management
SSRI	Selective Serotonin Reuptake Inhibitor

TESS	Treatment Emergent Side Effects Scale
THIN	The Health Improvement Network
UCL	University College London
UCLH	University College London Hospital
UK	United Kingdom
US/USA	United States of America
WHO	World Health Organization

Preface

The purpose of this research was to explore and describe the drug utilisation and effectiveness of pharmacotherapy in individuals with AN. The thesis comprises nine chapters. Below is the layout and structure of this thesis.

Chapter 1: Introduction

This chapter presents an overview of the background information on the topic, the importance of the topic and research scope.

Chapter 2: Rationale, aim and objectives of thesis

This chapter provides the rationale of the thesis. In addition, it presents the main aim of this thesis and the specific objectives within each part.

Chapter 3: Methodology

This chapter is divided into three main sections. First, it provides a brief overview of study designs. Then, it summarises the details of the healthcare system in the UK and THIN database, as well as describes the specialist Child and Adolescent Mental Health Services (CAMHS), which are the data sources used in this thesis. Finally, it provides a description of the ethical challenges faced in the process of this PhD.

Chapter 4: The efficacy and safety of psychotropic drug treatment in adolescents with anorexia nervosa: a systematic review

This chapter details the knowledge related to this thesis and provides a better understanding of the current research status in this area. Since the findings of the existing evidence on psychotropic treatment in adolescents with AN were not consistent, a systematic review was conducted which is detailed in this chapter. It describes the methodologies used in the systematic review and the results of the included studies in a narrative synthesis.

Chapter 5: A survey on self-reported psychotropic drug prescribing practices of eating disorder psychiatrists for the treatment of young people with anorexia nervosa

To understand pharmacotherapy among individuals diagnosed with AN, a survey on prescribing practices of eating disorder psychiatrists for the treatment of young people with AN was conducted. This chapter provides information on the patterns of psychopharmacological care and medication treatment for child and adolescents with AN. In addition, olanzapine treatment and continuation patterns have been provided. The details of the methodology, results, and discussion of this study are described in this chapter. A version of this chapter has been published as Y Beykloo, M., Nicholls, D., Simic, M., Brauer, R., Mills, E. & Wong, I. C. K. 2019. Survey on self-reported psychotropic drug prescribing practices of eating disorder psychiatrists for the treatment of young people with anorexia nervosa. *BMJ Open,* 9**,** e031707.

Chapter 6: Incidence, prevalence and comorbidities in anorexia nervosa, 1996-2016: a retrospective population based descriptive study using The Health Improvement Network (THIN) database

In order to comprehensively understand the topic of this thesis, an investigation into AN in the UK had to be conducted. This chapter presents the incidence and prevalence of AN in primary care, using information from THIN database. In addition, it describes the comorbidities, in particular those of psychiatric disorders, experienced by those diagnosed with AN in THIN database. The methodology, results and discussion of the study are provided within this chapter.

Chapter 7: Pharmacotherapy in anorexia nervosa, 1996-2016: a retrospective population based descriptive study using The Health Improvement Network (THIN) database

According to the gap of knowledge identified from the systematic review in Chapter 4 and the survey study in Chapter 5, a descriptive longitudinal study was performed to describe the prescribing of psychotropic medication in individuals diagnosed with AN and measure the prescribing duration and cessation of these medications. In addition, potential adverse events were also assessed and described in this chapter. Similar to Chapter 6, the results and discussion of this study are provided in this chapter.

Chapter 8: Pharmacotherapy and weight change in adolescents with anorexia nervosa: a multisite eating disorder clinics study

In order to present a multidimensional depiction of pharmacotherapy in the AN population, psychotropic prescribing practices in adolescents with AN in specialist UK secondary care services are described in this chapter. In addition, the difference in BMI before and after pharmacotherapy and the adverse event profile associated with psychotropic medications in adolescents with AN are described. The details of the methodology, results, and discussion of this study are described in this chapter.

Chapter 9: Discussion and conclusion of thesis

This chapter summarises the overall findings and the contribution of this thesis. It also discusses the strengths and limitations of the thesis, provides implication for clinical practice and suggests recommendations for future research. Finally, a conclusion of the overall thesis is also provided.

This thesis delivers an insight into the effectiveness of pharmacotherapy in AN within the UK. It provides empirical evidence that psychotropic medications are currently being prescribed in individuals with AN despite a lack in guidelines and can be used concomitantly with psychotherapy for the management and treatment of AN.

Chapter One

Introduction

1.1 Introduction to eating disorders

1.1.1 Overall

The National Health Service (NHS) defines eating disorders (EDs) as an abnormal attitude towards food that causes someone to change their eating habits and behaviour towards becoming thin (NHS, 2018), thus it is characterised by abnormal eating habits adopted by the individual. In layman's terms, a person with an ED may focus excessively on their body shape and weight, resulting in them making unhealthy choices about food and causing damaging results to their health (Fairburn, 2001). Symptoms of EDs include intense fear of weight gain, dramatic reduction in food intake and self-perception of body shape or weight. These may be achieved through significant levels of self-induced emesis, laxative abuse, and strenuous exercise.

EDs are classified as a mental disorder that negatively affects an individual's physical, psychological and social wellbeing (Fairburn and Harrison, 2003). Mental health disorders are divided into neurotic and psychotic classes (Jenkins et al., 1997). In neurotic mental health disorders, individuals try to escape a feeling, situation, or event by showing unusual fear or anxiety at a subconscious level, causing disturbances in daily life routines. EDs are classified under neurotic disorders due to their effect on eating patterns and the anxiety resulting from them. Therefore in accordance with the National Institute of Mental Health (NIMH), EDs are defined as real, treatable medical illnesses featuring serious disturbances in eating behaviour and weight regulation (National Collaborating Centre for Mental Health, 2004).

EDs are of various natures and are typically categorised into four main types according to the NHS; Anorexia Nervosa (AN), Bulimia Nervosa (BN), Binge Eating Disorder (BED) and other specified feeding or eating disorder (OSFED).

1.1.2 Anorexia nervosa

The literal meaning of AN is “loss of appetite for nervous reasons”. It is defined as a condition in which individuals maintain a low weight due to a pre-occupation with weight, constructed either as a fear of fatness or a pursuit of thinness (National Collaborating Centre for Mental Health, 2004). Individuals with AN try to reduce their weight to the lowest amount possible through means of starvation or excessive exercise (Shih, 2017). They are characteristically underweight in accordance to their sex and age, despite viewing themselves as overweight. Typically an individual with AN repeatedly weighs themselves, carefully plans and portions their food and only eats certain foods in small quantities (Pisetsky et al., 2016). In some cases, individuals may misuse laxatives, indulge in excessive exercise, or self-induced vomiting to achieve their goal.

In standard diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-V), AN is expressed as two sub-types; a) the restricting and b) the binge/purge type (Mancuso et al., 2015). In the restricting type of AN, individuals only restrict their food intake, however individuals with the binge/purge type, lose control of their eating habits periodically and compensate by purging (Peat et al., 2009).

Symptoms of AN include, but are not limited to:

- Extremely low body weight; Body mass index (BMI) below 17.5 kg/m^2
- Severe food restrictions
- Intense fear of weight gain
- Constant need to be thin and unwilling to maintain healthy weight
- Distorted body image and self-esteem influenced by perceptions of body shape and weight (Kaye et al., 2009)

As a result of these symptoms, further medical complications arise in individuals with AN (Mitchell and Crow, 2006). These include:

- Osteoporosis or osteopenia
- Anaemia and low blood pressure
- Muscle wasting and weakness
- Severe constipation
- Damage to the heart, brain, and vital organs
- Drop in internal body temperature, brittle hair and nails, dry and yellowish skin
- Feeling lethargic, tired, and out of breath
- Infertility

AN is often associated with many other psychological problems, such as depression, anxiety, low self-esteem and in some cases deliberate self-harm (Fairburn et al., 1999). This is mainly down to them believing their self-value hinges on their appearance or weight. The focus of this PhD project will solely be on this type of ED.

1.1.3 Bulimia Nervosa

BN literally translates as “hunger of an ox for nervous reasons”. It is characterised by recurrent binge eating incidents subsequently resulting in compulsory vomiting, purging, fasting or exercise abuse in order to control their weight (Le et al., 2017). In BN, individuals are of normal weight, ensuring to maintain their BMI above 17.5 kg/m^2 (Scott J. Crow et al., 2009). In lay words, individuals with BN go through cycles of eating large amounts of food and then experiencing guilt and deliberately becoming sick and misusing medications to empty their bowels in order to control their weight. Similarly to AN, individuals with BN often fear weight gain and desperately want to lose weight. Due to the feeling of disgust and shame accompanied with the condition,

individuals often carry out their bulimic behaviour in secret (Hayaki, 2009). This cycle can happen anywhere from a few times a week to many times a day.

Symptoms of BN include, but are not limited to:

- Swollen salivary glands in the jaw and neck
- Chronically inflamed and sore throat
- Severe dehydration
- Acid reflux disorder
- Intestinal distress and irritation
- Worn out tooth enamel and sensitive, decaying teeth
- Electrolyte imbalance (Hayaki, 2009)

1.1.4 Binge Eating Disorder

BED is similar to BN in many aspects, however there are some distinct differences. The main difference is that individuals who binge will not purge, vomit, or misuse laxatives. This will result in them eventually becoming unhealthily overweight and at a higher risk of developing a high blood pressure and cardiovascular disease (Hutson et al., 2017). It is a condition mainly enabling individuals to escape from difficult feelings or situations and provide some comfort. As a result, the feelings that follow are typically of shame and disgust for their lack of self-control.

1.1.5 Other specified feeding or eating disorder

OSFED is a classification of ED when the symptoms of the condition do not match the other main three categories. It has previously been named as eating disorder not otherwise specified (EDNOS). It is arguably the most common type of ED as most individuals do not experience the expected symptoms and thus do not meet the strict diagnostic characteristics of the main categories.

1.2 Proposed pathophysiology of AN

Recent evidence suggests that genetic factors play a role in an individual's vulnerability to eating disorders like AN. Genetic studies on twins have shown that monozygotic twin pairs have higher concordance rates of AN than dizygotic twins (Klump et al., 2002). An estimated range of 58% to 76% of variance in the occurrence of AN has been linked to genetic factors (Wade et al., 2000, Klump et al., 2001). Studies have found that AN is most likely not as a direct result of polymorphism of one gene, but rather a multiple hit process where a trait which may be linked to certain genes is expressed under particular environmental circumstances (Klein and Walsh, 2004).

Peripheral systems and dysregulations in the central nervous system neuropeptides due to abnormal functions in various hormones such as gonadal, growth, cortisol and thyroid hormones can contribute to mechanisms for controlling food intake in eating disorders. Examination of monoamine systems as a result of 5-HT disturbances can be due to appetite dysregulation, anxious and obsessional behaviours as well as extremes of impulse control, which studies have shown occur in individuals AN (Kaye, 2008). A recent study by Watson et al. (2019) has identified that the genetic architecture of AN mirrors its clinical presentation. They found independent of the effects of common variants associated with BMI, AN has significant genetic correlations with psychiatric disorders, physical activity and metabolic, lipid and anthropometric traits (Watson et al., 2019). Although so far many studies have yielded inconsistent results, the search to establish genetic elements in EDs continues.

1.3 Diagnosis

1.3.1 Diagnostic instruments and screening

Diagnosing EDs can be challenging for health care professionals mainly because of the patients' unwillingness and lack of motivation to cooperate with and disclose their symptoms and behaviours (Gray et al., 2015). The most straightforward eating disorder to diagnose is that of AN. The initial diagnosis is made by taking a history and account from the individuals' family and friends. This is then confirmed through physical examinations of the individuals' weight, height and BMI in order to evaluate the extent of the condition (NICE, 2018).

In early studies, researchers have designed and explained a diagnostic process for assessing AN. A description of the four level process that was found to be useful in early diagnostic procedures for AN patients (Crisp, 1977) is shown below:

Level 1 - An always present desire to maintain a low body weight and avoid weight gain. This is achieved by dieting to become slim.

Level 2 - The individual has a need to retain control of impulse eating and to compensate its occurrence with purging, vomiting and excessive exercise. Among this, the individual will have a psychological need to weigh themselves regularly and may become despaired, restless, and secretive. All the mentioned factors may result in the individuals distancing themselves from family and peers.

Level 3 - Sensitivity on physical changes occurring on the adolescent body, accompanied with a need to become slim. This could be due to a background in premorbid obesity, childhood over nutrition and the presence of weight extremities like anorexia and obesity in the family.

Level 4 - Individuals are found isolated and often have difficulties with a sense of low self-esteem. Therefore, they develop anorexia nervosa as a coping mechanism to survive this depression and social avoidance.

Based on this, many questionnaires and scales were designed in order to assess AN behaviours in individuals. Initially, an observer rating scale used for an inpatient

setting for assessing three dimensions of AN behaviour was designed (Slade, 1973). To build on this, an Eating Attitudes Test (EAT), which was a self-reported measure of anorexia symptoms, was developed (Garner and Garfinkel, 1979). It was used to detect cases of AN in high risk groups for the condition. As more studies provided evidence for a better understanding of eating disorders, additional questionnaires and screening tools were designed for ED, specifically AN, that followed similar structures to previous tools (Garner et al., 1983).

For the diagnosis of an ED requiring treatment, like AN, positive screening according to the criteria of the World Health Organization's (WHO) International Classification of Diseases 10 (ICD-10) (World Health Organization, 1992) or Diagnostic and Statistical Manual of Mental Disorders 4 (DSM-IV) (Bell, 1994) should be made. Based on these screening criteria, the following questions named the SCOFF questionnaire were implemented (Morgan et al., 1999):

1. "Do you make yourself **S**ick because you feel uncomfortably full?"
2. "Do you worry you have lost **C**ontrol over how much you eat?"
3. "Have you recently lost more than **O**ne stone in a 3-month period?"
4. "Do you believe yourself to be **F**at when others say you are too thin?"
5. "Would you say that **F**ood dominates your life?"

It is calculated by appointing one point for every "yes" answer to the question above. A total of 2 or more points is considered to be a likely case of an ED like AN. In addition to the SCOFF questions and alongside height and weight measurements, other questions can aid in the screening process (Herpertz et al., 2011) as shown below:

- "Are you happy with your eating behaviour?"
- "Are you worried about your weight or your food?"

- “Does your weight affect your feeling of self-worth?”
- “Do you worry about your figure?”
- “Do you eat in secret?”
- “Do you vomit when you feel uncomfortably full?”
- “Are you worried because sometimes you can’t stop eating?”

1.3.2 Challenges

The main difficulty in diagnosing EDs like AN is the reluctance of the individual affected and the guard they may put up during assessment. A lack of motivation or eagerness to overcome and recover from the condition can also add to this reluctance (Surgenor and Maguire, 2013). Therefore the role of a health professional is essential in helping to build this engagement and highlight the various options available to them (Nordbo et al., 2008). However, in some cases, clinicians themselves can be considered barriers to diagnosis because of the anorexia individuals’ fear of being criticised or judged by a health professional. To tackle this, it is essential that clinically experienced and trained professionals are assigned to diagnosing EDs, who are able to empathise and build a relationship with the AN patients (Reid et al., 2010).

1.4 Epidemiology of AN

1.4.1 Incidence and prevalence

EDs are serious mental health illnesses that affect over 1.6 million men and women of all ages in the United Kingdom (UK). The lifetime prevalence of the different ED subgroups differ due to the nature of the conditions. The lifetime prevalence estimate of AN is 0.21%, whereas for BN and BED this percentage is 0.81% and 2.22%, respectively (Qian et al., 2013). The National Collaborating Centre for Mental Health UK (2004), has reported that in any year, 1.9% of women and 0.2% of men experience

AN, with the condition usually lasting 6 years (National Collaborating Centre for Mental Health, 2004).

The age and sex adjusted incidence rate of AN as diagnosed in primary care within the UK's Clinical Practice Research Datalink (CPRD) (formerly known as the General Practice Research Database) remained stable from the year 1993 at 4.2 (95% CI 3.4-5.0) per 100,000 person years to 4.7 (95% CI 3.6-5.8) per 100,000 person years in the year 2000 (Turnbull et al., 1997).

1.4.2 Mortality

The highest mortality rate among mental illnesses is that of EDs, which can result in the premature death of one in five of those individuals most seriously affected by it (Qian et al., 2013, Smink et al., 2012). Young people between the ages of 15 to 24 years who have been diagnosed with AN have 10 times the risk of dying in comparison to their peers who are the same age (Smink et al., 2012). According to the Eating Disorders Coalition (EDC), at least one person dies as a direct result from an ED every 62 minutes (Eating Disorders Coalition, 2014). Similarly, AN is often associated with a higher risk of suicide in comparison to other EDs. One study estimated a score of 31 for the suicide Standardised Mortality Ratio (SMR) (Harrington et al., 2015) for AN, which is over four times higher than that of BN (score=7.5) (Preti et al., 2011). Studies have shown that 20% to 40% of deaths in individuals with AN are found to be as a result of suicide (Papadopoulos et al., 2009).

1.4.3 Associations of anorexia nervosa with comorbidities

Comorbidities are common in patients with AN, particularly those of psychiatric disorders (O'Brien and Vincent, 2003a), mainly major depressive disorder (Herzog et al., 1992). Due to the nature of AN, nutritional disturbances cause a severe impact on metabolic rate and drug response and can result in adverse events. Osteoporosis and bone fracture (Nagata et al., 2017) are regularly linked to EDs as excessive food

restrictions disrupt attainment of peak bone mass resulting to the mentioned comorbidities (Seeman et al., 1992). A study in the US measured the bone density of 18 AN females and 28 controls and found a significantly reduced mean bone density in the females with AN (0.64±0.06g) compared to the controls (0.72±0.04g) (Rigotti et al., 1984). Cardiac complications such as structural alterations, conduction abnormalities and hypotension (Kalla et al., 2017) are found to be co-existing disorders that challenge the recovery of AN. In a study of 214 women with AN, bradycardia and hypotension was observed in 43% and 16% of the individuals, respectively (Miller et al., 2005). In addition, the imbalance of hormones in individuals with AN often cause menstrual cycle complications in young females and can interrupt therapeutic treatment for patients (Cominato et al., 2014).

1.4.4 Associations of anorexia nervosa with gender

Many studies have been undertaken examining the association of AN between genders. It has been found that AN is more common among females than it is in males (Hoek, 2006). In one study they had found that the incidence of AN per year in females aged 15-19 years was 109.2 per 100,000 person years in 1995-1999. However, the incidence among males was found to be less than 1 per 100,000 person years in the UK (Currin et al., 2005). Similarly, in another study, EDs in females were found to be more common, with a sex ratio estimates ranging from 3:1 to 18:1 (Raevuori et al., 2014).

1.4.5 Associations of anorexia nervosa with age

The most typical period of onset in AN is adolescence (Harbottle et al., 2008). EDs are the third leading cause of chronic illness among adolescence. In majority of cases, the onset of EDs is at the critical age of adolescence, reaching a peak at 13 to 18 years of age (Steinglass and Walsh, 2016). Similarly, another study supported that the rate of first diagnosis of AN in females and males was highest in individuals aged 15 to 20 years (Keski-Rahkonen et al., 2007). Correspondingly, a study using the

CPRD identified the peak age of onset as 15 to 19 years, with the average duration of the condition lasting about 6 years (Micali et al., 2013).

1.4.6 Associations of anorexia nervosa with the 21st century

With the 21st century comes the era of the internet and social media sites such as Facebook, which can affect the perception of young people towards their body image (Grabe et al., 2008). A study of 1,087 young female participants with a mean age of 13.7 years found an association between internet exposure and the internalisation of being thin and a drive for thinness among its population (Tiggemann and Slater, 2013). Following this study, the authors conducted another study on 438 of young females with a similar mean age of 13.6 years, to examine the relationship of Facebook use and body image across time. The study revealed that Facebook use was associated with higher levels of body image concerns. The longitudinal results showed that engagement with Facebook is "temporally antecedent" to drive for thinness (Tiggemann and Slater, 2017). Similarly, another study examining into the social media website Facebook found that more frequent Facebook users were associated with a higher risk of disordered eating (Mabe et al., 2014). In a booklet published by the British Medical Association in 2000 titled "eating disorders, body image and the media", it was suggested that the media has a significant role in causing EDs in vulnerable individuals due to its portrayal of thinness as being ideal (Giordano, 2015). A study examining the effects of social media on the body image of young females illustrated a transactional model as shown in Figure 1 below (Perloff, 2014), where it suggested that females who tuned into ED related social media contents had a greater likelihood of increasing body dissatisfaction and negative effects with body image and eating disturbances.

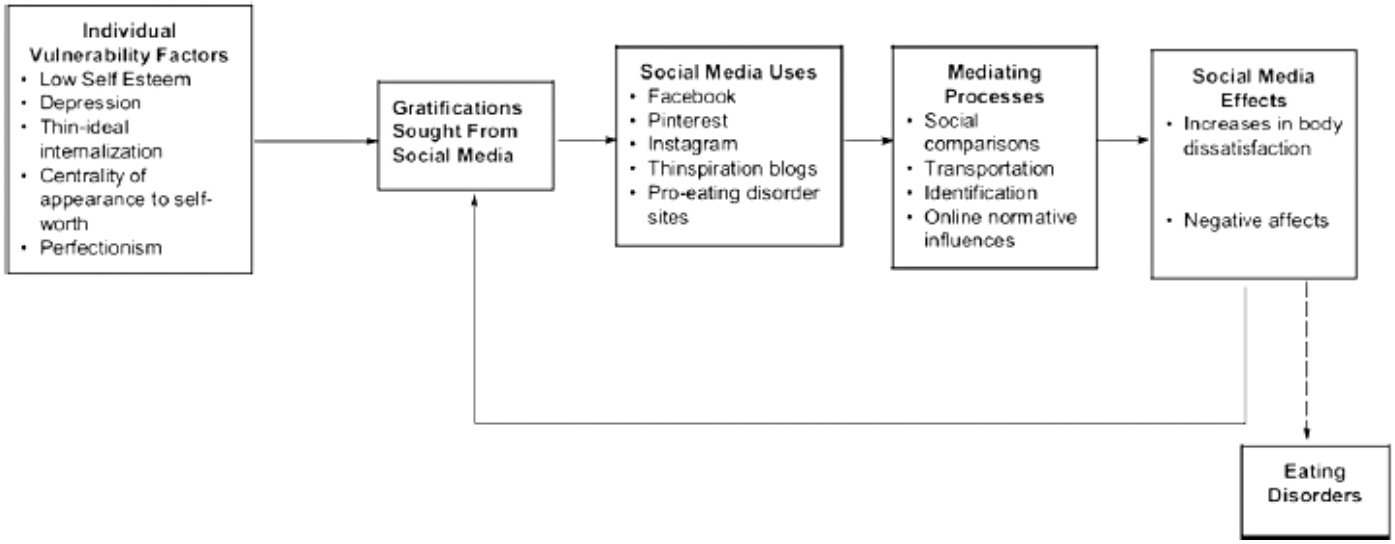

Figure 1. Transactional model of social media and body image concerns (Perloff, 2014)

1.5 Economic factors

It is thought that in the UK, over 1.6 million people are directly affected by EDs, although this number may be seen as an underestimate due to the high number of people who are undiagnosed (Joint Commissioning Panel for Mental Health, 2013).

Mental health represents up to 23% of the total burden of diseases in the UK, where approximately 11% of England's annual secondary care health budget is spent on it (Department of Health, 2012). It is estimated that around £80-100 million are spent annually by England on EDs alone. This includes inpatient, outpatient, primary and private care that the individuals may receive. Treatment for AN presents financial implications to healthcare services due to the repeated episodes of hospitalisation and long-term health care services that must be provided. With the inclusion of indirect economic costs and quality of life calculations, the total economic cost will account for over £1.25 billion annually for England alone (Pro Bono Economics, 2012).

1.6 Treatment

In accordance to the National Institute for Health and Care Excellence (NICE) guidelines, all individuals with AN must be put into contact with specialist ED services. NICE also recognises the importance of patient and carer satisfaction in the assessment of effective treatment options for EDs (NICE, 2018).The support provided by the multidisciplinary services must include:

- Psychoeducation of the condition
- Monitoring of weight, physical and mental health
- The involvement of the individual's family/carer

Individuals with AN will initially be treated in a secondary care outpatient service, such as Child and Adolescent Mental Health Services (CAMHS) ED services through GPs or self-referrals. Depending on the extent and progression of the condition, individuals may be transferred to an inpatient setting. Treatment of AN is mainly carried out on a multidisciplinary level, with a combination of nutritional, social, medical and psychological care (Moore et al., 2013a). However, the treatments often remain unsuccessful, with a 40% dropout rate (La Via et al., 2000). The most crucial aspect of ED treatments is the involvement and engagement of the individual with the treatment options. This will result in enhancing motivation and maximising adherence to comply with the treatment chosen. The aims of AN treatment are a) to restore the individuals' weight to a healthy level, b) to treat any medical complications that were caused due to the starvation, c) to treat comorbid psychiatric conditions like anxiety and depression, d) to improve motivation in treatment participation, e) to educate the individual and their family about healthy eating patterns and nutrition and f) to prevent relapse (Yager et al., 2006). Treatment options for AN consist of psychological and pharmacological interventions.

1.6.1 Psychological treatment

Psychological treatments offered to children and adolescents differ to that of adults. The first line treatment for children and adolescents with AN according to NICE is focused family therapy (FT-AN). This may be in the form of separate sessions with the individual and their family members, or it may be a session with them together (Kaplan, 2002). Typically, FT-AN consists of 20 sessions extended over a period of one year. In the first month of treatment initiation, a review is conducted to establish the progress and assess the regularity of the sessions. This is then continued on a three monthly basis throughout the duration of the treatment (Le Grange et al., 2016). The main aim of family therapy is to emphasise the role the family has in aiding the recovery of the individual (Eisler et al., 2016). Studies have shown family therapy to be more effective than other forms of therapy in AN (Godart et al., 2012, Russell et al., 1987, Couturier et al., 2010, Gabel et al., 2014).

An alternative to family therapy is cognitive behavioural therapy (CBT) in individuals with AN. This includes up to 40 sessions over 40 weeks, which comprises of twice weekly sessions for the first 2 to 3 weeks and around 10 brief family sessions with the individual and their parents/carers (NICE, 2018).

For adults, the treatment approach differs slightly to that of children and adolescents. Many models and systems have been put in place to offer treatment and support for these individuals in a specialised setting. One of these is the Maudsley Model of Treatment for Adults with Anorexia Nervosa (MANTRA) which was developed in order to address the high rates of non-response to AN treatment. It was found that it aided individuals with AN in symptom improvements (Kass et al., 2013). The use of MANTRA suggested that patients improved better with specialty treatments, particularly those with severe and enduring AN. Similarly, the Specialist Supportive Clinical Management (SSCM) model aims to mimic outpatient treatment offered to

individuals with AN by ED professionals in typical clinical practice (McIntosh et al., 2006).

1.6.2 Pharmacological treatment

Medication treatment as the sole treatment for AN is not recommended by the NICE guidelines, due to a lack of evidence based studies (NICE, 2018). However, because medication prescribing will be based on the judgement and discretion of the health care professional, risk management procedures are put in place to ensure treatment efficacy. These include considering the impact of malnutrition on medication effectiveness and side effects, assessing the effect of the ED on compliance to medication and ensuring that necessary monitoring procedures are offered for medications that require so (NICE, 2018).

There is weak evidence available for the efficacy of any pharmacological treatments of AN (Aigner et al., 2011) and limited research has been conducted to support the use of medications in adolescents with AN (Couturier and Lock, 2007) (McKnight and Park, 2010). Nevertheless, clinicians often prescribe medications adjunct to psychological therapies or as a primary step of treatment (Gowers et al., 2010a), despite no evidence for long-term improvement in individuals with AN (Crow et al., 2009). According to Crow et al. (2009), there are many factors that play a role in medications not being selected as the primary mode of treatment in AN, with pharmacological compliance accounting for the main one as patient drop-out rates are found to be between 35% and 75% (Halmi et al., 2005). Poor medication response because of starvation in AN and, adverse events resulting from prescribed medications such as metabolic disruptions, extrapyramidal symptoms and sexual/reproductive events must also be considered, particularly in patients with comorbid conditions (Jerrell et al., 2010). In addition, individuals with AN are often reluctant to engage in treatment, particularly if there is an aim of weight gain involved (Hoek, 2006). Despite this, treatment with medications are often proposed,

particularly with the use of atypical antipsychotics and antidepressants (Fazeli et al., 2012).

From the medications listed, selective serotonin reuptake inhibitors (SSRIs) have shown to be effective in the treatment of AN in individuals with depression. In a study on 52 female patients of whom 19 were given citalopram as treatment for restricting type AN, improvements were seen after three months in patients with depression and obsessive-compulsive like symptoms. However, no significant differences were observed from the start until three months of the study between the citalopram (BMI difference of 1.28) and control (BMI difference of 0.71) groups with regards to BMI (Fassino et al., 2002). Similarly, the use of fluoxetine in an open trial with six individuals with AN was shown to improve weight gain as a result of the diminishing of depressive symptoms from 41.1kg to 49.9kg (Gwirtsman et al., 1990). In a double-blind placebo-controlled trial using fluoxetine in 35 individuals with AN, 16 were given fluoxetine and 19 were put on placebo. The study found that 63% of individuals who completed their medication after one year of treatment initiation, had a reduced relapse rate and significant weight increase in comparison to those in the placebo group (Kaye et al., 2001). Another SSRI used in an open controlled trial was sertraline, where it was prescribed to 11 patients with restricting AN at a starting dose of 50mg/day, while the 11 patients on no medications were used as control. The dosage was increased to 100mg daily after one month in four of the patients who did not respond satisfactory to the lower dose. The patients were assessed at baseline and after 14 weeks and it was found that BMI gradually increased in the sertraline group from 15.6 ±1.2 to 17.1 ±1.5 in comparison to the BMI of the control group 16.4 ±0.9 to 17.6 ±1.2. A follow-up was carried out on the patients at 52 to 87 weeks that observed the rate of improvement in the sertraline group to be 82% compared to 45% in the control (Santonastaso et al., 2001).

In the same way, the use of second generation (atypical) antipsychotics in AN individuals with anxiety and psychotic-like behaviour has shown to be helpful (Yager et al., 2006). Many studies have been conducted on the use of olanzapine as a treatment for AN. A randomised controlled trial on eight patients receiving olanzapine at a dose range of 5-20mg daily and seven patients receiving chlorpromazine 25-200mg found that individuals on the olanzapine treatment had reduced anorexia thoughts (Padua inventory mean 35 (11.6)/16.29 (7.3)), in comparison to chlorpromazine which was 27.6 (14.4)/25.1 (12.9). However, no evidence was found to support BMI increases between the two groups as all patients had gained an average of 5.5kg (Mondraty et al., 2005). Another study conducted was a double-blind placebo-controlled trial on 15 female patients with AN using olanzapine and cognitive behavioural therapy for three months and 15 female AN patients on placebo and CBT. The olanzapine was given at a dose of 2.5mg daily for one month and increased to 5mg daily for the next two months. Despite finding no significant differences between the placebo group and olanzapine with regards to weight gain, it was found that in the binge-purge subtype of AN, significant differences in BMI ($p=0.01$, $F=3.77$, $d.f.=3$) was established (Brambilla et al., 2007). Similarly, in another double-blinded placebo controlled trial in AN individuals who received a placebo (18 patients) and olanzapine (16 patients) at a mean dose of 6.61mg/day for 10 weeks, the olanzapine group showed a significant increase in weight gain rate and 87.5% of the patients achieved complete weight restoration in comparison to the 55.6% of the placebo group (Bissada et al., 2008).

Another atypical antipsychotic medication trialled in an open label study is quetiapine, where in a group of eight individuals who received a dose of 50-800mg daily, it was suggested in the study that its use had benefits on weight gain and psychological thoughts in AN individuals as five patients had a statistically improved BMI ($F=2.790$, $p=0.018$) (Bosanac et al., 2007). Similarly, a 12-week open label randomised

controlled trial was conducted on 21 patients of whom 11 received a combination of psychotherapy and 10 patients who received quetiapine at a dose range 50-400mg/day. The study showed weight gain in both quetiapine and control group by 5.0kg and 4.5kg, respectively. Low dose quetiapine resulted in improvements in patients with AN both physically and psychologically, with minimal side effects (Court et al., 2010). In contrast, an open labelled study (Powers et al., 2007) on 18 outpatients with AN receiving a minimum quetiapine dose of 150mg/day showed no statistically significant improvements in weight gain despite nine of the patients gaining an average of 2.4kg in the 10-week treatment phase.

At present, all the studies reviewed thus far suffer with the same limitation; they have a considerably small sample size, making it difficult to generalise and therefore must be interpreted with caution, as the variability is increased. This limitation leads to difficulty in statistical analysis of the data as it becomes impossible to detect any true differences in outcomes between the groups and questions the generalisability of the data to the total population (Faber and Fonseca, 2014).

Monitoring also plays an important role in assessing the progress and adherence to the treatments offered. It is recommended for GPs to offer physical and mental assessments at least on an annual basis for individuals diagnosed with AN, such as a) weight or BMI, b) blood pressure, c) relevant blood tests, d) electrocardiogram (ECG) and e) discussions regarding treatment options (NICE, 2018).

This chapter demonstrates a need for research to be conducted on psychotropic medications as treatment of AN in patients, specifically adolescents. Therefore, this thesis aims to explore the gaps in this research.

Chapter Two

Rationale, aim and objectives of thesis

2.1 Rationale of thesis

As mentioned in the introduction, there is a gap in current literature with regards to pharmacological treatment for AN. Despite it having the highest mortality rates amongst psychiatric illnesses, it is a relatively understudied condition.

There is currently very limited evidence base for prescribing antidepressants or antipsychotics in young people with eating disorders, despite studies showing they are sometimes prescribed if there is a less than optimal treatment response with first line psychological treatments. It has been noted that this lack of evidence of the safety and effectiveness of the prescribing of psychotropics is partly due to current literature primarily focussing on diagnosis based, rather than symptom-based prescribing. As highlighted in the introduction of this thesis, the greatest limitation in current studies is the small sample size, and consequentially minimal or no power to detect differences in effects of psychotropic medications for individuals with AN. In addition, lack of follow-up periods and short lengths of study duration prove to be a challenge for most observational studies and randomised controlled trial (RCT) studies.

The National Institute for Health Research (NIHR) has called for greater understanding of psychotropic prescribing in individuals with AN within the UK in order to deliver empirical evidence and provide guidance for their use in clinical practice. With this in consideration, a mixed-method approach was used to explore pharmacotherapy with psychotropic medications in individuals with AN from multiple dimensions; 1) reviewing current literature on the area to build a foundation for studies, 2) through the means of CAED psychiatrists within England, 3) in a primary healthcare setting using The Health Improvement Network (THIN) database, and 4) in multisite specialised CYP EDS within secondary healthcare settings.

2.2 Aim of thesis

The aim of this PhD thesis was to explore and describe the drug utilisation and effectiveness of pharmacotherapy with psychotropic medications, in individuals with AN.

2.3 Objectives of thesis

To achieve the aim of this PhD, the following objectives were put in place:

a) To conduct a systematic review on current literature assessing the efficacy and safety of psychotropic drugs treatment with regards to its impact on weight change, psychiatric symptoms, and adverse events in adolescents with AN
b) To describe and explore contemporary prescribing practices of eating disorder psychiatrists in England
c) To assess annual trends in the incidence and prevalence of AN over a 20 year period using The Health Improvement Network database (an electronic primary health record database) in the UK
d) To evaluate psychotropic drug utilisation among individuals with AN in primary and secondary care settings;
    i. To measure the rate, initiation, and cessation of psychotropic prescribing in individuals between 1996 and 2016 with AN using THIN database
    ii. To describe the psychotropic prescribing from patient records at four participating eating disorder service clinics in the UK from 2015 to 2017
e) To assess the effect of psychotropic medication treatment on weight change in adolescents with AN at four participating eating disorder service clinics in the UK from 2015 to 2017

f) To describe the adverse events of antidepressant and antipsychotic medications in primary and secondary care settings

g) To investigate the adverse events of antidepressant and antipsychotic medications in individuals with AN from THIN database.

Chapter Three

Methodology

Outline

In this chapter a brief overview of study designs is given. This is followed by a description of the health care data sources that were used to conduct the studies in this PhD thesis. This includes a summary of THIN database which is used in Chapter 6 followed by a description of the extraction, cleaning, and preparation of the dataset for analysis. Subsequently, the data used in Chapter 7 is detailed and the challenges faced during the process of obtaining the data for Chapter 8 is described.

3.1 Pharmacoepidemiology

Pharmacoepidemiology is defined as the study of investigating and evaluating how drugs are used in large populations with regards to an outcome of benefit or risk (Strom, 2005). As a relatively new applied field, it builds a bridge between epidemiology and clinical pharmacology by applying the methods used in epidemiology to the content area of clinical pharmacology (Strom, 2005). Pharmacoepidemiology studies quantify drug use patterns and measure the association between drug exposure and adverse drug effects by, for instance, studying the patterns of drug prescribing, the appropriateness of use, medication adherence and identification of predictors for medication use. The results of such studies can be used as evidence in guideline development and decision making for treatment options (Steinke, 2019).

3.2 Study designs

3.2.1 Experimental (interventional) studies

Experimental studies are studies in which the conditions are under the direct control of the investigator. Experimental studies can be categorised as randomised or non-randomised controlled trials. RCTs are considered the gold standard for assessing the effectiveness of therapeutic drugs for clinical studies (Hariton and Locascio, 2018). The randomised allocation of an intervention in the study ensures that

comparative groups are equal, in particular when all parties are blinded (Aggarwal and Ranganathan, 2019). The differences between the groups in an RCT are caused either by the intervention and/or because of differences due to chance (Thiese, 2014). Experimental studies are also less susceptible to bias and confounding, in particular RCTs that allow for balancing of confounders during the design stage. This is because the investigator is responsible for determining the exposed and unexposed groups and performing the study (Concato, 2004). Although RCTs are considered the gold standard, they do have certain implications which can limit the study. One of these limitations is that there are ethical constraints on conducting experimental research in animals and exposing individuals participating in the study to potentially serious harm. This can mean high risk patients are often excluded and the study sample may not be a true representative of the target population (Mulder et al., 2018).

3.2.2 Observational (non-interventional) studies

Observational studies, sometimes called non-experimental studies, examine the existing distribution of variables in populations within naturalistic contexts (Grimes and Schulz, 2002). They draw conclusions about the effect of an outcome without the influence of investigators. Clinically, pharmacoepidemiology studies are often used for hypothesis testing. Observational studies allow for non-random allocation to exposure to be determined outside of the study, as opposed to RCTs where they are determined randomly by the investigator (Thiese, 2014). The disadvantage of observational studies in contrast to RCTs is that they allow for the possibility of selection bias. One of the major advantages of observational studies is that data is selected from the general population and therefore it can be very large and more representative of the target population, compared to RCTs which are often limited in numbers as it can be expensive to conduct (Carlson and Morrison, 2009). This means that the results of observational studies can be more generalizable and allow for the detection of rare effects. In addition, unlike RCTs which are relatively short in duration

of follow-up, observational studies can have very long follow-ups and depending on the study design, there may be minimal wait for the follow-up to occur (in the case of case-control studies) (Thiese, 2014). This is particularly beneficial in studies assessing rare and delayed onset adverse effects. Observational studies are typically categorised into two groups: 1) descriptive and 2) analytical studies.

3.2.2.1 Descriptive studies

For health service users, observational research can further the understanding and management of disorders. In disorders such as AN, off-label medications are frequently evaluated in relatively small sample size RCTs of limited duration, often without the consideration of measuring health outcomes in AN individuals or assessing the direct measures of cost (Sloman, 2010). Descriptive observational studies which include uncontrolled cohorts, largely aim to describe clinical practice and outcome, and can be hypothesis generating. They allow for analysis when time and resources do not permit for more thorough analytical studies to be conducted, however they are limited by not being able to determine causality (Grimes and Schulz, 2002). Causal knowledge, through the means of RCTs and analytical studies, can be helpful in prevention of a disease and for identifying new treatments. However, the primary concern after a diagnosis of a disease is made is to set appropriate indications and contra-indications for action. Thus descriptive studies highlight the need for diagnostic and prognostic research in order to predict the presence of a certain disease taking into consideration the clinical and non-clinical profile and to predict the future of patient care and treatment (Grobbee, 2004).

3.2.2.2 Analytical studies

Analytical studies aim to test hypotheses by measuring the association between exposure and outcome. There are many types of analytical studies, however the most common types are cross sectional, case-control, and cohort studies (Ranganathan and Aggarwal, 2019).

Cross sectional studies analyse data from a population at a specific point in time. It is mainly used to assess health needs of a population, evaluation of diagnostic and attitude and options about health services (Mann, 2003). It allows for multiple outcomes and exposures to be studied, however it proves difficult in determining whether the outcome followed exposure in time or exposure resulted from the outcome, thus any associations identified may be difficult to interpret.

Case-control studies are where two groups with different outcomes are compared to identify an association with an exposure, by comparing the frequency of exposure in the case to the control group. Thus it allows for analysis of multiple exposures which may be associated to a single outcome (Lewallen and Courtright, 1998). Case-control studies are particularly useful in studies of rare diseases or outcomes. However they are subject to bias like researcher bias where caution must be taken in collection of data for past risk factors, or recall bias where patients may remember exposure details negatively compared to the control group (Mann, 2003).

A cohort study is where investigators select a group of exposed and a group of non-exposed individuals and follow-up both groups to compare the outcome of interest (Song and Chung, 2010). Cohort studies can be prospective or retrospective. Prospective cohorts refer to a cohort who are free from the outcome of interest selected. Over an allocated time period, the cohort is observed to determine whether they developed the outcome of interest. Retrospective cohorts analyse data that has already been collected. The methodology of the studies are the same however the study is performed post hoc (Carlson and Morrison, 2009). Cohort studies are useful when RCTs are not feasible or appropriate. An advantage of cohort in contrast to case-control studies is that it allows for the assessment of various outcomes of interest (Mann, 2003). One of the disadvantages is that factors differentiating the two cohort groups cannot be controlled. These confounding variables are independently associated with both exposure and outcome of interest, thus a challenge in analysis

(Song and Chung, 2010). They may also mask actual associations in a study, or falsely portray an apparent association between the treatment and outcomes. In epidemiological studies, appropriate adjustment for confounding factors is complex as exposure can range from complex interaction of patients, healthcare professionals and healthcare system factors (Skelly et al., 2012). This challenge if particularly pronounced in database studies where information on potential confounders may be missing and the robust definition of variables may be unclear. Confounding effects are often removed of data using statistical approaches such as stratification, propensity score methods and multivariable outcome models (Brookhart et al., 2010).

3.3 UK healthcare system

The UK health care system provides preventative medicine, primary care, inpatient care, outpatient care, mental health services, ophthalmology, and dentistry. The systems vary slightly in each of the countries in the UK, however all are designed to support children and adults in need of care or treatment from illness, disability, old age or poverty through health care services and programmes.

Within England, the NHS England is responsible for overseeing the clinical commissioning groups (CCGs), specialist services and national contracts for GP practices and dentists. These CCGs comprise of GP practices in their geographic area and are also responsible for services such as urgent and emergency care (A&E), elective hospital care (such as outpatient services and surgery), community health services that are more specialised than GP care, maternity and new-born, and mental health and learning disabilities services (Peckham, 2014). Each of these services are provides with the knowledge of local health care needs and responding to these needs.

Typically, in England, patients will seek diagnosis, treatment, or support for a condition by visiting a local, general practice known as GP, who is based in the

community and can act as a gatekeeper for other healthcare services. They will help with treating common illnesses, managing long term conditions and preventing future conditions through advice, medications, immunisation and screening programmes (Tobin-Schnittger et al., 2018). They will also refer patients if they are in need of more specialist services, which are labelled as secondary care services. These services are usually based in a clinic or hospital and include planned operations or surgeries, specialised clinics (such as cardiology), or rehabilitation services (such as physiotherapy). Occasionally, patients may need to visit more specialist centres which offer tertiary care. The health care professionals in tertiary care provide access to more specialised equipment and expertise for the conditions of the patient. It is a requirement by NHS England for a clear communication and transfer of care between secondary and tertiary care with primary care, in particular at stages such as outpatient pathway in order ensure good patient care.

3.4 Data sources

3.4.1 Description of The Health Improvement Network (THIN) Database

In the UK, essentially all of the patient's care is coordinated by the GP through the NHS. When patients are referred for secondary or specialty care, a treatment plan is initiated by the consultant but future therapies are commonly directed through the GP, ultimately allowing for this information to be captured by the GP, who will often prescribe and monitor subsequent treatments (Gov.uk, 2012). As a result, primary care data should fundamentally record all the care received by patients within the UK, thus making it a good source of data for scientific studies.

THIN is an ongoing longitudinal anonymised database composed of GP medical records data from participating GPs throughout the UK (Collin et al., 2017). As of 2017, THIN covered over 15 million patients from around 744 GP practices across the country, of which just under 4 million are active patients, alive and currently registered, accounting for around 6% of the UK population as a whole (IQVIA, 2018).

The data recorded in the THIN database include patient demographics, diagnoses, prescribing information, and test results. Databases such as THIN allow for the study of rare events, medication utilisation patterns and effectiveness in daily practice (Schneeweiss and Avorn, 2005). THIN has recently linked in with the Hospital Episode Statistics (HES) data which covers secondary care inpatient and outpatient care data (Clegg et al., 2016) for a subset of people. However, this linkage was not available for use in this thesis in Chapters 6 and 7. As THIN captures longitudinal health information on patients, it offers the opportunity to perform retrospective studies in large numbers of patients in a timely and cost efficient manner. It allows for the coverage of under-researched subpopulations, such as AN, in their naturalistic conditions (Davis et al., 2019).

3.4.1.1 THIN data validity and representativeness

Studies have shown that THIN is generalisable to the UK population, particularly in terms of demographics such as age and sex, and basic prevalence of conditions in the UK population (Blak et al., 2011). Thus, the use of THIN database ensures the sample size is nationally representative. THIN allows for studies of well-defined populations for which data have been collected in a reliable and routine fashion. These studies offer an advantage over RCTs, as they improve the internal and external validity of the study (Schneeweiss and Avorn, 2005).

3.4.1.2 Data collection

All the practices collaborating with THIN use the Vision software which enables electronic patient records to be collected and analysed through appropriate coding systems. The data for THIN is automatically collected from practices by In Practice Systems ltd (InPS), who are owners of the Vision software used in GP practices on behalf of THIN (InPS, 2020). The frequency of the data collected by InPS varies depending on the practice from weekly to monthly. This data is then processed by THIN and data sets are created up to three times per year by THIN for research use.

In order to retrieve the required data for this study, it is important that an appropriate system is identified, which is suitable for the purpose of the study in Chapters 6 and 7. Due to the anonymised nature of THIN, the data is accessed via Read codes, which is a hierarchical clinical classification system that consists of over 96,000 codes enabling the extraction of the required data (Herrett et al., 2015). The Read code language was developed in the UK and funded by the NHS. Read codes provide a comprehensive, structured list of clinical terminology that can be used to describe the signs and symptoms, diagnoses, treatments and therapies, drugs and appliances and any administrative procedures of the patient (Thompson et al., 2017). The Read system of coding, was adopted by the British National Health Service in 1990 (Bonney et al., 2017). Throughout the years, updated versions have been introduced which allows common codes to be shared across healthcare.

The process of compiling code lists for Chapters 6 and 7 was replicated as recommended by Davé and Petersen (2009). It was suggested that the use of Stata do-files can be efficient in recording the syntax required for the study and ensures a clear record of the code compiling process (Davé and Petersen, 2009). Initially, synonyms for AN and other comorbidities were identified in collaboration with two consultant CAED psychiatrists currently in practice who were part of the research team (Dr Dasha Nicholls and Dr Mima Simic). The Read codes for the variables mentioned in Chapters 6 and 7 were identified from THIN drug and medical dictionaries for Read codes. This was done by typing the applicable medications and comorbidities into the dictionary excel sheet and noting down the corresponding Read codes. Similarly, the target population for the study was identified through Read codes. Initially, these codes were identified similar to that of comorbidities, by searching the medical dictionary. Once identified, it was compared with the inclusion and exclusion criteria of the study in Chapters 6 and 7. To ensure the desired population was identified by the codes and exclude any unwanted codes, three

approaches were made. Firstly, previously validated and used Read codes by other researchers were used for comparison. This included the code lists created by researchers at the Department of Public Health and Primary Care Unit at the University of Cambridge (Cambridge, 2017). Secondly, the author of the most recent study conducted on the incidence of eating disorders, using a large UK database like GPRD was contacted via email (Micali et al., 2013). The Read codes provided by the author were compared with those used in this study to ensure the list was comprehensive for the chosen population (Appendix 1). Thirdly, the Read codes were reviewed by the two consultant CAED psychiatrists currently in practice.

Due to a lack of electronic data record or poor documentation of data prior to the introduction of Vision, the study period for the study in Chapters 6 and 7 was chosen as 1996-2016, which was the latest date that data was available for the study.

3.4.1.3 Data structure and cleaning

The data analysis and statistical software used for this study is Stata, version 14.0. The data collected from the Vision software in each practice is split into four main files; patient, medical, therapy and additional health data (AHD) (refer to Figure 2).

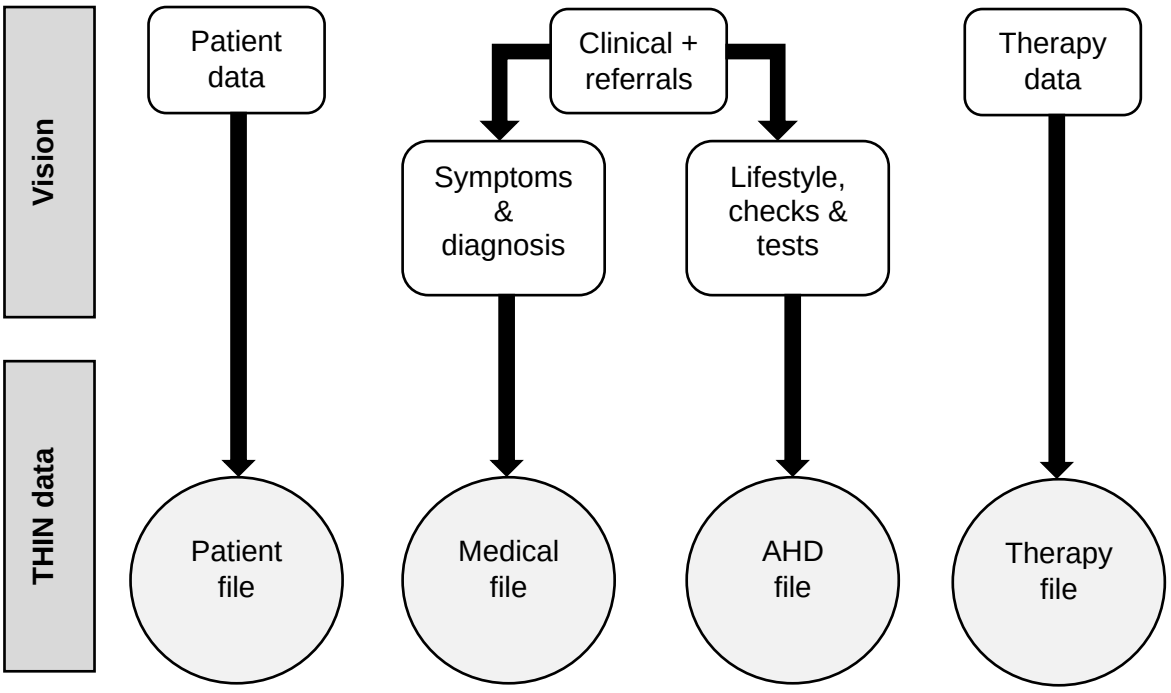

Figure 2. The process of data collection and THIN data structure. AHD = additional health data

1. Patient files: The information recorded on the patient files are of patient characteristics and registration details. These include a unique patient ID, year of birth, gender, patient's registration date, and registration status, information date of transfer or death, marital status and prescription exemptions.
2. Medical files: These include a record of events such as symptoms, diagnoses, interventions etc. that have been recorded by the GP, as well as information transcribed from hospital discharge summaries or referral letters sent by specialists. The medical files contain the variables patient ID, event date (diagnosis date), end of event date, medcode (diagnostic Read codes), source of record and priority (for life threatening conditions).
3. Therapy files: These contain details of prescriptions issued to the patients. Each medication is generated as a new record, including repeat prescriptions and consists of the formulation, strength, dose, and quantity of the medication prescribed. The variables in these files are of the patient ID, prescription date, the drug code, the dose code, the quantity prescribed, the duration of the prescription, whether prescriptions are private or NHS, if the prescription was acute or repeat and other various details.
4. Additional health data: This provides a range of data types, including information on BMI, blood pressure, smoking status, alcohol status, immunisation, and test results, as well as free text. The variables include patient ID, the event date, medcode (diagnostic Read codes) and anonymised free text comments.

Patient identifiers are organised by GP practices that participate in the database. This meant that patient ID was unique per practice, however once combined with all practices, it no longer remained unique. Thus, to create unique patient IDs for the database, the practice ID and patient ID were combined. This ensured that each patient had a unique patient ID for the entire THIN data set and prevented duplication

of unique patient data. Another important aspect of THIN data is anonymization. Prior to providing the data for researchers, it is anonymised. This is done so by changing the date of birth into year of birth and removing any names or addresses from both the patient records and free text files. For the purpose of the study presented in Chapters 6 and 7 and to be consistent with the mid-year reference dates, I adjusted the date of birth as 1st of July for all patients, in accordance with their year of birth (01-07-Year).

3.4.1.4 Patient identification in THIN

The patients in Chapters 6 and 7 were identified through Read codes corresponding to the predefined code list to identify individuals with AN. The Read codes used can be found in Appendix 1. From the group of individuals with a definite diagnosis of AN, only those with a minimum of 6 months continuous follow-up were included in the study. This was to exclude individuals with temporary or limited registration at GP surgeries as a result of them being visitors, moving to a new house or death, which may affect the accuracy of my estimates. I ensured all patients diagnosed with anorexia nervosa had registered with the GP at least 6 months prior to their recorded diagnosis date to capture incident recordings of AN. Refer to Figure 3 for further details.

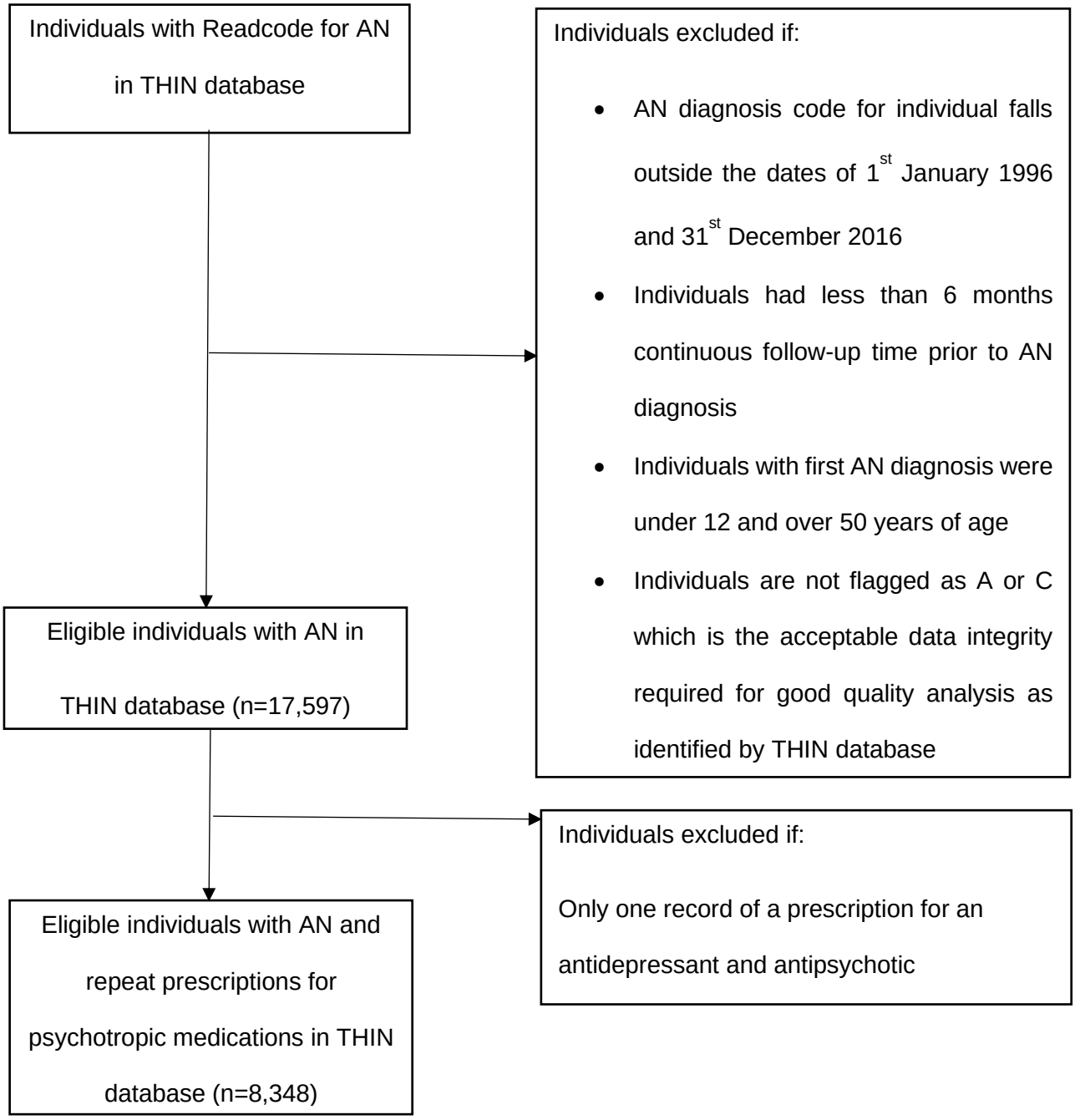

Figure 3. THIN population selection

To identify the registration and demographic details of the individuals with a recorded diagnosis of AN, the medical files and patient files were merged. To identify the number of AN individual's receiving treatment, only those who had a repeat prescription (more than one prescription) of antidepressant or antipsychotic

medications after their AN diagnosis date were included. The enhanced dosage determination method developed by the University of Nottingham Division of Epidemiology and Public Health was used for the prescribed antidepressants and antipsychotics, as they developed a new algorithm of coding dosage for THIN making it feasible to code every instruction. This method was essential in calculating the duration of drug cessation in Chapter 7. It has increased the availability of dosage values for some therapies, enabled for more detailed analysis in less time and better understanding of the use of the drug in terms of timing. The enhanced dosage determination method calculations were done by calculating the variable *dosgval*, flagging data for non-numeric information such as time of day of dose, quantity and conditional instructions, identifying the lower and upper limit of a range as specified in the text and calculating the corrected *dosgval* and ranges which take into account the conditional dosing. This enabled the manual calculation of how long a prescription for the psychotropic medication was prescribed for and the expected end date for that prescription, based on the quantity and frequency of the prescription. In addition, to ensure that the medication was continuously used, as opposed to being reinitiated, a gap of less than 90 days (3 months) was considered as continuous use. For individuals with a gap of more than 90 days, individuals were censored and considered to have stopped medication treatment.

3.4.1.5 Advantages and disadvantages of electronic databases

One advantage of using large electronic medical databases for research is that it allows for large cohorts to be identified in order to evaluate incidence of rare events. Another advantage is the ability to study these events among sufficiently large numbers of patients with certain comorbidities. It also allows the estimation of incidence and prevalence of exposures to drugs as the standardised databases provide both numerators and denominators for calculations. Electronic databases like THIN also allow for a variety of additional information to be obtained from medical

records, which can be beneficial in most pharmacoepidemiologic studies (Steinke, 2019).

Medical records are not standardised or designed for research purposes but rather for patient care and thus the information recorded or quantified by THIN may not reflect the interests of researchers. Therefore, a disadvantage of healthcare databases is that some information may not be available or only partially recorded, such as information on race/ethnicity. Another limitation of electronic healthcare data may be the lag or duration required for the database to retrieve and update all the necessary information and variables for a given time frame (Steinke, 2019). As THIN is a primary care database, the data it captures is limited to primary care. Thus, without linkage to other databases, it misses hospital data. With regards to THIN prescription records, it must be noted that the presence of a prescription record does not guarantee that the prescription has been dispensed or that the patient has actually taken the medication.

3.4.2 Description of specialist Child and Adolescent Mental Health Services (CAMHS) in the UK

The data used for the study described in Chapter 8 was obtained from CAMHS. Children and adolescents can access the service with four different tiers of service provision, as follows (Health Advisory Service, 1995) (Aggett et al., 2006) (Duffy and Skeldon, 2014):

1. Tier one: universal services, which promote mental well-being and recognise when to refer to more specialised services
2. Tier two: more targeted services, which fundamentally aim for health care professionals, who often work individually, to support those with less severe mental health conditions

3. Tier three: specialist community CAMHS, which provide a range of interventions through multi-disciplinary teams of health care professionals
4. Tier four: highly specialist services, which include day and inpatient services.

Child and Adolescent Mental Health Services (CAMHS) are NHS services that work with children and young people who have difficulties with their emotional, behavioural, or mental wellbeing. They are made up of multidisciplinary teams consisting of psychiatrists, psychologists, social workers, nurses, and therapists. Each country in the UK has its own policy for their CAMHS services. In England, as of 2019 there are currently 77 CAMHS, which may vary slightly in strategy, however, essentially provide preventative, early intervention and specialist services. They also primarily offer day patient, outpatient, and community services, and some also have inpatient beds to help those with severe mental health conditions.

CAMHS deal with a wide range of mental health conditions that may affect children and adolescents. These include but are not limited to eating disorders, attention deficit hyperactivity disorder (ADHD), depression, anxiety, schizophrenia, autistic spectrum disorder (ASD), psychosis, early developmental trauma and individuals at risk of self-harm and suicide (NHS, 2019). Available help from specialist CAMHS can be found through their own website, which will vary depending on the location that the affected individual lives. In most cases, GP referrals are made to the CAMHS, however, there are also contact numbers available for self-referrals by parents, schools or young people (Department of Health, 2015, Charman, 2004).

Despite CAMHS throughout the UK being affected by chronic underinvestment and receiving less than 1% of NHS funding, the NHS England has initiated a five year plan to support CAMHS improvements in England with the government's pledge of £1.25 billion by 2020 (Department of Health, 2015).

3.5 Challenges with obtaining ethics

Data for the clinic study (Chapter 8) required ethics from the NHS. This was done through the health research authority (HRA). The HRA protect and promote the interests of patients and the public in health and social care research by ensuring research is ethically reviewed and approved, promoting transparency, overseeing committees and providing advice and recommendations on research projects (hra.nhs.uk, 2017).

In order to assess the appropriate ethical body approval that is required to conduct Chapter 8 in England, the HRA decision tool was used (Appendix 2). Based on the decision tool, the clinics study in Chapter 8 required overall HRA approval, however, did not need research ethics committee (REC) or confidentiality advisory group (CAG) review, due to its nature of using retrospective, anonymised data. Thus accordingly, an Integrated Research Application System (IRAS) application was initiated and completed to reflect this process (IRAS number 228242). The ethics process was as shown in Figure 4.

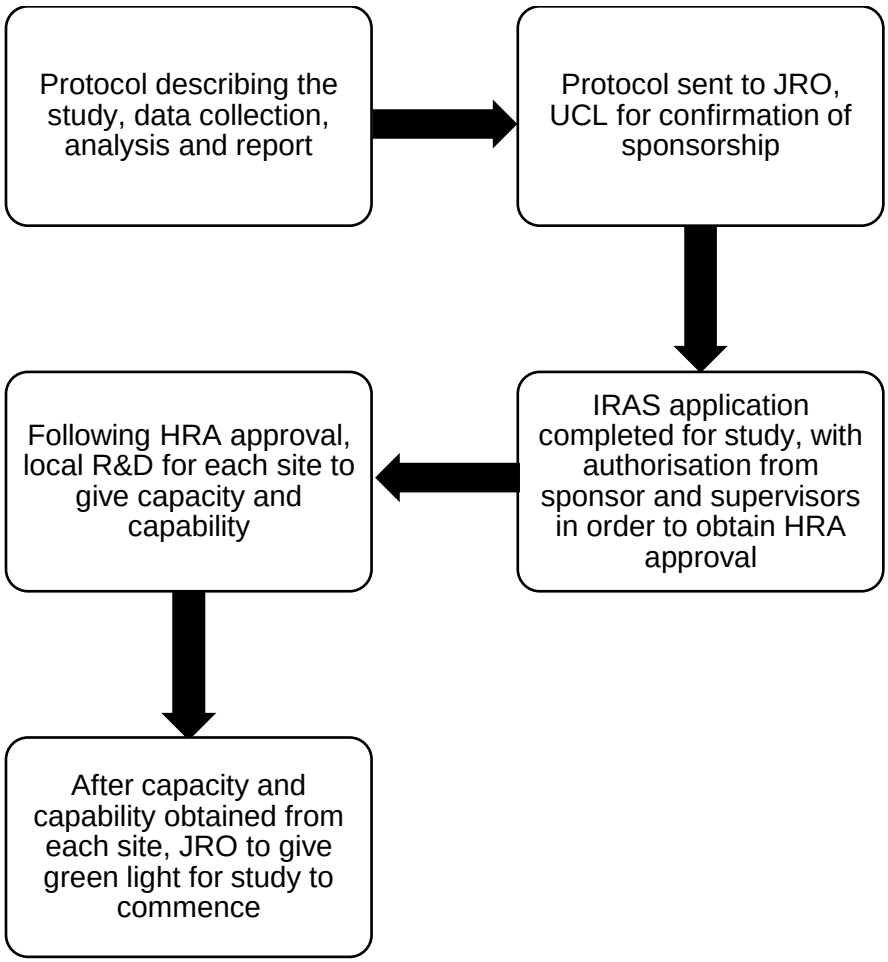

Figure 4. Ethical approval process for obtaining ethics for the study described in Chapter 8 of this thesis. JRO = Joint Research Office, IRAS = Integrated Research Approval System, HRA = Health Research Authority, R&D = Research and Development

As the studies from this thesis were part of a research doctorate, all the studies were categorised as academic research. Thus, they required sponsorship from the university (UCL) as the host. The financial implications and health and safety of conducting such studies also must be considered. The joint research office (JRO) are the relevant body responsible for research sponsorship at UCL/UCLH. They provide advice on completing the IRAS application, give guidance on the process and ensure that the ethics process is carried out appropriately. After approving the protocol of the study and ensuring that the study was methodologically, statistically, and analytically correct, they authorised the study on the IRAS application online. This was also done

by the chief investigator, which as per HRA guidance, is typically the primary supervisor (in this case Professor Wong) for PhD researchers. As my study was a multi-site study, local collaborators were required from each site to represent and lead the ethical procedures that are required at the local R&D for each site. A total of eight sites had shown interest in the study and had initially requested to collaborate. However, considering the time that would be required for conducting the study, the manpower needed and total duration of the PhD, only four sites contributed to the final data for the study in Chapter 8. As the study was initiated with the collaboration of one main site, it was recommended by JRO that the data would be personally collected by the research student (myself) and anonymised on-site prior to transferring to UCL for analysis. Thus, an honorary contract was put in place, which included Disclosure and Barring Service (DBS) and occupational health checks (Appendix 3). A consensus was reached that the other three sites would collect the data in-house by the direct clinical care team onsite, anonymise the collected retrospective data and transfer the anonymised data to the research team at UCL for the purpose of the study in Chapter 8.

The original allocated time of six months based on the HRA website, guidance of other researchers within the department and advice from UCL's JRO team proved to be a great underestimation of the true duration it takes for completing and obtaining all ethical approvals required for a study, with the consideration of the time needed to collect all the necessary data. Therefore, two non-substantial amendments were made; the first was to cover the additional sites that had shown interest to participate in the study and the second was to extend the overall end date of the study. In addition to these, a substantial amendment was documented in order to account for the increase in total UK sample size that had occurred as a result of the new sites. In the original application, the total UK sample size was documented as 200 anonymised patient data, which should've been adequate based on an estimation calculation of

AN individuals from previous years of one CAED site. However, with the addition of new sites, this number had to be increased to account for the larger population. Thus, a substantial amendment for increasing the total UK sample size to 400 was submitted, along with an extension of the study end date, to ensure ethical approval would cover the total study duration.

The challenges faced with obtaining appropriate ethical approvals for the studies conducted in this PhD are not limited to academic research. Rather, there have been publications that have evaluated whether the rules for getting retrospective clinical studies ethics are too strict. To combat issues around administrative research approval that descriptive retrospective studies face like the one conducted in Chapter 8, it has been suggested that senior physician-scientists in a field be issued permanent permits for conducting retrospective clinical studies, or that a web-based fast track application route is designed for these types of studies which will ensure the questions are more befitting of the type of study conducted (Stefánsson et al., 2008). Despite the challenges, the process of applying for and obtaining NHS ethics was an interesting and beneficial experience which taught fundamental lessons in time commitment, project management, strategic networks, and stakeholder engagement (Jones and Nazarpour, 2018).

The following chapter presents the findings of the first study of this thesis, a survey which explored the prescribing practices of specialist CAED psychiatrists in secondary care setting for individuals with AN.

Chapter Four

The efficacy and safety of psychotropic drug treatment in adolescents with anorexia nervosa: a systematic review

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Outline

First, a systematic review was conducted to explore the current literature on the efficacy and safety of psychotropic drug treatment in adolescents with AN. The findings are reported in this chapter.

4.1 Introduction

Anorexia nervosa is known to have a typical onset in adolescents, often reaching a peak age of 13 to 18 years (Kimura et al., 2007, Steinglass and Walsh, 2016). Recent systematic reviews and meta-analyses have tried to aggregate studies in order to suggest suitable treatments for anorexia nervosa based on different outcomes. Lebow et al. (2013) conducted a systematic review and meta-analysis on the effects of antipsychotics in mainly adult patients with AN (one study included adolescents down to age 12, and another was age >16). They investigated eight RCT studies and found that atypical antipsychotics had no significant effect on BMI (weighted mean difference=0.18, 95% CI (-0.36 to 0.72); I^2=26%) or eating disorder cognitions in patients with AN compared to placebo. Anxiety symptoms significantly increased while depressive symptoms decreased with antipsychotic use in the studies. To further assess their BMI outcome, the authors limited their analysis to the antipsychotic olanzapine, however found no significant effect on BMI (Lebow et al., 2013). Claudino et al. (2006) conducted a systematic review on the efficacy and acceptability of antidepressants in AN treatment. Seven studies were included in which an antidepressant drug was compared to either a placebo or another antidepressant, of which four were trials. Patients were mainly young adults with mean ages between 20 and 30 years, although one study included adolescents. The study failed to show a significant difference in weight gain of antidepressants despite a meta-analysis conducted on two of the included studies (relative risk=0.83, 95% CI (0.41 to 1.67); Z=0.53, p=0.60) compared to placebo. The systematic review also did

not demonstrate any effect on eating disorder symptoms in comparison to placebo (Claudino et al., 2006).

A similar systematic review was conducted by Balestrieri et al. (2013) comparing differences in efficacy and tolerability of antidepressants and antipsychotics for AN treatment in adolescents and other mixed-aged populations. A total of eight studies were included and the publication reported that the results for the use of antidepressant or antipsychotic medications in AN are discouraging with regards to weight gain and do not allow for any firm conclusions to be made for their use. They concluded the results obtained in adults for the use of these medications are not easily transferable to the adolescent age group and that further investigations need to be carried out to assess pharmacotherapy in adolescents with anorexia nervosa (Balestrieri et al., 2013).

A more recent systematic review and meta-analysis by Murray et al. (2018) aimed to determine the impact of pharmacological and psychological treatments on the weight and psychological symptoms of AN. They identified 35 RCT studies which contained three populations: a) adolescents, with a mean age of 15.01 years, b) adults, with a mean age of 27.1 years and c) mixed populations with mean age of 21.86 years. They found that current specialised treatments (such as psychosocial, pharmacological, medical and alternative treatments) are more adept than comparator interventions at reporting change in weight-based AN symptoms at the end of treatment (g=0.16, 95% CI (0.05 to 0.28), p=0.006), but not at follow-up stage (g=0.11, 95% CI (-0.04 to 0.27), p=0.15) (Murray et al., 2018b). However, when the results were further explored in the adolescent population, most of the treatments assessed were not pharmacological, rather psychotherapy based.

There is a current lack in reviews exploring pharmacotherapy in the adolescent population of individuals with AN. Therefore, the focus of this review was to explore the use, the efficacy, and the safety of psychotropic medications in AN adolescents.

4.2 Research question

The central research question in this systematic review was: “In adolescents with AN, what is the efficacy and safety of treatment with psychotropic drugs with regards to weight change in current literature?”

4.3 Aim and objectives

The aim of this systematic review was to synthesise peer-reviewed literature assessing the efficacy and safety of psychotropic drug treatment with regards to its impact on weight change, psychiatric symptoms, and adverse events in adolescents with AN.

4.4 Methods

4.4.1 Inclusion & exclusion criteria

Inclusion criteria for this study were: 1) the population of the studies must include adolescents aged 13 to 18 years, either as the sole focus, or stratified alongside other age groups; 2) the studies must focus on AN, either as the sole focus, or alongside other eating disorders or conditions; 3) studies must include pharmacotherapy, specifically psychotropic drugs, which include all antidepressants, antipsychotics, neuroleptics and tranquilizers; 4) studies must be RCT or observational studies, such as cohort, cross sectional or case-control; 5) studies can be published in any language; and 6) only studies with full text articles will be included. Exclusion criteria were: 1) studies where weight change was not reported, even if the studies were evaluating the safety of the medications; 2) publications that are of an editorial, meeting abstract, expert opinion and systematic review nature. This is due to the lack of peer review process and methodological descriptions that facilitate quality assessment in these types of publications (Adams et al., 2017); and 3) studies that focused on study populations with other eating disorders, such as BN, BED or OFSED.

4.4.2 Outcome measures

The primary outcome of interest was weight change, as used in many other previous studies as a measure of outcome (Davies and Jaffa, 2005, Herzog et al., 2004, Lund et al., 2009, Sly and Bamford, 2011). This was measured by:

a) The body mass index

b) The number of patients achieving a normal BMI of >18 (Cornelissen et al., 2017)

c) The mean rate of weight gain

d) Other consistent measures of weight change.

Other outcomes were of psychiatric evaluations and the safety of psychotropic medications in anorexia nervosa. These were measured by:

a) Levels of psychiatric symptoms measured by validated rating scales such as the German version of the child depression inventory (DIKJ), Multidimensional Anxiety Scale for Children (MASC), the children's version of the Yale Brown obsessive-compulsive scale (CY-BOCS) (Holtkamp et al., 2005)

b) Assessment for adverse events measured by Simpson-Angus Scale (SAS) and Abnormal Involuntary Movement Scale, Treatment Emergent Side Effects Scale (TESS) (Kafantaris et al., 2011)

c) The number of subjects reporting side effects and adverse events

d) Safety measurements measured by electrocardiograms and laboratory blood test results

e) Death.

4.4.3 Search terms

The systematic search was constructed using the PICO model for framing clinical questions (Aslam and Emmanuel, 2010). This model enables the identification of clinically relevant evidence in literature and the formulation of the research questions. The elements in PICO include: Population, Intervention, Comparison and Outcome. The facets used for this systematic search along with their justifications are shown in the table below (Table 1).

Table 1. Facet terms for the systematic review

Number assigned to each facet	Facet	Boolean connection	Justification for facet term used
1	Adolescents	**1 AND 2 AND 3 AND 4**	The focus of this review was on adolescents, which were the *population* of the study.
2	Anorexia nervosa		This target *population* of this review was adolescents with AN.
3	Psychotropic drugs		The *intervention* of this review was the use of psychotropic drugs as treatment of AN. The *comparator* could have been looking at one psychotropic drug with another, or a different form of treatment such as psychotherapy or comparing the use of psychotropics to placebo.
4	Weight		The *outcome* that of the review was any weight change reported with the use of psychotropic drugs, in order to assess the effect on weight gain.

The facets for the searches were inserted into the databases and relevant Medical Subject Heading (MeSH) terms and free texts were identified from the search, as shown below. These MeSH terms and free texts were then included within the search

strategy to ensure all required terminologies were picked up for the review (as shown in Appendix 4). Truncation marks " " were used to ensure the search was comprehensive and included all possible roots of the free text search. The search strategy applied combined the following terms: 'adolescent' AND 'anorexia nervosa' or 'anorexia' AND 'psychotropic drug*' or 'psychotropic agent' (these terms included the following subheadings: psychoactive agent* or psychoactive drug* or psychodynamic agent* or psychopharmaceutic agent* or psychotropic adj2 treatment*) OR 'antipsychotic*' or 'neuroleptic agent' (these terms included the following subheadings: antipsychotic agent* or butyrophenone adj2 antipsychotic agent*) or phenothiazine adj2 antipsychotic agent* or antipsychotic drug* or antipsychotic* or butyrophenone adj2 tranquilizer* or classical antipsychotic* or classical antipsychotic agent* or classical antipsychotic drug* or long acting adj2 neuroleptic* or major tranquilizer* or neuroleptic* or neuroleptic drug* or neurolepticum or phenothiazine adj2 tranquilizer* or major tranquilizing agent* or typical antipsychotic* or typical antipsychotic agent* or typical antipsychotic drug* or typical neuroleptic* or typical neuroleptic agent* or typical neuroleptic drug* or olanzapine or atypical antipsychotic* or atypical antipsychotic agent* or atypical antipsychotic drug* or first generation adj2 antipsychotic* or second generation adj2 antipsychotic*) AND 'body weight' or 'weight change' or 'weight' (these terms included the following subheadings: thinness or total body weight* or body weight* or body weight change* or body weight disorder* or weight adj2 change*) OR 'weight' or 'body mass' or 'BMI' (these terms included the following subheadings: body mass index or thinness or total body adj2 weight). The systematic search strategy for each database can be found under Appendix 4.

4.4.4 Electronic data source

The most commonly used and recommended databases for searching articles and papers related to health care interventions are the Medical Literature Analysis and

Retrieval System Online (MEDLINE) and Excerpta Medica database (EMBASE) (Dunikowski, 2005). The MEDLINE database has over 26 million records and EMBASE has over 32 million records, both containing papers dating back to the 1950s. The MeSH terms can be used as descriptors in extracting and expanding the search to all relevant terms. PsycINFO is a database that deals primarily in the psychology field and contains over 3.5 million records. With regards to all the mentioned databases, they are easily exported to reference management software's like Endnote.

The searches were performed initially in September 2017, and updated searches were made in August 2019. The following sources were searched from the beginning of each database to the specified date of August 2019. No restrictions were placed on the language of the publication. The databases that were used for these searches were:

1. Medline (Ovid version) - Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (4th August 2019)
2. Embase (Ovid version) - Embase Classic+Embase 1947 to 2019 August 4
3. PsycINFO (Ovid version) - PsycINFO 1806 to Aug Week 2 2019

The Cochrane Review was also searched for systematic reviews with the same objectives as this review in order to manually find further studies with similar inclusion and exclusion criteria from their references and include in this chapter's systematic review. Any additional relevant keywords that were identified in the searches were modified and incorporated in the strategies for this review.

4.4.5 Data selection

Once the search had been carried out and the publications identified, they were screened for duplications across the three databases. This was done in two ways;

firstly, through the Endnote de-duplication programme and secondly manually in order to ensure all the duplicates are identified and removed. A review author (myself) first screened the titles and abstracts of the papers to remove duplicates and irrelevant records. Then, a second review author (Abdallah Naser) independently screened the titles and abstracts that were determined relevant by the first review author, to minimise errors that may result from the review. The full texts of remaining eligible papers were further assessed and compared with the inclusion and exclusion criteria of the systematic review. Studies that did not meet the inclusion criteria were excluded with reasoning. Any discrepancies were resolved by the review authors through discussion until a unanimous decision was reached. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive reporting of the studies (Moher et al., 2009) and has been registered with PROSPERO (CRD number: 42018076901).

4.4.6 Quality assessment

Quality assessment of the included studies were conducted differently for RCT and observational studies. RCT studies were assessed using the Cochrane's risk of bias assessment tool (Higgins et al., 2011) and observational studies were assessed for methodological quality using the modified Newcastle-Ottawa scale (NOS), which is a four-point scale recommended by the Cochrane Collaboration. Scores of the modified NOS assessment could be allocated for the selection, performance, detection, and information bias of the studies, where a higher score indicated better quality. The scale for quality assessment ranged from 0 to 3, where a lower score indicated a higher risk of bias and in contrast a higher score meant a lower risk of bias was assessed. Two authors (myself and Abdallah Naser) independently reviewed and scored each study. Any disagreements were resolved through discussion between the authors.

4.4.7 Data extraction

The process of data extraction was carried out by two authors (myself and Abdallah Naser) who independently reviewed and extracted data for the studies that fulfilled the inclusion criteria, using the Cochrane data extraction template (Cochrane, 2017) to ensure reliability. The extracted data included study design and duration, data source and setting, sample size, intervention, and outcome characteristics. The included studies did not allow for a meta-analysis to be conducted in order to provide quantitative analysis of the results due to clinical heterogeneity, where the included patients were of different clinical and demographic characteristics, and methodological heterogeneity, where the studies were of a small trial size, with large confidence intervals and not conducted in a similar manner. Therefore, results were summarised using a narrative synthesis approach.

4.5 Results

The search strategy provided a total of 986 citations. The Cochrane review search added a further five studies to the total number of identified articles. After exclusion of duplicates, the title and abstract of the papers were assessed by an initial review author (myself) and the process was replicated by a second reviewer (Abdallah Naser). The full text of 156 potentially relevant studies were obtained of which ten fulfilled the inclusion criteria as demonstrated by a PRISMA flow diagram (Figure 5).

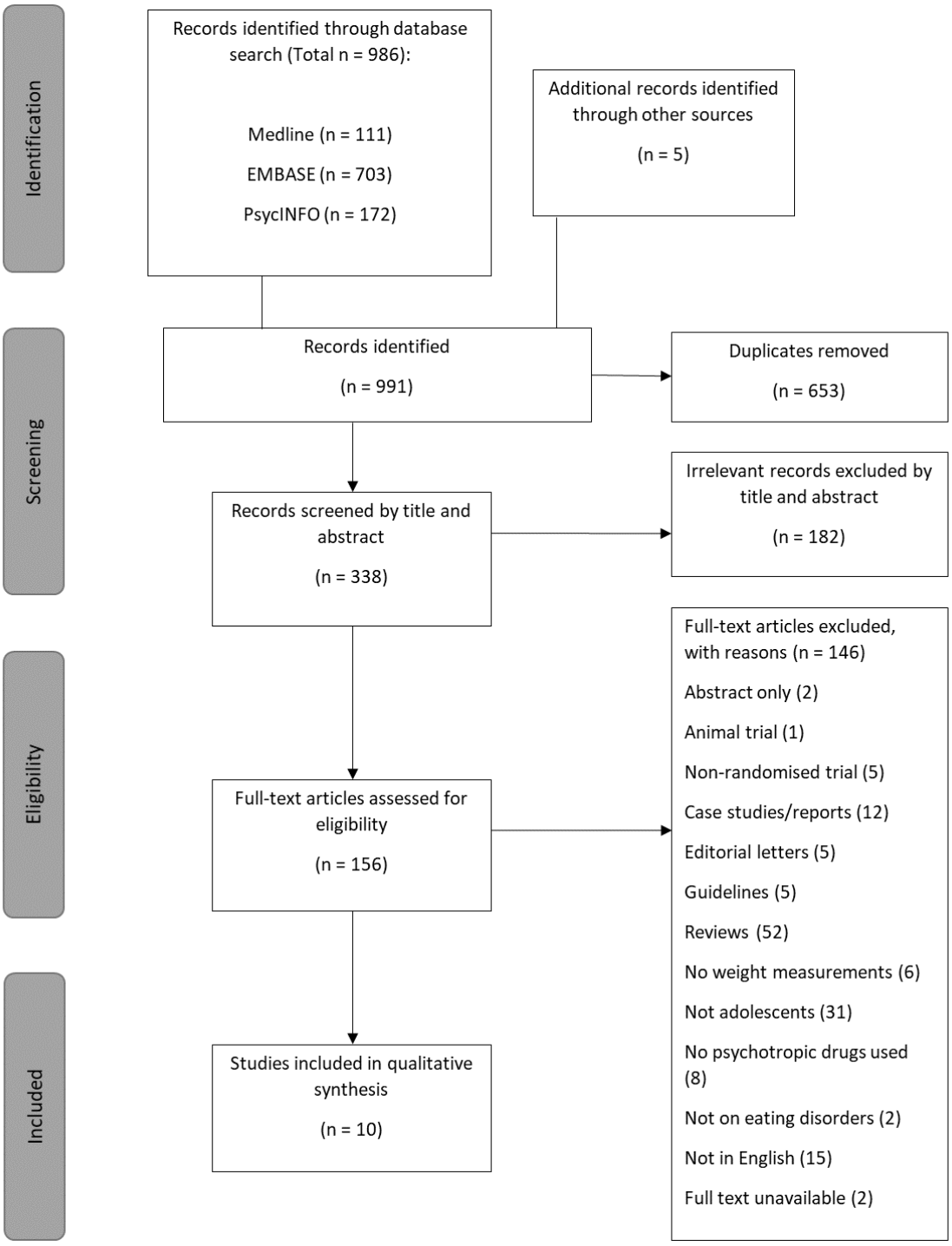

Figure 5. PRISMA flow diagram for studies selection process

4.5.1 Quality assessment

The quality assessment of the included studies is shown in Table 2. The three RCT studies were evaluated to be of low risk (Kafantaris et al., 2011, Hagman et al., 2011) and unclear risk (Weizman et al., 1985), according to the Cochrane risk of bias

assessment tool (Appendix 5). The majority of the observational studies were of adequate quality with respect to the methodology (Couturier et al., 2013, Frank et al., 2017, Hrdlicka et al., 2008, Monge et al., 2015, Norris et al., 2011), as assessed by the modified NOS quality assessment. Studies by Holtkamp et al. (2005) and Grewal et al. (2014) were considered of good quality, although the highest scored on the modified NOS assessment tool was Monge et al. (2015), indicating a lower risk of bias.

Table 2. Risk of bias assessment for observational studies based on the Modified Newcastle Ottawa Scale (NOS)

Study	**Domain of evaluation**				**Total**
	Selection bias	Performance bias	Detection bias	Information bias	
Holtkamp, et al. (2005)	1	2	3	4	10
Hrdlicka, et al. (2008)	2	3	4	4	13
Norris, et al. (2011)	2	4	4	4	14
Courturier et al. (2013)	2	2	4	4	12
Grewal, et al. (2014)	1	2	3	4	10
Monge, et al. (2015)	3	4	4	4	15
Frank, et al. (2017)	2	3	4	4	13

From the ten studies included in this review, three were RCTs (Hagman et al., 2011, Kafantaris et al., 2011, Weizman et al., 1985) and seven were observational studies (Couturier et al., 2013, Frank et al., 2017, Grewal et al., 2014, Holtkamp et al., 2005, Hrdlicka et al., 2008, Monge et al., 2015, Norris et al., 2011). Four of the studies were

conducted in the United States of America, three in Canada, one in Germany, one in the Czech Republic and one in Israel. All the studies were published in English. The total number of participants in the studies was 1,032 individuals, ranging from 10 (Weizman et al., 1985) to 635 (Monge et al., 2015) with a focus on both genders. Participants ranged from 10 to 21 years of age.

Three trials and seven observational studies compared medicinal treatment of AN with a control treatment. Medication treatment was compared to a variety of control groups, which consisted of: a) any therapy but no medication treatment (n=5), b) placebo (n=2), c) specialised psychotherapy (n=1), d) completion of a specialised eating disorder program (n=1), and e) other (n=1). The baseline characteristics of the studies are shown in Table 3.

Table 3. Characteristics and results of included studies

Author, year, country	Study design	Setting	Sample size	Mean age (SD), year	Intervention group	Control group	Results
Couturier et al., (2013), Canada	Retrospective cross sectional study (observational)	McMaster University	62 patients	16.2 years (2.65) in drug group 16.0 years (2.0) in control group	31 patients with AN using SSRI	31 patients with AN as control (not using SSRI)	SSRI users had significantly lower bone mineral density z-scores, compared to controls (–1.094 vs. –0.516, p<0.035), suggesting that exposure to SSRIs may be a risk factor for lowered bone mineral density.
Frank et al., (2017), United States of America	Retrospective cross sectional study (observational)	Children's Hospital Colorado	106 patients	15.0 years (2.2) in AN with aripiprazole group 14.4 years (2.5) in AN group	22 patients with AN on aripiprazole	84 patients with AN	Mixed model ANCOVA found a greater gain in BMI (6% higher) and BMI percentile (20% higher) in the aripiprazole group compared to the non-aripiprazole group.

Author, year, country	Study design	Setting	Sample size	Mean age (SD), year	Intervention group	Control group	Results
Grewal et al., (2014), Canada	Retrospective cross sectional study (observational)	The Hospital for Sick Children, Toronto	65 patients	At admin: 15.6 years (1.4) At onset of illness: 13.3 years (1.4)	38 AN patients who completed the Eating disorders Day Hospital program	27 AN patients who did not complete the program	Adolescents who completed the program were more likely to have been prescribed antidepressants and less likely to purge. The two groups did not differ significantly on age of onset, duration and percentage of gained weight.
Hagman et al., (2011), United States of America	Double-blind, placebo-controlled pilot study	The Children's Hospital Denver, Colorado	40 patients (16 with concurrent antidepressants)	16.2 years (2.5) in risperidone group 15.8 years (2.3) in placebo group	18 patients with AN receiving risperidone (37% of which are on anti-depressant)	22 patients with AN receiving placebo (41% of which are on antidepressant)	Subjects taking risperidone had a significant decrease on the Eating Disorder Inventory 2 Drive for Thinness subscale over the first 7 weeks (effect size, 0.88; p=0.002) and the Eating Disorder Inventory 2 Interpersonal Distrust subscale (effect size, 0.60; p=0.03). Those taking risperidone had increased prolactin levels (week 7; p=0.001). There were no

Author, year, country	Study design	Setting	Sample size	Mean age (SD), year	Intervention group	Control group	Results
							significant differences between groups at baseline or the end of the study for change in weight.
Hrdlicka et al., (2008), Czech Republic	Cohort study	Department of Child Psychiatry, Charles University	18 patients	15.2 years (1.9) in mirtazapine group 14.7 years (1.7) in control group	9 patients with AN using mirtazapine	9 patients with AN & no pharmaco-therapy	ANOVA Repeated Measures found no significant differences between those on mirtazapine and no medication regarding weight (p=0.981) or BMI (p=0.576).
Holtkamp et al., (2005), Germany	Retrospective naturalistic study	Department of Child and Adolescent Psychiatry of the Technical	32 patients	14.8 years (1.2) in SSRI group 13.9 years (1.3) in non-SSRI group	19 patients with AN on SSRI medications	13 patients with AN not medicated with SSRI	Repeated measures ANOVA revealed no significant group with time interactions for BMI-SDS (p=0.84), core eating disorder symptoms (ANIS, p=0.79), depression (DIKJ, p=0.75), and obsessive-compulsive (CY-BOCS, p=0.40) scores indicating

Author, year, country	Study design	Setting	Sample size	Mean age (SD), year	Intervention group	Control group	Results
		University of Aachen					minimal or no effects of SSRI medication on the course of these variables.
Kafantaris et al., (2011), United States of America	Randomised, parallel-group, double blind, placebo-controlled pilot study	Cohen Children's Medical Center, New York	20 patients	16.41 years (2.2) in olanzapine group 18.10 years (2.04) in placebo group	10 patients with AN receiving olanzapine	10 patients with AN receiving placebo	No significant difference between olanzapine and placebo in age (years) (18.10±2.04 vs. 16.41±2.20, t=1.78, p=0.09, df=18), weight in pounds (92.20±8.11 vs. 94.77±8.66, t=-0.66, p=0.52, df=18), or height in inches (63.87±3.10 vs. 62.80±2.61, t=0.85, p=0.40, df=18) at baseline.
Monge et al., (2015), United States of America	Retrospective cross sectional study (observational)	Adolescent Medicine Sites throughout US	635 patients	All patients: 15.3 years (2.4)	Group 1: 359 AN patients with 1 year follow-up.	Group 1: 276 AN patients without 1 year follow-up	At intake, 20.4% of Group 1 was taking psychopharmacologic medication and 58.7% at 1 year (p≤.0001). Among Group 2, SSRI/SNRI use was most common, and 62.6% had a reported psychiatric comorbidity. Presence of any psychiatric

Author, year, country	Study design	Setting	Sample size	Mean age (SD), year	Intervention group	Control group	Results
					Group 2: 256 AN patients with 1 year follow-up and additional data on psychopharmacological medications & comorbidities	Group 2: 103 AN patients with 1 year follow-up and no additional data on psychopharmacological medications & comorbidities	comorbidity was highly associated with medication use; odds ratio, 10.0 (5.6, 18.0).
Norris et al., (2011), Canada	Retrospective matched-groups comparison group	The Children's Hospital of Eastern Ontario	86 patients	14.4 years (1.9) in olanzapine group	43 patients with AN treated with olanzapine	43 patients with AN not treated with olanzapine	Results found that although not statistically significant, the rate of weekly weight gain (mean=6.96 vs 2.97) and BMI at discharge (18.26, SD=0.92; vs 16.63, SD=1.78) was greater in the olanzapine group compared to those not on olanzapine.

Author, year, country	Study design	Setting	Sample size	Mean age (SD), year	Intervention group	Control group	Results
				14.8 years (1.6) in comparison group			
Weizman et al., (1985), Israel (Palestine)	Randomised controlled trial	Geha Psychiatric Hospital	10 patients	16.0 years (1.3) Group 1: 16.2 years (1.3) Group 2: 15.8 years (0.8)	5 patients with AN treated with behavioural therapy (group 1)	5 patients with AN treated with Pimozide 3mg daily (group 2)	An increase in body weight was observed in both groups, however there was no significant difference between the two groups at any time point during the study. Significant increase in serum prolactin levels were observed in the pimozide group in comparison to the behavioural therapy group.

Narrative synthesis and tabulation were used to report the characteristics and findings of the included studies in this review, stratified by study design (i.e. RCTs and observational studies). The findings of the included studies were further sub-categorised based on the drug class of psychotropic medications as described below.

4.5.2 Description of randomised controlled trial studies

4.5.2.1 Atypical antipsychotics

Hagman et al. (2011) conducted a double-blind, placebo-controlled pilot study on the use of risperidone as treatment for female adolescents with AN. They compared 18 AN patients receiving risperidone, of whom 37% were on antidepressants, to 22 patients receiving a placebo, of whom 41% were on antidepressants. Risperidone was started at a dose of 0.5mg daily and titrated by 0.5mg weekly to a maximum daily dose of 4mg until study endpoint. Participants completed weekly study visits for medication adjustments, vital sign measurements and side effects (Hagman et al., 2011). These included a) the Eating Disorder Inventory 2 (EDI 2) which is a self-reported measurement of symptoms associated with AN, b) Body Image Software Program (BIS) which measures body size distortion and body image dissatisfaction, c) Color-A-Person Test (CAPT), which assesses body dissatisfaction using colours which correspond to feelings of satisfaction/dissatisfaction, d) MASC, which is a self-reported assessment of common anxiety symptoms, e) Resting Energy Expenditure (REE) which is used to determine the effect of risperidone on body metabolism with regards to weight gain, f) SAS and Abnormal Involuntary Movement Scale which assessed for extrapyramidal symptoms and g) safety measurements such as ECG, blood tests for liver enzymes, glucose, cholesterol and prolactin. They found no significant difference between the two groups with regards to age, medication dose, medication duration, level of care, percentage of IBW, BMI, REE, EDI 2, CAPT, BIS tasks and MASC. Despite a statistically significant decrease on EDI 2 for participants

on risperidone in the first 7 weeks of the study (effect size=0.88; p=0.002), this decrease was not sustained until the end of the study (Hagman et al., 2011).

In 2011, a randomised, double blind, placebo controlled pilot study by Kafantaris et al. was conducted on olanzapine as an addition to eating disorder treatment programs for adolescents with restricting type AN. Twenty female patients entered the study and were randomly assigned to olanzapine or placebo, but only fifteen completed the 10 weeks study duration. The medications were started at 2.5mg in the evening for one week and increased by 2.5mg per week to a target dose of 10mg per day by the fourth week. Self-reported medication adherence and olanzapine serum levels were assessed (Kafantaris et al., 2011). The mean body weight percentage was measured at baseline, 5 and 10 weeks and tolerability of medications were assessed by laboratory measurements and ECGs, psychological symptoms and adverse effects were recorded on the TESS. No significant difference in age (years), weight (pounds) and height (inches) was found between the 10 individuals in olanzapine group and 10 in placebo group at baseline. They found that although the mean percentage of mean body weight improved in both groups in the 10 weeks, there was no further increases in the olanzapine group at any time point in comparison to the placebo. No immediate safety concerns were observed with olanzapine use in the 10 weeks however it was suggested that for long-term use, close monitoring must be done (Kafantaris et al., 2011).

4.5.2.2 Typical antipsychotics

A randomised controlled trial by Weizman et al. (1985) including 10 adolescent females with AN was conducted for 20 weeks. They compared 5 AN patients that were treated with behavioural therapy to 5 AN patients with 3mg daily of pimozide. Body weight and serum prolactin levels were assessed weekly for the 20 weeks. An increase in body weight was observed in both groups, however there was no significant difference between the two groups at any time point during the study.

Significant increase in serum prolactin levels were observed in the pimozide group in comparison to the behavioural therapy group (Weizman et al., 1985). From the two patients with secondary amenorrhoea in the behavioural therapy group (2/5), one had restored menstruation by the end of the study, compared to none of the three patients from the pimozide group (3/5).

4.5.3 Description of observational studies

A retrospective chart review study by Monge et al. (2015) was conducted in the US using 635 patient medical files. They examined the data in two phases. In group 1, 359 patients with restrictive eating disorder and one year of follow-up data and 276 patients with restrictive eating disorder but without one year follow-up were identified. From those in group 1 with one year follow-up, 256 patients were categorised into group 2, which consisted of patients with additional psychopharmacological medication and psychiatric comorbidity data, and 103 patients were found to not have this additional data. 21.5% of patients in group 1 were reported to be using psychopharmacological medications such as antidepressants, antipsychotics, mood stabilizers, anxiolytics, or stimulants at intake. This number significantly increased to 57% at the 1 year follow-up visit. In group 2, 20.7% of patients reported to be on psychopharmacotherapy, and a significant increase ($p<0.0005$) was observed at 1 year follow-up (55.9%). At 1 year, the most common medication reported was SSRIs (82.5%), followed by anxiolytics (17.5%), antipsychotics (16.8%) and other psychotropic medications. 62.6% of patients had reported psychiatric comorbidities at one year, most commonly anxiety (43.7%) and depression (25.7%). The authors reported that there was no significant difference in weight restoration between patients taking medication for AN treatment at 1 year follow-up to those not taking medications (Monge et al., 2015).

4.5.3.1 Antidepressants

In 2013, Couturier et al. conducted a study in Canada using retrospective chart reviews from patients seen in a specialized eating disorder program to investigate effect of SSRI use for treatment of adolescents with AN on bone mineral density. They matched 31 patients on SSRI attending the program with 31 patients as controls, who attended but were not exposed to SSRIs in a 1:1 ratio. Data recorded from the patients' records included age, height, weight, duration of amenorrhea, menstrual period timings and the duration and dose of the SSRI given as treatment. Within their exposure group, fluoxetine was the most commonly prescribed SSRI (51.6%), followed by sertraline (35.5%) and citalopram (22.6%). A statistically significant difference ($p<0.035$) was observed in bone mass density scores as the SSRI group had significantly lower levels (-1.094) in comparison to the control group (-0.516) (Couturier et al., 2013).

Grewal et al. (2014) also conducted a retrospective chart review on patients admitted to the eating disorder day hospital program in a hospital in Canada from 2002 to 2008. Two groups were identified: 1) 38 adolescents who had completed the program using the family-based therapy model (Maudsley approach) adapted for a day treatment setting and 2) 27 who left before completing the program. They found that individuals who had completed the program were less likely to have a history of purging and more likely to be prescribed antidepressants for treatment of AN. No difference was observed between the two groups with regards to factors such as age, eating disorder family history, age of onset, duration and percentage of gained weight (Grewal et al., 2014).

In 2005, a retrospective naturalistic study was conducted in Germany by Holtkamp et al. on SSRI treatment in female adolescents with AN. 32 AN patients were investigated of which 19 had received SSRI during their first inpatient treatment due to depressive or obsessive-compulsive symptoms and 13 AN patients who did not

receive any SSRI. The authors reported on the BMI, eating disorder symptoms, general psychopathology during inpatient treatment and the rate of relapse. The SSRI medications patients received were fluoxetine (max dose 60mg/day), fluvoxamine (max dose 150mg/day) and sertraline (max dose 150mg/day). The assessment conducted included a) Structured Interview of Anorexia and Bulimia nervosa (SIAB) which assessed eating disorder symptoms, b) Anorexia Nervosa Self Inventory (ANIS) which assessed psychopathology, c) DIKJ which assessed depressive symptoms and d) CY-BOCS which assessed the obsessive-compulsive symptoms. They found upon admission, no significant difference between the two groups with regards to BMI, DIKJ score and CY-BOCS but a significant difference in SIAB and ANIS score. After 10 weeks, the authors found higher scores in the SSRI group for DIKJ ($p=0.05$) and ANIS scores ($p=0.02$), however no significant difference was found in BMI and CY-BOCS scores (Holtkamp et al., 2005). During the time of follow-up, repeated measures ANOVA found no significant group with time interactions for BMI ($p=0.84$), DIKJ ($p=0.75$) and CY-BOCS ($p=0.40$) scores.

Hrdlicka et al. (2008) reported to have conducted a case control study, however upon reading the publication, it is best identified as a cohort study. In this study they compared 9 female adolescents with AN who were treated with mirtazapine for depression or anxiety during hospitalisation with 9 AN female patients matches who did not receive any medication treatment as controls. No significant difference was found at baseline between the two groups with regards to mean age, mean BMI and mean weight. The weight and BMI of patients were evaluated during the 4 weeks of treatment and no significant difference was found between the cases and controls. The results did however show a non-significant increase in the mirtazapine group in BMI improvement at the end of weeks 1, 2 and 3 of the study (Hrdlicka et al., 2008).

4.5.3.2 Atypical antipsychotics

In 2017, Frank et al. conducted a retrospective chart review comparing 22 patients with AN initiated on aripiprazole treatment in the program to 84 matched patients with AN not on aripiprazole treatment. The BMI in both groups were found to be similar upon admission however the aripiprazole group had a significantly higher proportion of patients with anxiety (chi-square=7.277, p=0.009), major depressive disorder (chi-square=7.926, p=0.007) and SSRI prescriptions on discharge (chi-square=4.830, p=0.033) in comparison to AN group not on aripiprazole. In further analysis using a mixed model ANCOVA, the authors found a greater gain in BMI (6% higher) and BMI percentile (20% higher) in the aripiprazole group compared to the non-aripiprazole group (Frank et al., 2017) from admission to discharge.

Norris et al. (2011) conducted a retrospective matched cohort study in Canada comparing 43 female adolescents with AN receiving olanzapine treatment at hospital with 43 AN patients not on olanzapine treatment. Patients were matched based on age, diagnosis, and treatment intensity (i.e. outpatient care, inpatient care, or day program) after assessment. The authors assessed demographic, diagnosis and clinical characteristics of patients such as laboratory results (Norris et al., 2011). They found that although not statistically significant, the rate of weekly weight gain (mean=6.96 vs 2.97) and BMI at discharge (18.26, SD=0.92; vs 16.63, SD=1.78) was greater in the olanzapine group compared to those not on olanzapine. Norris et al. reported that over half of the total 43 AN patients observed rates of at least one side effect attributed to olanzapine, most commonly sedation (40%).

4.6 Discussion

The NICE guidelines specify clearly that the first goal of treatment in AN is weight restoration and specify the weekly weight gain expected in AN inpatients and outpatients (NICE, 2018). Thus the primary metric of outcome for this review was weight change, as a measure of the effectiveness of psychotropic medications for

treatment in AN (Murray et al., 2018a, Lund et al., 2009). Weight change was observed in three small trials, investigating the efficacy of risperidone versus a placebo, olanzapine versus a placebo and pimozide versus behavioural therapy. Based on the results of these studies, there is no significant evidence to indicate that the use of psychotropic drugs influences weight change in adolescent patients with AN. Weizman et al. (1985) suggested there is some evidence that the antipsychotic drug pimozide increases body weight, however there was no significant difference between the pimozide group and the behavioural therapy group (Weizman et al., 1985). Kafantaris et al. (2011) also supported this as they suggested there is some evidence that olanzapine increases the mean percentage of mean body weight, however there was not enough evidence to suggest the increase in the olanzapine group was higher than the average weight gain in the placebo group (Kafantaris et al., 2011). Overall, the RCTs included in this review were not able to demonstrate the advantages of psychotropic medications as treatment for adolescents with AN, in terms of weight change, compared to placebo (two studies with 61 participants) or psychotherapy (one study with 10 participants). Where differences were observed, the studies did not have enough power to ensure confidence in the findings, due to small sample sizes.

Of the seven observational studies included in this review, all reported no evidence of weight change associated with psychotropic treatment in adolescents with AN. It was suggested by Norris et al. that, although not statistically significant, the rate of weekly weight gain and BMI at discharge was greater in the 43 patients in the olanzapine group in comparison to the 43 matched control patients not on olanzapine treatment (Norris et al., 2011). Similarly, in mixed model repeated measures ANCOVA analysis, Frank et al. found a greater gain in BMI percentile and BMI in the aripiprazole group in comparison to the group not on aripiprazole (Frank et al., 2017). Hrdlicka et al. reported a non-significant increase in BMI at the end of each week in

the 4 weeks study period in the mirtazapine group, however they found no significant difference between the exposure (mirtazapine treatment) and the controls (Hrdlicka et al., 2008).

Thus, no firm conclusions can be drawn on the basis of these studies and further studies on the effect of pharmacotherapy on weight gain in adolescents with AN are needed. One hypothesis is that the lack in evidence for the effect of psychotropic treatment on weight gain in AN is that the literature is primarily focused on diagnosis based, rather than symptom-based prescribing. In practice, specific behaviours such as high emotional dysregulation and uncontrolled exercise are the factors that lead to medication prescribing, rather than the diagnosis of AN alone.

The studies included in this review all reported varying findings with regards to the safety of psychotropic medications in the treatment of AN in adolescents. Two of the RCTs did not find any significant differences between the medication groups (risperidone and olanzapine) and the placebo groups. Kafantaris et al. reported that no immediate safety concerns were observed for the 10 week duration of their trial with olanzapine treatment but emphasized close monitoring for long-term use (Kafantaris et al., 2011). Pimozide treatment for AN resulted in a significant increase in serum prolactin levels in comparison to behavioural therapy in one of the RCTs (Weizman et al., 1985). Due to the heterogeneity of reporting of findings in the observational studies included in this review, the results of psychotropic safety varied. The safety of the psychotropic drugs varied based on the results of the observational studies included in this review. The most notable difference was reported by Couturier et al. where it was reported the SSRI group had a significantly lower level of bone mass density score in comparison to the control group (Couturier et al., 2013). Data from the studies that investigated pharmacotherapy with atypical antipsychotics found higher observed rates of side effects attributed to atypical antipsychotics. In the Norris et al. study, sedation was reported as the most common side effect of olanzapine as

reported by the 43 female adolescents in the group in comparison to those not on olanzapine (Norris et al., 2011). Frank et al. reported significantly higher proportions of patients had anxiety and major depressive disorder on discharge compared to the matched control group (Frank et al., 2017). Similarly, the reported comparisons made in the study by Holtkamp et al. found higher scores in depressive symptoms (DIKJ scores) and psychopathology (ANIS scores) in the SSRI group at the end of the 10 weeks study period (Holtkamp et al., 2005). Together, these data suggest that there is a lack of evidence for effectiveness of pharmacotherapy but there is some evidence of potential harm.

4.6.1 Strengths and limitations

In all the studies, although limited by deficiency, the findings have failed to demonstrate a clear benefit of the use of psychotropic drugs for the treatment of AN in adolescents. The use of antipsychotics has been shown to help with weight gain in some observational studies despite reports of higher rates of side effects. The greatest limitation of the studies was the small sample size in the trials. This led to a decreased power to detect differences in effects and can be seen in the large confidence intervals found in most of the analyses. Another important limitation was the short length of study duration or a lack of follow-up period in the trials. Additionally, patient to patient variability, the adherence of patients to their drug treatment and the dosage of medications given varied in each study, proved difficult to demonstrate a benefit for medication use. Another methodological shortcoming was the reporting of the outcomes. Weight change was identified as the primary outcome and medication safety as the secondary outcome in this review, however the reporting of these outcomes varied between studies due to a lack of a common numerator, and prevented aggregation of the results for further analysis such as a meta-analysis. Systematic reporting of the results would allow for better comparisons of the studies to be made.

4.7 Conclusion

In conclusion, the findings from this review fails to provide strong evidence for any increase in weight associated with the use of psychotropic drugs in adolescents with AN. With the current evidence available for the effectiveness of psychotropic drugs in weight gain and their safety in adolescents with AN, there is no consensus for their use in routine clinical practice. In addition, I found some evidence of harmful effects that may be associated with psychotropic medication use. These preliminary findings demonstrate a need for further exploration of the therapeutic efficacy and safety of psychotropic medications in the treatment of adolescents with AN.

Chapter Five

A survey on self-reported psychotropic drug prescribing practices of eating disorder psychiatrists for the treatment of young people with anorexia nervosa

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Outline

The results from the systematic review (Chapter 4) indicate a gap in studies investigating pharmacotherapy in patients with anorexia nervosa. The purpose of this chapter is to report and provide a better understanding of pharmacotherapy in AN treatment, as provided by eating disorder specialists in England. The majority of the findings from this study has been published as Y Beykloo, M., Nicholls, D., Simic, M., Brauer, R., Mills, E. & Wong, I. C. K. 2019. Survey on self-reported psychotropic drug prescribing practices of eating disorder psychiatrists for the treatment of young people with anorexia nervosa. *BMJ Open,* 9**,** e031707.

5.1 Introduction

As a psychiatric illness that is characterised by severe weight loss, fear of weight gain and body shape conflicts, AN poses a great risk for physical, social and emotional impairment to the adolescent population (Balestrieri et al., 2013). In instances where a potential diagnosis for AN is made by a healthcare professional in a primary health care setting, the NICE guideline (NICE, 2018) recommends the involvement of a physician with an appropriate specialism in the treatment of AN. Patients with AN are recommended by NICE to be under the care of secondary care services such as dedicated CYP EDS. Most dedicated CYP EDS offer evidence based psychological interventions as the primary intervention, delivered within the context of a multidisciplinary team (MDT). One of the roles of the MDT is to recognise and manage complications associated with AN, such as medical instability and comorbidities. In order to better understand the treatment provided CAED psychiatrists, it is important to explore medication prescribing practices for the treatment of individuals with AN.

During the past decade, psychotropic medications have played a notable role in the management of some psychiatric disorders in children and adolescents (Balestrieri et al., 2013), predominantly stimulants (Man et al., 2017), SSRI antidepressants (Murray

et al., 2004) and atypical antipsychotics (Rani et al., 2008). Despite a lack of guidelines for the use of antidepressant and antipsychotic medications in the treatment of eating disorders like AN (Couturier and Lock, 2007, McKnight and Park, 2010), they are sometimes prescribed to treat the symptoms associated with AN or to treat comorbidity, particularly if there is a less than optimal treatment response with first line psychological treatments (Gowers et al., 2010a). A retrospective chart review study in the United States investigated the rates of psychopharmacological medication use in adolescents and young people in the US that were referred to adolescent medicine-based eating disorder programs for the treatment of eating disorders (Monge et al., 2015). They found that at one year follow-up, psychopharmacological medications continue to be prescribed at a high rate (58.7% compared to 20.4% at intake) in adolescents and young people with AN. Similarly, a study in the US aimed to investigate the use of psychotropic medications in women with AN between 1997 and 2009 and found that the use of atypical antipsychotics had doubled during the study period, from 8.9% to 18.5%, while the use of antidepressants had remained stable (Fazeli et al., 2012).

A small number of clinical trials and observational studies focus on the safety and efficacy of atypical antipsychotics, specifically olanzapine, as adjuncts to treatment of AN (Mondraty et al., 2005, Brambilla et al., 2007, Bissada et al., 2008, Kafantaris et al., 2011, Norris et al., 2011). The focus on olanzapine in clinical and research practice may be due to its favourable safety and efficacy profile derived from the daily practices of health care professionals, which encouraged researchers to conduct more studies with a focus on olanzapine to determine the evidence behind prescribing practices of health care professionals. Based on this, it is important to explore the prescribing practices of psychotropic drugs with emphasis on olanzapine prescribing by eating disorder psychiatrists in a specialist secondary care setting for individuals with AN. This will provide a better understanding of AN pharmacotherapy in practice

as there is currently no evidence base for prescribing antidepressants or antipsychotics for young people with eating disorders. It will also contribute to the limited knowledge of current prescribing by providing a template for prescribing protocols for future research.

5.2 Aim

This study aimed to explore contemporary prescribing practices of specialist CAED psychiatrists prescribing in a specialist secondary care setting for individuals with AN, with special emphasis on olanzapine.

5.3 Objectives

i. To identify the drugs that are most commonly prescribed by specialist CAED psychiatrists for the treatment of young people with anorexia nervosa; including the initiation dose, the frequency, and the maximum dose of the drugs
ii. To describe the prescribing practices of CAED specialists for the treatment of young people with anorexia nervosa
iii. To describe the procedure for continuing pharmacotherapy in young people with anorexia nervosa by the specialist CAED psychiatrists.

5.4 Methods

5.4.1 Study design

The design of this study was of an exploratory cross-sectional self-reported survey. The questionnaire can be found under Appendix 6.

5.4.2 Development of questionnaire

The study was conducted using a questionnaire tool that was developed to explore three main areas; a) the proportion of patients with AN prescribed psychotropic medications and frequency of the medication reviews (pattern of

psychopharmacological care), b) the most common medications prescribed for young people with AN, dosage and protocol for monitoring side effects (medication treatment pattern) and c) the process of continuing pharmacotherapy. The questionnaire had a total of 10 questions; two related to the pattern of psychopharmacological care provided by eating disorder psychiatrists, four related to the medication treatment pattern, three related to pharmacotherapy continuation and one on consent for future studies.

5.4.3 Survey participants

In October 2016 South London and the Maudsley and Great Ormond Street Hospital NHS Trusts were awarded a training grant by Health Education England (HEE) to develop a training programme implementing the Community Eating Disorders Whole Team Training Specification (Health Education England, 2016). The main aims of the programme were: a) to equip whole teams with the basic knowledge and skills needed to provide an expert eating disorders service to CYP, b) use this increase in knowledge and skills to maximise their impact as multi-disciplinary teams, and c) support the ongoing process of team development. The training took place over a year (2017-18). The 77 CYP EDS teams across England, which included both well-established teams and newly developing ones, were invited to take part. All members of the multidisciplinary team, including psychologists, psychotherapists, nurses, psychiatrists, paediatricians, dietitians, were invited. The population targeted for this study was all the CAED psychiatrists from the 77 CYP EDS teams in England who had attended the Health Education England national training days in June to September of 2017. However, 13 of the CYP EDS teams had no psychiatrist in post at the time of the programme.

5.4.4 Data source & collection

Questionnaires were distributed by two consultant CAED psychiatrists (Dr Dasha Nicholls and Dr Mima Simic), to all CAED psychiatrists who attended the HEE national

training held in the summer of 2017. These CAED psychiatrists represented child and young people eating disorder services in England. Questionnaires were collected at the end of the training day. Participants who did not return their questionnaires were followed-up by email in order to improve the response rate.

5.4.5 Ethical consideration

Ethical approval was not required for this study as the research involved the use of non-sensitive, completely anonymous educational survey, however, consent was obtained from all participating psychiatrists. Content and face validity were checked by two senior consultant CAED psychiatrists (Dr Dasha Nicholls and Dr Mima Simic), who assessed whether the questionnaire was likely to elicit the desired outcomes and whether the content was readable, feasible and the layout and design were clear.

5.4.6 Statistical analysis

The data were entered on a Microsoft Excel database independently by two reviewers (myself and Kirstie Wong) and results were compared to ensure homogeneity of data documentation. The descriptive analysis was reported as mean (μ) ± SD for quantitative variables using STATA version 14.0. Descriptive statistics were used to describe the respondents' basic information. Categorical data was reported as percentages and frequencies. Graphical representation of the data was also displayed. This provided a summary of the results collected from the questionnaires, allowing simple interpretations of the data to be made. Similarly, it allowed assessment of any patterns that may arise from the results.

5.5 Results

A total of 44 CAED psychiatrists from England participated in the study (Figure 6). As 13 of the CYP EDS had no psychiatrists in post at the time of the study, this accounted for 69% [44/(77-13)] of child and adolescent psychiatrists treating CYP with ED in England who had attended the training day.

Figure 6. Showing the geographical location of the CYP EDS as represented by the CAED psychiatrists who responded

5.5.1 Patterns of psychopharmacological care

Psychiatrists were questioned in this survey to estimate the proportion of young people with AN under their care, for whom they prescribe psychotropic medications. Results are presented in Table 4, with 40% of CAED psychiatrists estimating that under 10% of the individuals with AN in their service are prescribed psychotropic medication.

Table 4. Percentage of young people with AN on prescribed psychotropic medication treatment as estimated by CAED psychiatrists in their service

Percentage of patients on psychotropic medication in your service	< 10%	10 - 20%	20 - 30%	30 - 40%	40 - 50%	50 - 60%	60 - 70%	70 - 80%	> 80%
Percentage of psychiatrists answering affirmatively (%)	40	22.5	15	17.5	0	2.5	0	2.5	0

Nearly a third of CAED psychiatrists reported that they met with their patients for whom they have prescribed, once a week during the first 18 weeks of treatment initiation. Majority of CAED psychiatrists (38%) reported meeting their patients every two weeks and 22% met their patients for a medication review once a month on average (Figure 7).

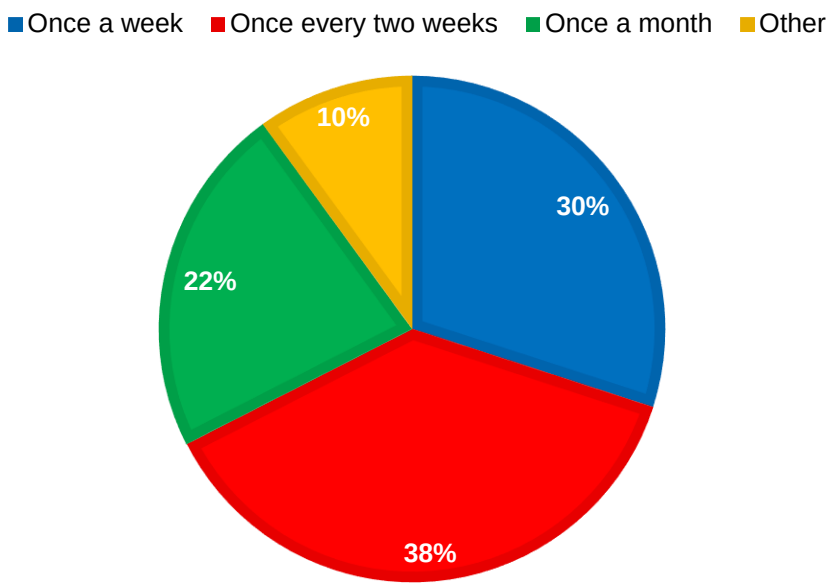

Figure 7. CAED psychiatrists' response to the average frequency of visiting individuals with anorexia nervosa in the first 18 weeks of initiating treatment

5.5.2 Patterns of medication treatment for child and adolescent AN

Psychiatrists were asked about medications specifically prescribed for AN, with olanzapine being the most commonly prescribed psychotropic medication for the treatment of children and adolescents with AN (38% of psychiatrists). The second most commonly prescribed medication for AN was fluoxetine (29%), followed by sertraline (10%), non-specified SSRIs (9%), risperidone and quetiapine (4%), citalopram (3%) and aripiprazole (1%) (Figure 8).

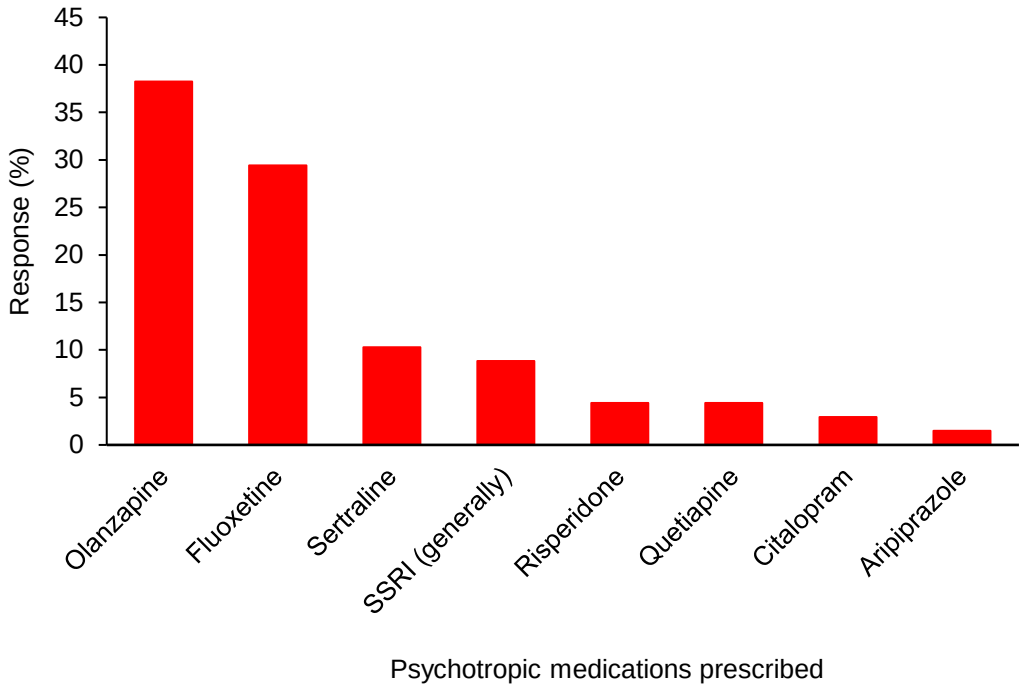

Figure 8. Response of CAED psychiatrists' to their most common psychotropic medication prescribed for young people with anorexia nervosa

Prescribing olanzapine as first choice psychotropic medication was reported by 40% of psychiatrists (Figure 9). This was followed by fluoxetine (35%), non-specified SSRIs (15%), sertraline (8%) and risperidone (3%).

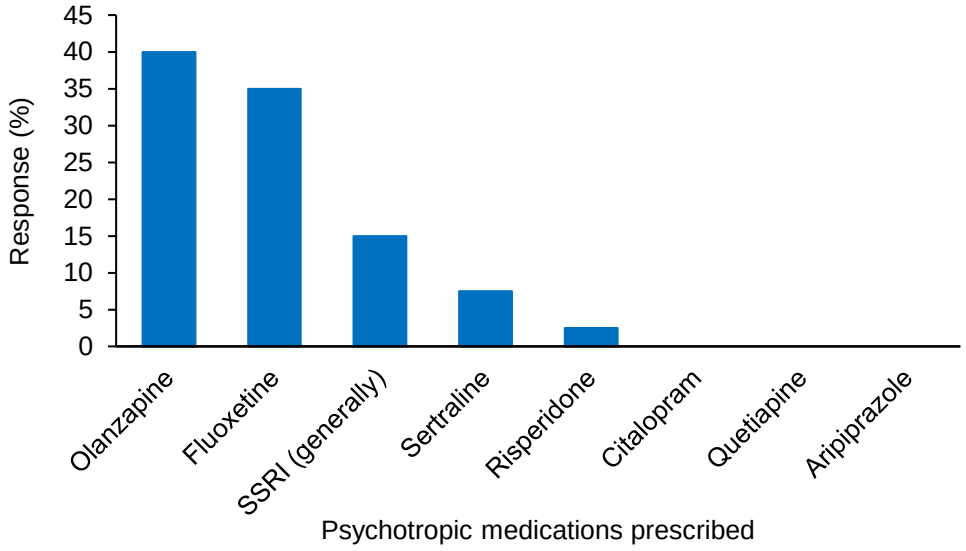

Figure 9. Response of CAED psychiatrists' to their first choice of psychotropic medication prescribed for young people with anorexia nervosa

Similarly, as second choice for the prescription of psychotropic medication in young people with AN, olanzapine was commonly selected by 33% of psychiatrists (Figure 10). Fluoxetine was selected by 22% and closely followed by sertraline with 19% of participants selecting it as second choice medication. Other psychotropic medications prescribed as second choice treatment includes quetiapine (8%), risperidone (6%), citalopram (6%), aripiprazole (3%) and non-specified SSRIs (3%).

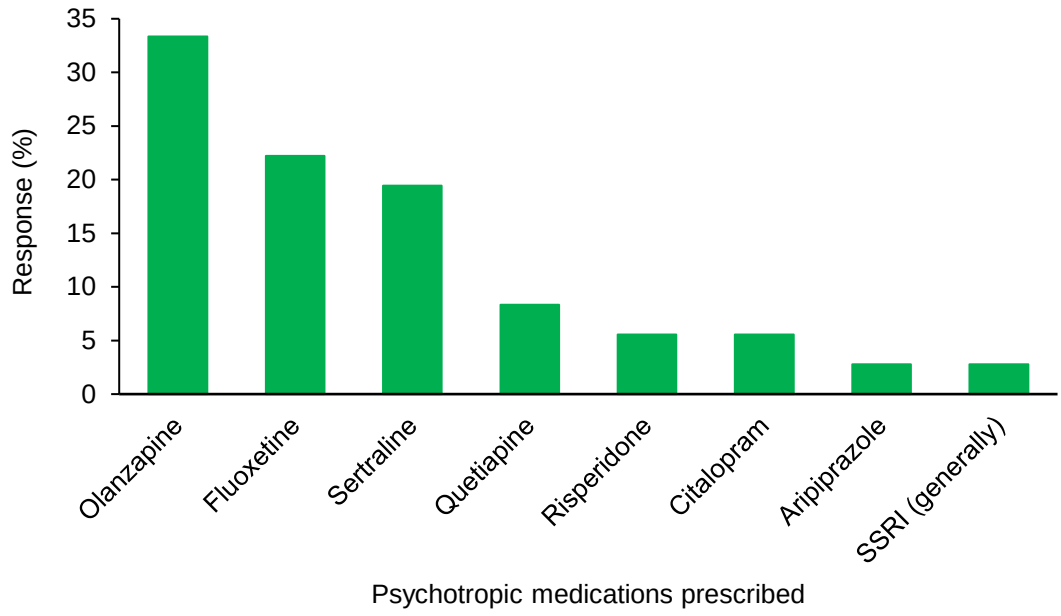

Figure 10. Response of CAED psychiatrists' to their second choice of psychotropic medication prescribed for young people with anorexia nervosa

5.5.3 Olanzapine treatment pattern

The majority of psychiatrists (69%) reported initiating olanzapine at a dose of 2.5mg daily. 28% reported initiation at a dose lower than 2.5mg/day, whereas a small percentage (3%) reported initiating olanzapine at a dose higher than 2.5mg/day (refer to Figure 11).

The starting dose of olanzapine was reported to be given for various durations before considering increase or reduction in the dose. The most common lengths of durations of olanzapine at the initial dose was less than a month (54%), and one to two months (39%). Only 7% of participants responded that they would give olanzapine at the initiation dose for more than two months (refer to Figure 12).

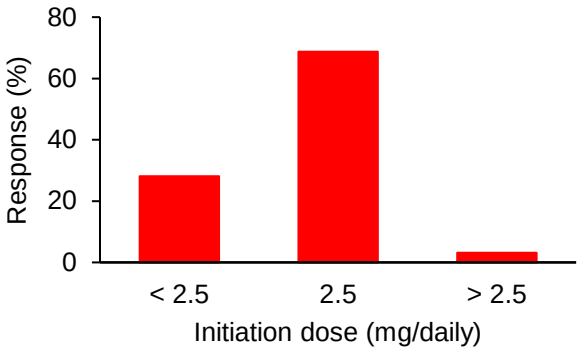

Figure 11. Proportion of CAED psychiatrists' response to daily initiation dose of olanzapine

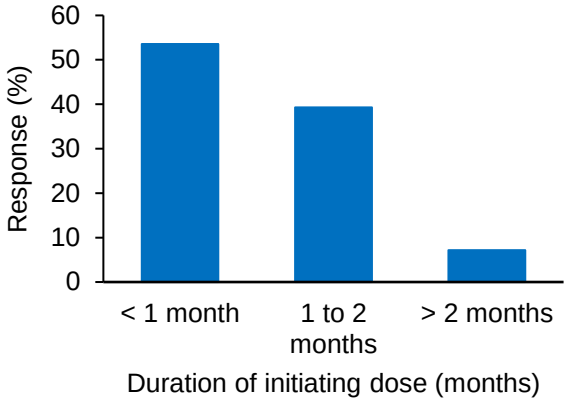

Figure 12. Proportion of CAED psychiatrists' response of duration for initiating olanzapine dose

Respondents were asked for information about their practice in escalating the dose and duration of olanzapine treatment in young people with AN. Over half of the psychiatrists (58%) reported that they increase the dose in 2.5mg increments while 35% stated that the incremental step in dosing was 1.25mg or less. Most psychiatrists reported increasing the dose of olanzapine in steps either every two weeks (35%) or under two weeks (30%), while 35% increased it every 2-4 weeks or monthly. Over half of the psychiatrists (53%) responded that the maximum prescribed dose of olanzapine was 5mg daily (Figure 13). Similarly, the majority (58%) reported the total duration of olanzapine treatment to be under six months (Figure 14).

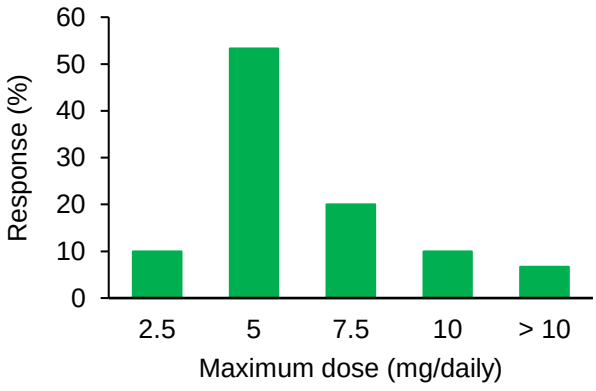

Figure 13. Proportion of CAED psychiatrists' response to maximum daily dose of olanzapine

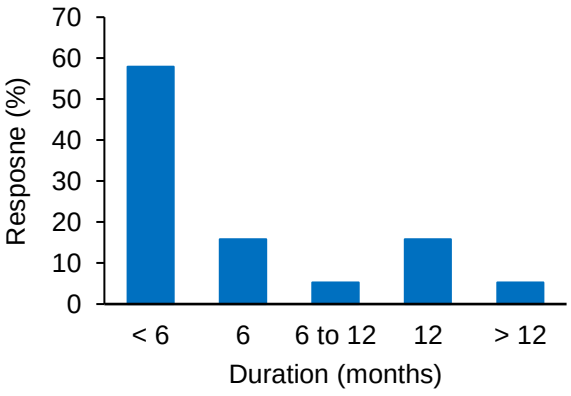

Figure 14. Proportion of CAED psychiatrists' response of duration for maximum olanzapine dose

A summary of the responses from psychiatrists regarding the initiation, escalation and maximum dosage and duration of olanzapine can be found in the table below (Table 5).

Table 5. Summary of responses regarding olanzapine treatment pattern

Initiation			
Dose	**Number of participants (%)**	**Duration**	**Number of participants (%)**
< 2.5mg	9 (28)	< 1 months	15 (54)
2.5mg	22 (69)	1 – 2 months	11 (39)
> 2.5mg	1 (3)	> 2 months	2 (7)
Escalation			
Dose	**Number of participants (%)**	**Duration**	**Number of participants (%)**
< 1.25mg	3 (12)	< 2 weeks	7 (30)
1.25mg	6 (23)	2 weeks	8 (35)
1.25 – 2.5mg	2 (8)	2 to 4 weeks	3 (13)
2.5mg	15 (58)	> 4 weeks	5 (21)
Maximum			
Dose	**Number of participants (%)**	**Duration**	**Number of participants (%)**
2.5mg	3 (10)	< 6 months	11 (58)
5mg	16 (53)	6 months	3 (16)
7.5mg	6 (20)	6 to 12 months	1 (5)
10mg	3 (10)	12	3 (16)
> 10mg	2 (7)	> 12 months	1 (5)

Majority of the psychiatrists (76%) stated that a monitoring protocol or guidance is available for olanzapine use in young people with AN in their service, including laboratory tests (liver function, prolactin, HbA1c, lipids and urea & electrolytes), anthropometrics (weight, height, body mass index and weight circumference), side effects experienced (sedation, drowsiness and metabolic side effects), symptoms experienced (e.g. psychiatric) and cardiac outcome measurements (electrocardiogram, pulse and blood pressure).

5.5.4 Patterns of olanzapine treatment continuation

Almost all (98%) of CAED psychiatrists reported that they inform the GPs about the treatment procedures undertaken with regards to olanzapine. Similarly, 97% of CAED psychiatrists reported that olanzapine prescribing is initiated from their service for the treatment of young people with AN rather than in primary care.

The findings for transfer of prescribing of olanzapine to the GPs to continue treatment varied between psychiatrists. Just over half of psychiatrists who responded to the survey (51%), stated that they would not pass prescribing of olanzapine to the GPs. The reasons for not passing on olanzapine prescribing to the GPs included that the patients must be stabilised in order to pass prescribing, or the patient must be over the age of 16-18 years, or only if the treatment will be for long term, or the GP declined to be involved with prescribing olanzapine to young people with AN. For the remainder, prescribing was on a shared care basis, with GPs prescribing with CAED psychiatrist oversight and clinical review.

5.6 Discussion

This study has found that CAED psychiatrists self-report prescribing psychotropic medications for young people with AN. To the best of my knowledge, this is the first study to address pharmacotherapy approach by CAED psychiatrists worldwide, specifically olanzapine, for the treatment of young people with AN in England. There is currently a paucity of evidence in the use of psychotropic medications for AN,

particularly in children and adolescents. This study highlights the need for further trial evidence for the use of medication in eating disorders, and what doses of medications should be used. The findings of this study are representative and generalisable within England, as this study targeted all 77 child and adolescent eating disorder service teams that exist in England, of which 69% responded.

The majority of CAED psychiatrists responded that under 10% of their patients were on psychotropic medications. This is significantly lower than what was reported in a US study that investigated the prescribing practice in eating disorders, which found that around 60% of patients with restrictive ED were prescribed psychotropic medication, most commonly SSRIs (Monge et al., 2015). In our English sample, only a few psychiatrists responded that the proportion of young people with AN on medication lies between 50-80%. This difference could be due to the inclusion of restrictive ED in the US sample, which may consist of conditions other than just AN and are associated with higher rates of comorbidities. Cultural differences between prescribing practices in England and the US must be accounted for. In the US study, respondents were mainly adolescent medicine doctors (paediatricians) rather than psychiatrists, reflecting cultural differences in service organisation. In addition, practice guidelines are clearer on the lack of evidence for prescribing in England as stated by NICE (NICE, 2018).

This study found that olanzapine is the most common psychotropic medication prescribed for the treatment of AN. This is in line with other studies conducted in the last decade (Kafantaris et al., 2011, Norris et al., 2011). A previous UK study conducted on drug prescribing in CAED services using case notes found that 26 different drugs were used for anorexia nervosa treatment, with fluoxetine and olanzapine being the most widely used medications (Gowers et al., 2010a). However, large randomised controlled trials, which are needed to support evidence-based

olanzapine prescribing (Brambilla et al., 2007, Mondraty et al., 2005, Mehler-Wex et al., 2008, Attia E, 2019), are lacking.

In terms of prescribing practice, my findings were comparable to other studies for the most common initial olanzapine dosage and duration. CAED psychiatrists reported prescribing initial doses of 2.5mg daily for less than 1 month. Kafantaris et al.'s study used olanzapine or a matching placebo, with an initial single oral dose of 2.5mg daily for one week (Kafantaris et al., 2011). Similarly, Kafantaris et al. reported increasing the dose of olanzapine by 2.5mg each week. My study found that the majority of psychiatrists escalated treatment dosage and duration by 2.5mg increments every 2 weeks and less. This could be because the smallest available oral dose is a 2.5mg tablet, thus it is easier for psychiatrists to alter the dosage of treatment accordingly and more convenient for individuals with AN to comply with their psychotropic medications.

This study found that the maximum reported dose of olanzapine prescription for young people with AN is 5mg/day, as reported by over half of the CAED psychiatrists (53%). However, this result was contrary and lower to previous studies, which have reported a maximum target dose of 10mg daily during the duration of their studies (Bissada et al., 2008, Kafantaris et al., 2011). Another study has reported the maximum olanzapine dose used as 7.5mg/day in 43 adolescent females aged 10 to 17 years old, of whom 31 were diagnosed with AN (Norris et al., 2011). Similarly, Gowers et al. found that the median dose of olanzapine prescribed was 7.5mg per day, with doses ranging from 1.2 to 20mg daily in some cases (Gowers et al., 2010a). These differences in dosage could be due to a lack in guidelines on psychotropic treatment in AN and are based on empirical judgements and experiences of the CAED psychiatrists.

This study found that the transfer of prescribing to GPs was different between CAED psychiatrists. Amongst those that believed a shared care approach must be taken,

the importance of GPs prescribing with the oversight and clinical review of CAED psychiatrists were emphasised. Those that responded they would not pass prescribing onto GPs expressed varied explanations, of which all primarily emphasised on the care of the patient. A study by Redmond et al. (2016) has highlighted the importance of coordination of care in complex illnesses as incomplete or inaccurate communication due to transitions of care between health care providers can lead to medication discrepancies and ultimately patient harm (Redmond et al., 2016).

5.6.1 Strengths and limitations

One of the main strengths of this study is that it is the first questionnaire conducted amongst eating disorder psychiatrists on pharmacotherapy in young people with AN. Thus, it provides a more detailed view on the prescribing practices of these individuals in England. Secondly, this study surveyed 69% of CYP EDS in England, which reflects their practices on a national level. Thirdly, the findings of this chapter were based on real-life practices by surveying practicing healthcare professionals.

This study did not investigate why psychiatrists are prescribing psychotropic medications with very little evidence to support their practices. This could be due to the lack of evidence for efficacy, as the literature primarily focused on diagnosis-based, rather than symptom-based prescribing of psychotropic medication (Gowers et al., 2010a). In practice, it is specific behaviours such as uncontrolled exercise & high emotional dysregulation that lead to the prescribing of psychotropic medications, and not the diagnosis of AN alone. Furthermore, the reasoning behind prescribing psychotropics by CAED psychiatrists was not questioned, making the results harder to interpret as they may have been prescribed for psychiatric comorbidities in children and adolescents with AN and not solely for the eating disorder itself. In order to ensure a good response rate was obtained for this study, this questionnaire was created in a short and simple format. As such, a limitation of this study was that I did not include

open ended questions which would have allowed us to investigate barriers to, limitations and enhancing factors of pharmacotherapy in individuals with AN in more detail. Similarly, as this was a self-reported survey, recall bias may be a contributing factor which must be acknowledged as it is not an entirely objective measure. Recall bias is identified as a systematic error that occurs when participants do not or cannot remember previous experiences accurately or omit details, thus questioning the accuracy and volume of the events. In addition, social acceptability may have led to CAED psychiatrists overestimating aspects of the survey. This is sometimes referred to as a response bias and may occur due to reasons ranging from misunderstanding proper measurements to social desirability bias where the participants may subconsciously want to look good in the survey (Rosenman et al., 2011).

5.7 Conclusion

In conclusion, this study found that despite a lack of strong evidence, psychotropic medications are prescribed, most commonly olanzapine, for the treatment of young people with AN, either as an addition or alternative to psychotherapy.

5.7.1 Implications for clinical practice and future research

The results from this study highlight the prescribing of psychotropic medications, specifically olanzapine and fluoxetine, for the treatment of AN as reported by CAED psychiatrists in England. This reflects the current practice of these specialists and is of particular importance due to the limited literature available on pharmacotherapy in understudied conditions such as AN. Further studies are needed to characterise prescribing practices of psychiatrists, and to explore the effects of these practices on patients' outcomes. Planned future works can include other qualitative study designs, such as interviews and focus groups, to enable us to generate thorough in-depth information in order to attain further information on pharmacotherapy in young people.

Summary

- First questionnaire study to address pharmacotherapy approach in anorexia nervosa in young people in England.
- This study found that olanzapine is the most common psychotropic medication prescribed for the treatment of AN.
- Continuation of care from secondary to primary care settings varied between CAED psychiatrists.
- Findings were based on real-life practices by surveying practicing healthcare professionals.

Chapter Six

Incidence, prevalence and comorbidities in anorexia nervosa, 1996-2016: a retrospective population based descriptive study using The Health Improvement Network (THIN) database

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Outline

The previous chapters have shown that there are gaps in current literature on eating disorders like AN. Thus far, AN appears to be an understudied topic, which must be explored. One area for exploration of AN is that of primary care, which are the first point of contact in the healthcare system in the UK. Therefore, as part of this PhD project, THIN database was used to identify a large cohort of patients with a diagnosis of AN. The incidence and prevalence of AN in the database are described in this chapter.

6.1 Introduction

It is thought that over 1.6 million people in the United Kingdom (UK) are affected by eating disorders, although this number may be an underestimation due to the high numbers of people who have an eating disorder but do not have a formal diagnosis (Joint Commissioning Panel for Mental Health, 2013). Of these, AN is the least prevalent but carries the highest morbidity, mortality, burden and cost (Joint Commissioning Panel for Mental Health, 2013). Eating disorders like AN are also often accompanied by a sense of distress, loss of control and feelings of depression or guilt (Flament et al., 2012). Due to the vulnerability of this cohort, there has been a lack of studies assessing individuals with AN with severe comorbid conditions and their long-term outcomes. The King's Fund reported that the service costs for eating disorders were an estimated £15.7 million in 2007, with 95% accounted for by AN related costs (McCrone P, 2008), primarily due to high proportions of admissions and long lengths of hospital stay (Thompson et al., 2004).

Studies have suggested some evidence in current literature on the similarities of psychopathology, genetics and neurobiological factors involved in eating disorders and other psychiatric symptoms and diseases. The most common comorbidities in individuals with AN are reported to be major depressive disorders, anxiety disorders

and OCD (O'Brien and Vincent, 2003a, Woodside and Staab, 2006). However a recent review (Marucci et al., 2018) has also reported comorbidities such as developmental disorders (like ASD and ADHD), personality disorders and borderline traits among AN individuals. They also highlighted that to ensure appropriate therapeutic management of AN, accurate diagnosis and assessments of psychiatric, psychological, somatic and nutritional risks for of great importance (Marucci et al., 2018).

The most recent study using routinely collected health care data reporting on the incidence of AN was conducted in 2012, where data from the General Practice Research Database (GPRD) was used from 2000 to 2009 (Micali et al., 2013). The age standardised annual incidence rate of all diagnosed eating disorders in patients aged 10-49 years in the year 2009 was reported to be 37.2 (95% CI 36.6 to 37.9) per 100 000 individuals. This report showed that the incidence of AN in both males and females remained stable between 2000 & 2009, despite minor fluctuations across the years. The importance of this study in evaluating the extent of AN has been reiterated in many studies, however contemporary data are needed to update the existing demographics of AN in the UK in the recent decade using generalisable population data.

Large computerised databases have made valuable contributions to research on various conditions and medications in primary practice (Gregory E. Simon et al., 2000). They allow for questions and hypotheses to be formulated and addressed in future studies. The study reported in this thesis has examined all the available data in the THIN database in order to 1) measure the incidence and prevalence of AN annually from 1996 to 2016, and 2) describe the comorbidity characteristics, in particular psychiatric comorbidities, experienced by the AN population before and after diagnosis.

6.2 Aim

The aim of this study was to use primary care medical records data to assess the incidence, prevalence and most common comorbidities in individuals diagnosed with anorexia nervosa in the UK from 1996 to 2016.

6.3 Objectives

i. To calculate the annual incidence and prevalence of anorexia nervosa in individuals on the THIN database from 1996 to 2016 by gender and age groups
ii. To describe the psychiatric, cardiac, bone, reproductive and nutrient and metabolic imbalance co-morbidities associated with individuals with anorexia nervosa by gender.

6.4 Methods

6.4.1 Study design

This study is a descriptive longitudinal observational study. The benefit of this study is that all the findings and outcomes can be described and calculated in order to generate new hypotheses and in-depth analytical studies in the future. It is ideal for estimating both the incidence and prevalence of a condition in a population, monitoring comorbidities, risk factors and health outcomes and can be repeated at various time points in order to assess the trends of a condition over time (Sedgwick, 2014).

6.4.2 Data source

This study was conducted using The Health Improvement Network (THIN) database. For more information on the data source, please refer to Chapter 3 on THIN.

6.4.3 Study population

The study population comprised a cohort of individuals in the THIN database who had a diagnosis of AN in their medical record between 1st January 1996 and 31st December 2016 and were registered with a GP for at least 6 months prior to AN diagnosis. Whilst GPs can diagnose individuals with eating disorders, most of the AN recordings in THIN will have been recorded by a GP following the receipt of correspondence from a secondary health care setting, such as a hospital or a specialist eating disorder clinic (NHS, 2018). The codes used to identify individuals with AN have been previously used in other studies (Micali et al., 2013, Demmler et al., 2019) and, for the purpose of this study, were confirmed by two consultant eating disorder psychiatrists (Appendix 1). The study period was chosen as 1996 to 2016 to ensure good quality of data and accuracy of recordings. In the main analyses, I excluded individuals with a diagnosis of AN who were younger than 12 years or older than 50 years. First onset AN in individuals below 12 years and over 50 years is rare (Turnbull et al., 1997, Currin et al., 2005). In addition, this chosen age range minimises diagnostic misclassification (e.g. feeding complications in children or older patients). Individuals were assigned the birth day and month of 1st July in their known year of birth. Follow-up started on 1 January 1996, 12th birthday, registration date with general practice, or the date that a practice started to contribute valid data to THIN, whichever occurred last. Follow-up ended at the individuals' 50th birthday, transfer out of practice, death, or end of the study period (31st December 2016), whichever came first.

6.4.4 Ethical consideration

A THIN protocol was filled out and submitted for ethical approval to QuintilesIMS (data provider). Approval for the study was granted by the Scientific Review Committee (SRC) of IQVIA, with reference number 17THIN063, as stated in their application forms (Appendix 7). No ethical approvals were required from UCL because the study

was exempt THIN data are anonymised and THIN SRC permission had been obtained.

6.4.5 Data collection/extraction

Demographic information included age group, gender, and GP visits. Additionally, data was collected for the following comorbidities: psychiatric, cardiac, bone, reproductive, and nutrient & metabolic illnesses (refer to Appendix 8).

6.4.6 Main outcomes

All individuals with a recorded diagnosis of AN were screened from the start date to identify cases throughout the study period (1996-2016). This was a dynamic cohort and individuals left the cohort and were excluded if they transferred out of general practice or had died. Similarly, individuals were excluded from subsequent annual calculations once they were diagnosed with AN. Both the annual incidence and prevalence of AN were stratified by gender and age groups. Age categories were chosen in accordance with UK clinical care practice guidelines for eating disorders, as agreed with two practicing consultant eating disorder psychiatrists: 12-17 years, 18-24 years, 25-30 years, 31-40 years, and 41-50 years.

6.4.6.1 Incidence of anorexia nervosa

The annual incidence of AN was calculated by dividing the number of AN incident cases aged 12-50 years in each year by the total number of the THIN mid-year population of the same year. The annual incidence rates were stratified by age groups and gender for each year.

6.4.6.2 Prevalence of anorexia nervosa

Prevalent cases of AN were defined as all individuals with any recorded diagnosis of AN in a given year. Similar to the annual incidence, the annual prevalence of AN was calculated by dividing the number of prevalent cases in each year by the total number of the THIN mid-year population of the same year. This can be an individuals' first or

5th diagnosis code, as some individuals may have not had a recording one year but have recordings for other years, therefore were included in the analysis for each year they had a record in. This was mainly to examine the true disease burden at any given time point, considering how in AN, individuals are able to fully recover, yet relapse in future years. For AN prevalence in the year 1996, all individuals with a recorded diagnosis of AN pre-1996 were calculated.

6.4.6.3 Prevalence of comorbidities

For this, individuals were considered as having AN until the end of the study. To describe comorbidities, individuals with AN who had a record of the comorbidities of interest were identified from the total AN population between the study period (1996-2016). These comorbidities included psychiatric, cardiac, bone, reproductive and nutrient & metabolic imbalance comorbidities that are often associated with AN in current literature. A breakdown of these comorbidities is presented below (Table 6). In addition, comorbidities were also described before and after an individuals AN diagnosis. AN individuals with a first comorbidity record were assessed six months and one year prior and six months and one year after their first record of AN in THIN.

Table 6. A breakdown of the comorbidities of interest associated with AN in current literature

Psychiatric	Cardiac	Bone	Reproductive	Nutrient & metabolic imbalances
Depression	Hypotension	Osteoporosis	Dysmenorrhoea	Iron deficiency
Personality disorder	Atrial fibrillation	Osteochondrosis	Amenorrhoea	Hypothyroidism
Anxiety	Heart failure	Fracture	Endometriosis	Hyperthyroidism
Affective disorder	Cardiomyopathy			
Hallucination	Arrhythmia			
Psychosis	Pericarditis			
Cognitive disorder	Cardiac arrest			

6.4.7 Statistical analysis

Descriptive statistics were primarily reported as percentages, and where appropriate, the median and interquartile range (IQR) is given as it is robust against outliers in comparison to the mean and gives a more appropriate idea of the data distribution. Where means have been given, the 95% confidence intervals (CI) were calculated so that the range has a 95% probability of including the true value of the variable. Incidence rate ratios (IRR) adjusted for gender and age were estimated using a Poisson regression model. The analyses were adjusted for clustering at practice level. All statistical procedures were performed using STATA version 14.0.

6.5 Results

In total, 17,597 individuals with AN were identified, with 10,062 (57.18%) individuals diagnosed between 1996 to 2005 and 7,535 (42.82%) individuals were diagnosed between 2006 and 2016 (Table 7). Females made up 81.98% of the population with AN. Amongst females, the age categories most diagnosed with AN were those aged 18-24 and 12-17, which are the two youngest age categories in this study. This was similar in males aged 18-24 years, however the difference between age categories were less pronounced as those aged 31-40 and 41-50 years also had similar percentages in males.

Table 7. Characteristics of individuals with AN within THIN population

Characteristics	Overall population with AN (N=17,597) (%)	Male (N=3,171) (%)	Female (N=14,426) (%)
Number	17,597	3,171 (18.02)	14,426 (81.98)
Year of diagnosis			
1996 – 2005	10,062 (57.18)	1,823 (57.49)	8,239 (57.11)
2006 – 2016	7,535 (42.82)	1,348 (42.51)	6,187 (42.89)
Age (years)			
Median (IQR)	22 (17-32)	28 (19-39)	21 (17-30)
12-17	4,922 (27.92%)	556 (17.53%)	4,366 (30.26%)
18-24	5,226 (29.70%)	748 (23.59%)	4,478 (31.04%)
25-30	2,460 (13.98%)	444 (14.00%)	2,016 (13.97%)
31-40	2,836 (16.12%)	734 (23.15%)	2,102 (14.57%)
41-50	2,153 (12.24%)	689 (21.73%)	1,464 (10.15%)

6.5.1 Incidence of AN

The overall incidence of AN remained fairly steady, despite fluctuations from 1996 to 2006 and a slight downward trend in the most recent years (2006-2016). In 1996, the incidence of AN was found to be 15.21/100,000 person years (95% CI 15.20-15.22), increasing in 2006 to 21.84/100,000 person years (95% CI 21.83-21.85) followed by a decrease again in 2016 to 18.25/100,000 person years (95% CI 18.23-18.27).

Incidence results were stratified by gender for males and females (Figure 15). The incidence of AN in females increased by just under 50% from 23.40/100,000 person

years (95% CI 23.38-23.41) in 1996 to 34.50/100,000 person years (95% CI 34.48-34.52) in 2006 before decreasing again in 2016 to 28.50/100,000 person years (95% CI 28.47-28.52). Males were less likely to have a record of AN compared to females [adjusted IRR 0.28, 95% CI (0.25-0.32)]. Similarly to females, the incidence of AN in males increased 34% from 1996 [7.31/100,000 person years (95% CI 7.29-7.33)] to 2006 [(9.79/100,000 person years (95% CI 9.77-9.81)] and decreased by 17% from 2006 to 2016 [(8.12/100,000 person years (95% CI 8.09-8.14)].

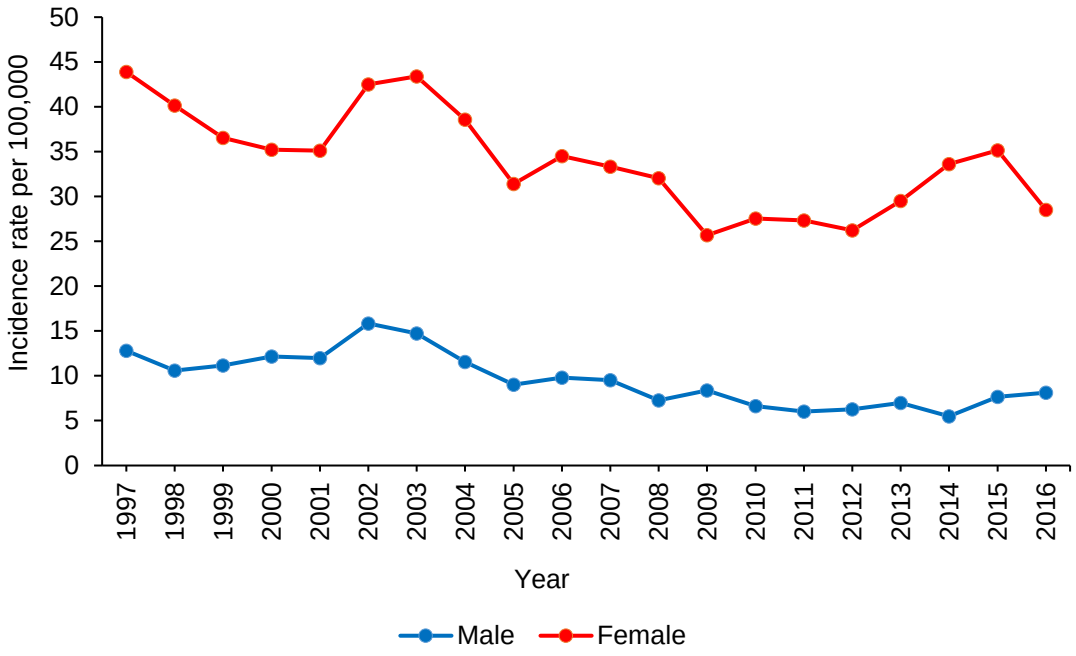

Figure 15. Incidence of AN specified by years for males and females aged 12 to 50 years. Note: the data for 1996 was omitted from this graph as it may be an artefact.

Stratification by age groups showed the overall incidence of 12-17 year olds and 18-24 year olds to be similar with 26.29/100,000 person years & 27.98/100,000 person years respectively (Figure 16). The incidence for the remaining three age groups was lower, with 41-50 year olds having an incidence of 8.44/100,000 person years. For all age groups except 12-17 year olds, there was a steady decrease in incidence of AN from 1996 to 2016.

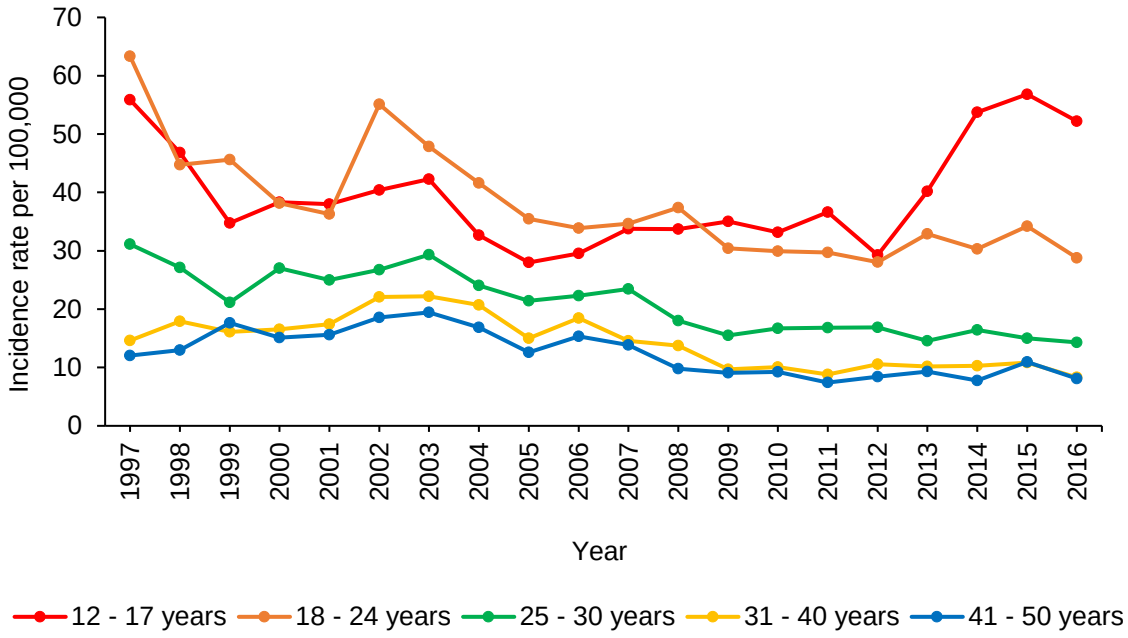

Figure 16. Incidence of AN specified by years stratified by age groups. Note: the data for 1996 was omitted from this graph as it may be an artefact.

In females, AN diagnosis was most commonly recorded in the youngest age group of 12-17 years and recording reduced with increasing age (refer to Table 8). The most commonly recorded age group for males with AN diagnosis was the 18–24 years compared to others [adjusted IRR 1.29, 95% CI (1.26-1.32)]. In 2016, the highest comparative incidence of AN was recorded in individuals aged 12-17 years, with 52.22/100,000 person years whereas the lowest incidence was observed in the group aged 41-50 years, with 8.11/100,000 person years (Figure 16). The incidence in 2016 for the remaining age groups 18-24 years, 25-30 years and 31-40 years was 28.77/100,000 person years, 14.30/100,000 person years and 8.30/100,000 person years, respectively.

Table 8. Recording of rate of individual incidence diagnosis by age and gender using multilevel poisson regression, with individuals nested in practices

Age, years	Rate per 100,000 PYAR (95% CI)		Adjusted IRR (95% CI)		P <0.001
	Male	Female	Male	Female	
12-17	11.42 (11.36-11.47)	70.16 (70.08-70.21)	1	1	
18-24	13.69 (13.64-13.73)	61.37 (61.31-61.43)	1.29 (1.26-1.32)	0.88 (0.87-0.90)	
25-30	8.55 (8.49-8.58)	33.08 (33.06-33.09)	0.85 (0.84-0.87)	0.57 (0.55-0.58)	
31-40	8.09 (8.02-8.15)	21.11 (21.09-21.12)	0.80 (0.79-0.81)	0.41 (0.39-0.42)	
41-50	8.26 (8.18-8.33)	16.49 (16.48-16.51)	0.82 (0.81-0.83)	0.32 (0.31-0.34)	

6.5.2 Prevalence of AN

Overall, the prevalence of AN in the population followed a downward trend, decreasing from 80.74/100,000 person years (95% CI 80.72-80.76) in 1996 to 45.39/100,000 person years (95% CI 45.37-45.41) in 2006 to 23.71/100,000 person years (95% CI 23.68-23.73) in 2016.

Where prevalence was stratified by gender, a sharp decrease in prevalence of AN from 1996 [(141.22 per 100,000 (95% CI 141.20-141.24)] to 2006 [(78.75 per 100,000 (95% CI 78.74-78.77)] and 2016 [(38.76 per 100,000 (95% CI 38.73-38.78)] was measured in females (Figure 17). Similarly, for males an overall decrease in the trend for AN prevalence was measured from 1996 [(22.40 per 100,000 (95% CI 22.37-22.42)] to 2016 [(8.83 per 100,000 (95% CI 8.81-8.86)].

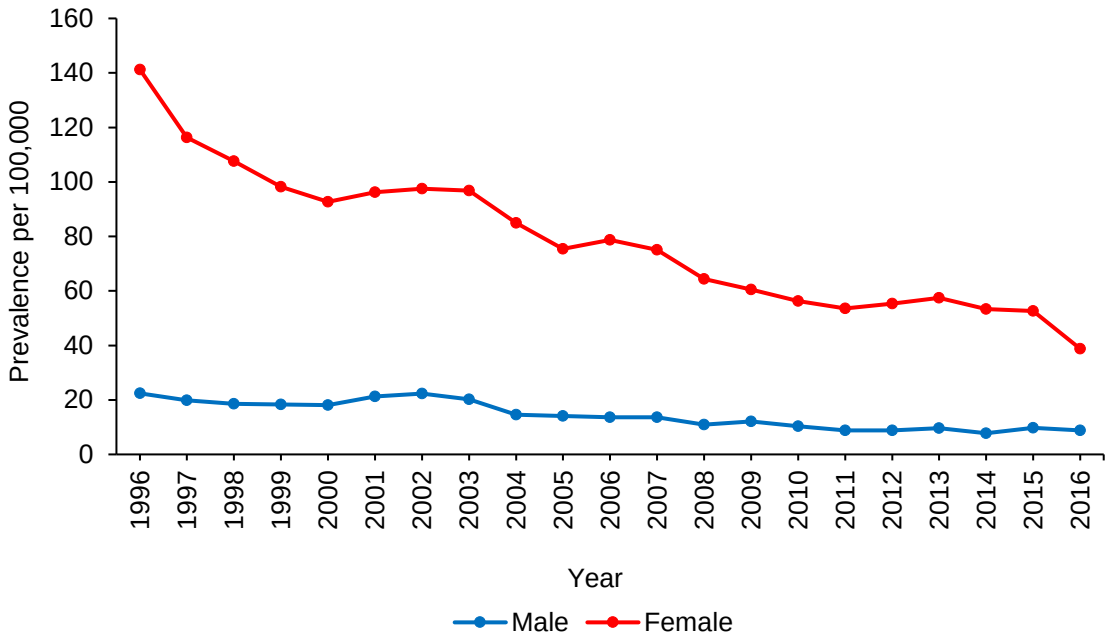

Figure 17. Prevalence of AN specified by years for males and females aged 12 to 50 years

When stratified by age groups, the highest prevalence in 1996 was observed in those aged 12-17 years (188.01 per 100,000), followed by 18-24 year olds (171.59 per 100,000), 25-30 year olds (62.68 per 100,000), 31-40 year olds (32.06 per 100,000), and 41-50 year olds (22.77 per 100,000). For all age groups, there was a steady decrease in prevalence of AN (Figure 18). In 2016, the prevalence of 12-17 year olds remained the highest out of the five age groups, with 57.25 per 100,000. The lowest prevalence was of the 41-50 year olds, with a prevalence of 8.97 per 100,000. The prevalence in 2016 in the remaining age groups was 42.23 per 100,000 for 18-24 year olds, 24.84 per 100,000 for 25-30 year olds and 10.99 per 100,000 for 31-40 year olds.

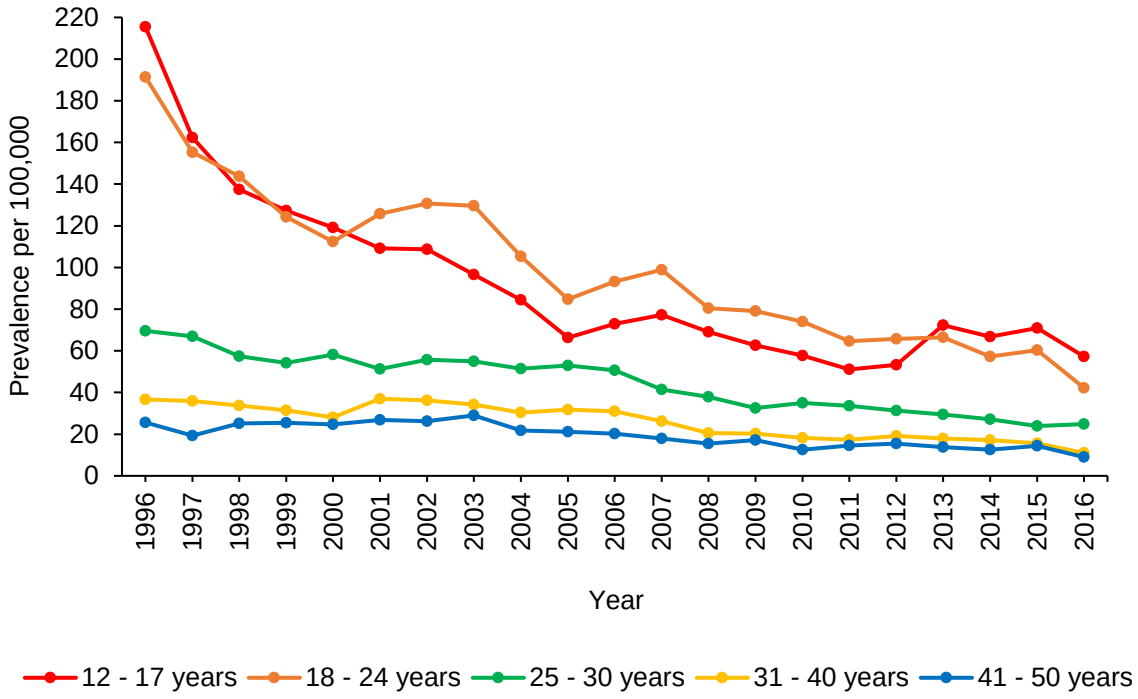

Figure 18. Prevalence of AN specified by years stratified by age groups

6.5.3 Comorbidities in anorexia nervosa

In this study, 11,040 individuals (62.74%) had a record for any comorbidity (Table 9). Psychiatric comorbidities were the most common comorbidity (45.64%) in individuals with AN, followed by reproductive (26.46%), nutrient & mineral imbalances (9.49%), bone (6.24%) and cardiac (2.68%).

Table 9. Individuals with AN with a record of comorbidities, stratified by gender (N=17,597)

Comorbidities of interest	Total AN population		Gender			
			Males		Females	
	Number	%	Number	%	Number	%
Any comorbidity	11,040	62.74	1,457	13.20	9,583	86.80
Psychiatric	8,031	45.64	1,274	87.44	6,757	70.51
Cardiac	471	2.68	110	7.55	361	3.77
Bone	1,098	6.24	155	10.64	943	9.84
Reproductive	4,656	26.46	10	0.69	4,646	48.48
Nutrient & mineral imbalance	1,670	9.49	128	8.79	1,542	16.09

When stratified by gender, comorbidities were predominantly recorded in females (86.80%) (Figure 19). This trend was reflected in all the comorbidity classifications.

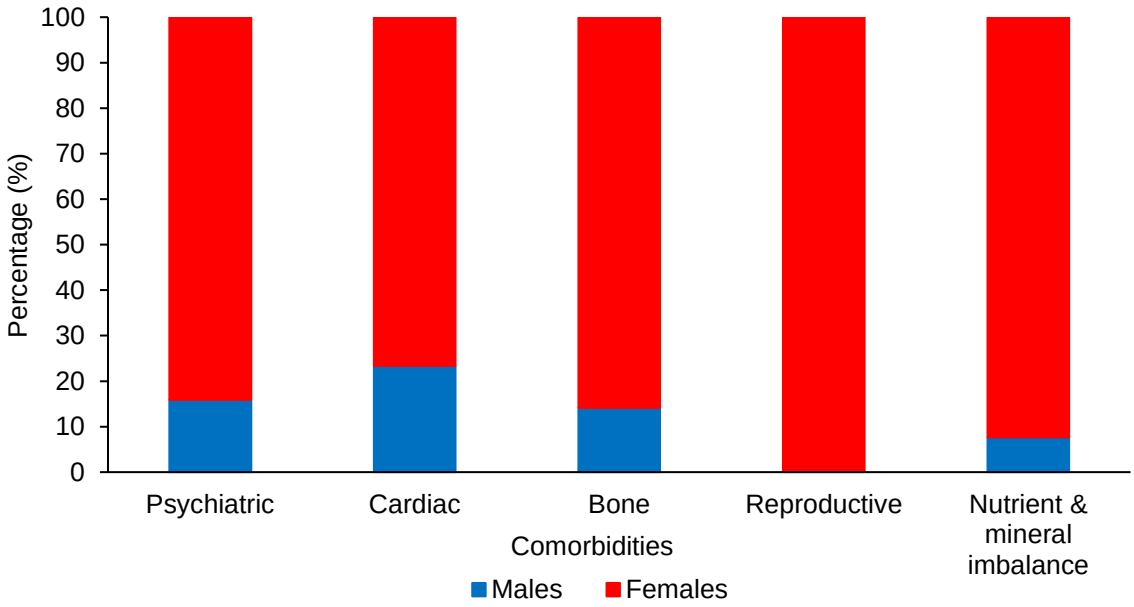

Figure 19. Percentage of individuals with AN with a first record of various comorbidities

Comorbidity classifications were subsequently stratified by specific conditions of interest. The most common comorbidity within the cardiac classification was hypotension (59.66%) and atrial fibrillation (14.23%). With regards to bone comorbidity classifications, 72.13% of AN individuals had a record of osteoporosis. Osteochondritis and fracture were also evident with 14.57% and 14.12% of individuals having a record respectively. The most prevalent psychiatric comorbidity was depression, with 91.32% of individuals with AN diagnosed. Personality disorders and anxiety were also observed among 10.06% and 6.13% of individuals respectively. Dysmenorrhoea and amenorrhoea were the most common comorbidities in the reproductive comorbidity classifications with 55.84% and 14.71% of individuals having a record within THIN. Similarly, iron deficiency and hypothyroidism were prevalent in nutrient and metabolic imbalance related comorbidities (66.11% & 35.57% respectively).

Around a fifth of individuals (20.96%) had a record for any comorbidity in the year prior to their AN record, whereas 30.55% of individuals had a record after their AN diagnosis date (Table 10). This was also reflected in the different comorbidity classifications in the year before and after AN record. Cardiac comorbidities were experienced in 11.04% of individuals up to one year before compared to 12.31% in the year after AN diagnosis, bone comorbidities were 6.65% to 16.21%, psychiatric comorbidities were 17.72% to 28.85%, reproductive comorbidities were 15.94% to 17.70% and nutrient & metabolic imbalance comorbidities were 9.40% to 13.47% respectively.

Table 10. Individuals with AN with a first comorbidity record before and after their AN diagnosis (N=17,597)

First record of comorbidity	Before AN diagnosis		After AN diagnosis	
	Up to one year (%)	Up to six months (%)	Up to six months (%)	Up to one year (%)
Any comorbidity	2,314 (20.96)	1,531 (13.87)	2,441 (22.11)	3,373 (30.55)
Cardiac comorbidity	52 (11.04)	33 (7.01)	41 (8.70)	58 (12.31)
Bone comorbidity	73 (6.65)	44 (4.01)	114 (10.38)	178 (16.21)
Psychiatric comorbidity	1,423 (17.72)	939 (11.69)	1,744 (21.72)	2,317 (28.85)
Reproductive comorbidity	742 (15.94)	475 (10.20)	490 (10.52)	824 (17.70)
Nutrient & mineral imbalance comorbidity	157 (9.40)	98 (5.87)	150 (8.98)	225 (13.47)

6.6 Discussion

To my knowledge, this study provides the most up-to-date information for AN incidence and prevalence. This study found that the incidence of AN remained relatively stable from 15.21/100,000 person years in 1996 to 18.25/100,000 person years in 2016. The results describing the incidence of AN are in line with other studies using GP data in the UK, which reported that the age-adjusted and gender-adjusted incidence rate of AN remained stable over three study periods of 1988-1994 (Turnbull et al., 1997), 1994-2000 (Currin et al., 2005) and 2000-2009 (Micali et al., 2013). Increased recognition and detection of a relatively new disorders in the mid to late 1990s has been suggested by Currin et al. as a possible reason for a peak in the incidence of AN, however its true level is now thought to have been stabilised (Currin et al., 2005). With regards to the incidence trend in females, both my study and Micali

et al. (2013) have shown a decrease in the first initial years overlapped, reaching a peak in 2003, followed by a series of fluctuations in the following years. Similarly, the incidence trend in males, shows an increase in 2000 reaching a peak in 2002, followed by a drop and plateau. When comparing this study with the most recent study publication in the incidence of eating disorders in the UK by Micali et al. (2013), it must be noted that there are variations in coding, software and recording of the data used in the studies (EPIC, 2008, Petherick et al., 2015).

This study found an increase from 2012, reaching the highest incidence among individuals aged 12-17 years in 2016, with 52.22/100,000 person years, of which 83.33% were females. In 2012, the junior MARSIPAN report (management of really sick patients under 18 with AN) was formed by the College of Psychiatrists to develop guidelines for young people with AN (College of Psychiatrists, 2012). The report provided guidance on many aspects including risk assessment, physical examination, location of care and transition between services, treatment, and management in primary care and paediatric out-patient settings. This clear guidance on management in primary care allowed for better detection and provided a pathway for the referrals onto the necessary services based on the diagnosis and severity of AN. Similarly in 2015, the national collaborating centre for mental health commissioned by NHS England produced a guide for access and waiting time standard for children and young people with an eating disorder (NHS England, 2015). They provided evidence that early intervention prevents long term morbidity and specialist services are more cost effective, which resulted in more services to be set up in England. This could explain the rise in incidence from 2012, which allowed for better detection and referral of AN from primary care to specialist services. There has also been evidence in previous literature to suggest a decrease in the age of onset of AN, and a rise in childhood and adolescent AN (Smink et al., 2012). In my study, the adjusted incidence rate ratio analysis demonstrated that AN diagnosis in females was more commonly

recorded in the youngest age group of 12-17 years. A study conducted in the Netherlands using a representative GP sample of the Dutch population found the highest incidence amongst females aged 15-19 years, in which the incidence increased significantly from 56.4 per 100,000 in the latter half of 1980s to 109.2 per 100,000 in the latter half of the 1990s (van Son et al., 2006).

This study found higher incidence rates in males with AN compared to other studies which reported less than 1 per 100,000 person years based on GP data in the UK and Netherlands (van Son et al., 2006, Currin et al., 2005). However it was still found to be lower than studies based on clinical or secondary care samples (Raevuori et al., 2014). This supports the hypothesis that AN is more common among males than previously assumed, and its apparent low incidence is mainly due to different help seeking patterns (Swanson et al., 2011, Hudson et al., 2007). This was especially evident in this study in 18-24 year old males, where AN diagnosis was more commonly recorded compared to other age groups [adjusted IRR 1.29, 95% CI (1.26-1.32)].

This study found that the prevalence of AN has been decreasing annually from 1996 to 2016. It was found that although there was a steady number of new AN cases every year, the number of reoccurring AN cases was decreasing over time. This reduction in prevalence was particularly pronounced in younger aged females, although a decrease was observed in every age group, as well as in male individuals. One explanation for this decrease can be the use of broad Read codes for AN in order to fit all types. Whereas nowadays there are many subtypes for eating disorders based on diagnostic criteria, thus not allowing for differentiation of subtypes. In this study, I included atypical and not otherwise specified (NOS) AN as subtypes of AN as a whole, however there are now many variations and subtypes of eating disorders that may have previously been grouped together with AN, and have now been recognised as a stand-alone condition. In addition, there may be a hesitancy from GPs in giving

a hard diagnosis as this is often done so by specialised healthcare professionals in secondary or tertiary level of care. Therefore, this may result in an initial diagnosis of AN and upon subsequent visitations, individuals being given a code for a subtype of AN or a more specific eating disorder Read code. It has also been reported that due to the way healthcare professionals code clinical events in primary care records, prevalence of diagnoses and conditions may be underestimated, as it has been noted that clinical events may only be recorded on their first occurrence (incidence) and not for any subsequent episodes, in particular if there are no changes in the clinical management of the condition (Hansell et al., 1999). The results of this chapter describing the prevalence of AN stratified by gender are in line with other studies in which AN prevalence has been reported to be three times higher in females than males (Hudson et al., 2007). However, it is thought that AN is more common among males than previously assumed, and its low prevalence is mainly due to it being frequently undetected in the primary health care (Hudson et al., 2007, Swanson et al., 2011).

A complexity of AN is the high prevalence of medical complications which are commonly present as part of the disorder, yet often exacerbated with psychotropic medications for pharmacotherapy of AN. Comorbidities were recorded in over 60% of the cohort. Records for psychiatric comorbidities were found to be greater than other comorbidities in the AN population in THIN (45.64%). This is in line with studies that have reported over half of adolescents with AN meet the criteria for at least one comorbid psychiatric illness (Bühren et al., 2014). Studies have found that eating disorders like AN have been strongly associated with mood and anxiety disorders, which are heavily dependent on the severity of the eating disorder (Aspen et al., 2014, Westmoreland et al., 2016, Hudson et al., 2007). Similarly, this was found in Welsh primary care data by Demmler et al (2019) where diagnoses of anxiety, neurotic disorders and depressive disorders were significant in individuals with eating

disorders (Demmler et al., 2019). Psychotropic prescribing for many of these psychiatric comorbidities are fairly common (Ohayon et al., 1998), as they are often recommended by NICE guidelines for mental health and behavioural conditions (NICE, 2019b).

6.6.1 Strengths and limitations

This is the most recent and comprehensive study on the incidence and prevalence trends of individuals with AN using a large database of UK primary care records. A strength of this study includes the large sample which is representative of the general UK population. The codes used to identify AN cohort have been previously validated (Micali et al., 2013) and its sensitivity and specificity was tested through multiple sub-analyses. This study is limited to patient data as recorded by GPs from a primary care setting. AN individuals managed by secondary care, receiving alternative healthcare, or receiving purely dietetic/nutritional care would not be identified in this study. However, although the responsibility for initiating prescribing treatments and monitoring normally lays with specialists in secondary care, the information is likely to be transferred to the GP shortly after AN diagnosis (Y Beykloo et al., 2019) for continuation of care. If this transfer is not made, it can lead to an underestimation of the findings (Hoek, 2006).

6.6.2 Implications in clinical practice and future research

The findings of this study provide an insight into the burden of AN in the UK population over a 20 year period. Knowing the number of people affected with AN allows to plan appropriately for their health care needs, with regards to the service costs for the NHS in the UK. In addition, the results of this study have confirmed findings of previous studies in highlighting the most common comorbidities in the AN population to help provide context for diagnostic decision-making. Future research should be conducted in secondary care settings to assess concomitant comorbidities diagnosed in individuals with AN.

Summary

- This study found that the incidence of AN remained fairly stable over a 20 year time period.
- In 2016, individuals aged 12-17 years had the highest incidence of AN, with 52.22/100,000 person years, compared to other age groups.
- This study reported that the prevalence of AN has been decreasing annually from 1996 to 2016.
- The most common comorbidities recorded on The Health Improvement Network database for the AN population was psychiatric comorbidities.

Chapter Seven

Pharmacotherapy in anorexia nervosa, 1996-2016: a retrospective population based descriptive study using The Health Improvement Network (THIN) database

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Outline

Chapters 1 and 4 have demonstrated a current gap with regards to sufficient data on pharmacotherapy in patients with AN. In this chapter, current prescribing trends of psychotropic medication in AN within UK primary care are described.

7.1 Introduction

Treatment of AN is carried out through multidisciplinary teams, by a combination of nutritional, medical, psychological and social care (Moore et al., 2013a). The NICE guidelines on eating disorders advocate psychological therapy supplemented with outpatient care for those diagnosed with AN (NICE, 2018). There is currently a lack in evidence for the effectiveness of medications to treat AN (Couturier and Lock, 2007, McKnight and Park, 2010) and therefore they are not recommended by NICE as the sole treatment of AN (NICE, 2018). They are however, sometimes prescribed if there is a less than optimal treatment response with first line psychological treatments (Gowers et al., 2010a). During the past decade, psychotropic medications, predominantly stimulants (Man et al., 2017), selective serotonin re-uptake inhibitor antidepressants (Murray et al., 2004) and atypical antipsychotics (Rani et al., 2008) have played a notable role in the management of psychiatric disorders in children and adolescents (Balestrieri et al., 2013). Adverse events resulting from prescribed psychotropic medications such as metabolic disruptions, extrapyramidal symptoms and sexual/reproductive events are carefully considered in patients with AN due to the nature of the condition, in particular in those individuals with comorbid conditions as it can make them more susceptible to adverse events (Jerrell et al., 2010). This likelihood of experiencing adverse events can lead to an increase in the complication of the condition and difficulty in early management of AN in some cases.

A recently published RCT found a statistically significant difference in weight gain, as a measure of BMI increase, over time when adults with AN receiving olanzapine

treatment and placebo were compared (Attia E, 2019). Although a modest therapeutic effect of olanzapine was documented, it failed to show a significant benefit for psychological symptoms of AN. The study is thought to be the largest medication trial conducted in AN population up to date, however it is not known how many patients receive treatment with psychotropic agents outside of clinical trials. Other studies have also tried to contribute to the literature with an emphasis on weight gain as an outcome of efficacy for the use of olanzapine in AN, however have either failed or provided weak evidence due to small sample sizes and study power (Bissada et al., 2008, Brambilla et al., 2007, Mondraty et al., 2005).

The NIHR in the UK has called for trials to be conducted on antipsychotic use for young people with AN to deliver empirical evidence and provide guidance for their use in clinical practice. Studies of such nature are fundamental as psychotropics, in particular antipsychotics, are routinely prescribed off-label (Y Beykloo et al., 2019) despite the lack of evidence with regard to their benefits and harms in this population. Medications for eating disorders are usually initiated in secondary care settings, but can be prescribed by GPs as an ongoing prescription under shared care arrangements (Y Beykloo et al., 2019). Therefore, and due to the complications of conducting RCTs in the AN population, this study set out to evaluate the medication use of individuals with AN in a primary health care setting.

The study reported in this thesis has examined all the available data in the THIN database in order to 1) describe the prescribing of psychotropic medication in the AN population and measure the prescribing duration and cessation of these medication, 2) describe the psychiatric comorbidities in AN individual's receiving psychotropic medications and 3) explore the potential adverse events of the psychotropic medications in AN.

7.2 Aim

The aim of this study was to measure the prescribing of psychotropic medications in individuals after a recorded anorexia nervosa diagnosis, as well as describe the psychiatric comorbidities and adverse events in THIN from 1996-2016.

7.3 Objectives

i. To identify and describe psychotropic medications that were prescribed after anorexia nervosa diagnosis, and measure the prescribing duration and cessation
ii. To describe the most common psychiatric comorbidities in individuals with anorexia nervosa who receive psychotropic medications
iii. To describe the adverse events commonly associated with antidepressant and antipsychotic drugs in individuals with anorexia nervosa after receiving a prescription; specifically, those of extra pyramidal symptoms, cardiovascular symptoms, and sexual dysfunction.

7.4 Methods

7.4.1 Study design

This study is a descriptive longitudinal observational study. For further information, please refer to Chapter 6.4.1.

7.4.2 Data source

This study was conducted using The Health Improvement Network (THIN) database. For more information on the data source, please refer to Chapter 3.3.1.

7.4.3 Study population

The study population comprised individuals in the THIN database who had a diagnosis of AN in their medical record between 1st January 1996 and 31st December 2016 and were registered with a GP for at least 6 months prior to their first AN

diagnosis. The age range of the study population was restricted to 12-50 years in the main analyses. Individuals were assigned the birth day and month of 1st July in their known year of birth. Follow-up for each individual started on or after their first AN diagnosis date as identified in THIN. Follow-up ended at the individuals' 50th birthday, transfer out of practice, death, or end of the study period (31st December 2016), whichever came first.

7.4.4 Ethical consideration

Approval for the study was granted by the Scientific Review Committee (SRC) of IQVIA, with reference number 17THIN063, as stated in their application forms (Appendix 7).

7.4.5 Data collection/extraction

The type of variables and their corresponding sub-types consisted of:

1. Antipsychotic and antidepressants prescribed in AN population. Prescriptions for medications were identified using relevant drug codes from the BNF and the drug dictionary provided by THIN (Appendix 9).
2. Psychiatric comorbidities identified in AN population in existing literature included depression, personality disorder, anxiety, affective disorder, hallucination, psychosis, and cognitive disorder (Appendix 8).
3. Adverse events recorded after the receipt of prescriptions for antidepressant and antipsychotic drugs, which were defined as serious by the eating disorder clinicians in the research team. These included a) extrapyramidal symptoms: parkinsonian symptoms, dystonia, akathisia and tardive dyskinesia, b) cardiovascular symptoms: QT prolongation, tachycardia, arrhythmias and hypotension, and c) sexual dysfunction: erectile dysfunction, amenorrhoea, and elevated prolactin levels (Appendix 10).

7.4.6 Main outcomes

7.4.6.1 Anorexia nervosa medications

A cross-sectional analysis was carried out by identifying all drugs prescribed by psychiatrists for the treatment of AN, listed in the BNF. These drugs belong to the class of antipsychotics and antidepressants (BNF chapters 4.2 & 4.3) and include amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, and sertraline. Age and gender specific prescribing rates were calculated by counting the number of individuals with one or more prescriptions for the study drugs per 100 individuals in the AN population. For all individuals I calculated the time between AN diagnosis and receipt of a prescription for a psychotropic medication.

7.4.6.2 Psychiatric comorbidities

For all individuals with AN and a prescription for psychotropic medications, subtypes of psychiatric comorbidities were measured. The number of individuals with a prescription for any type of psychotropic agent and with a diagnosis of the aforementioned comorbidities were mentioned. Psychiatric comorbidities were only considered if there was a record after AN diagnosis and before receiving a psychotropic medication. The categories were not mutually exclusive, and individuals were included each time a record was observed.

7.4.6.3 Initiation pattern

Analysis was conducted in individuals with AN to determine the rates of time from the first AN diagnosis to the first psychotropic medication prescription. These results were stratified and compared by age and gender.

7.4.6.4 Discontinuation pattern (drug cessation)

A longitudinal analysis was conducted in the cohort of individuals with AN and exposed to psychotropic drugs to determine the duration and cessation of treatment with psychotropic agents. If individuals had no new recorded prescription for a minimum period of three months from the last recorded prescription, I considered this

indicative of treatment cessation. For individuals who stopped and restarted treatment within three months during the inclusion time frame, the total duration of treatment from the first to last recorded prescription was considered. Analysis of psychotropic discontinuation was conducted at month one and six for both males and females, to take into consideration that psychotropic medications are often prescribed for short term use.

7.4.6.5 Adverse events

The adverse events associated with the use of antidepressant and antipsychotic medications that were examined were extrapyramidal symptoms (parkinsonian symptoms, dystonia, akathisia and tardive dyskinesia), cardiovascular symptoms (QT prolongation, tachycardia, arrhythmias and hypotension), and sexual dysfunction (erectile dysfunction, amenorrhea and elevated prolactin levels). The rates of individuals with AN who had experienced the mentioned adverse events were calculated after a first prescription of a psychotropic medication. Individuals with a record of more than one adverse event were included in each analysis. These results were stratified by age, gender, and times of first symptoms recorded in the AN population after receipt of a psychotropic medication.

7.4.7 Statistical analysis

Descriptive statistics were primarily reported using frequency tables. Median and IQR were calculated for categorical data. Kaplan Meier survival analyses were used to estimate the rates of time from the first AN diagnosis to the first psychotropic medication prescription and Cox regression was used to compare individuals by age and gender. The assumption of proportional hazards was tested using Schoenfeld residuals. Kaplan Meier plots were also used to estimate cessation of treatment in AN individuals with a psychotropic prescription. Confidence intervals were calculated using a significance level of 5%. All statistical procedures were performed using STATA version 14.0.

7.5 Results

In total, 17,597 individuals with AN were identified (Table 11). From the 17,597 individuals aged 12-50 year old with an AN diagnosis, 8,348 had received prescriptions for psychotropic medications during the study period 1996 to 2016 (47.44% overall). Most individuals receiving medication were prescribed antidepressants (N=8,192 individuals, 98.13%), whilst 1,443 (17.29%) were prescribed antipsychotics. With regards to age groups, those aged 18-24 years were more likely to be initiated on an antidepressant or an antipsychotic in comparison to other age groups.

Table 11. Characteristics of individuals with AN within THIN population

Characteristics	**Overall population with AN**	**Male (N=1,302) (%)**	**Female (N=7,046) (%)**
Received any psychotropic medications	8,348	1,302 (15.60)	7,046 (84.40)
Antidepressants	8,192 (98.13)	1,261 (96.85)	6,931 (98.37)
Antipsychotics	1,443 (17.29)	256 (19.66)	1,187 (16.85)
Both antidepressants and antipsychotics	1,287 (15.42)	215 (16.51)	1,072 (15.21)
Age receiving any psychotropics (years)			
Median (IQR)	24 (18-34)	31.5 (22-41)	23 (18-33)
12-17	1,821 (21.81)	125 (9.60)	1,696 (24.07)
18-24	2,427 (29.07)	292 (22.43)	2,135 (30.30)
25-30	1,326 (15.88)	206 (15.82)	1,120 (15.90)
31-40	1,592 (19.07)	351 (26.96)	1,241 (17.61)
41-50	1,182 (14.16)	328 (25.19)	854 (12.12)

7.5.1 Psychotropic medications in anorexia nervosa

From the population that were exposed to psychotropic drugs at any time after their AN diagnosis, 98.13% (N=8,192) received an antidepressant (see Table 12), 17.29% (N=1,443) received an antipsychotic medication (see Table 13) and 15.42% (N=1,287) received both antidepressants and antipsychotics at any time. Within the antidepressant medication class, fluoxetine was most prescribed (60.86%), followed by citalopram (49.67%). For individuals with a record of an antipsychotic medication, the most commonly prescribed medications amongst antipsychotics were olanzapine, quetiapine and risperidone with 51.49%, 45.81% and 27.58% respectively. Females had a higher likelihood of being initiated on antidepressants or antipsychotics after their AN diagnosis compared to males.

Table 12. Summary of individuals receiving any antidepressant medication after their AN diagnosis from 1996 to 2016 (N=8,348)

Medication*	Total number (N=8,192) (%)	Female (N=6,931) (%)	Any psychiatric comorbidity (%)	Psychiatric comorbidities** (N=5,621) (%)						
				Depression	Personality disorder	Anxiety	Affective disorder	Hallucination	Psychosis	Cognitive disorder
Antidepressants	8,192 (100)	6,931 (100)	5,621 (68.62)	5,241 (93.24)	569 (10.12)	332 (5.91)	204 (3.63)	172 (3.06)	154 (2.74)	120 (2.13)
Citalopram	4,069 (49.67)	3,427 (49.44)	3,053 (75.03)	2,886 (94.53)	274 (8.97)	201 (6.58)	105 (3.44)	97 (3.18)	73 (2.39)	63 (2.06)
Escitalopram	745 (9.09)	629 (9.08)	579 (77.72)	551 (95.16)	67 (11.57)	51 (8.81)	30 (5.18)	18 (3.11)	14 (2.42)	12 (2.07)
Fluoxetine	4,986 (60.86)	4,332 (62.50)	3,461 (69.41)	3,270 (94.48)	327 (9.45)	192 (5.55)	113 (3.26)	101 (2.92)	87 (2.51)	75 (2.17)
Mirtazapine	1,967 (24.01)	1,575 (22.72)	1,588 (80.73)	1,493 (94.02)	256 (16.12)	101 (6.36)	78 (4.91)	74 (4.66)	70 (4.41)	40 (2.52)
Paroxetine	1,450 (17.70)	1,200 (17.31)	1,093 (75.38)	1,019 (93.23)	114 (10.43)	72 (6.59)	53 (4.85)	42 (3.84)	38 (3.48)	29 (2.65)
Sertraline	2,621 (31.99)	2,253 (32.51)	2,009 (76.65)	1,872 (93.18)	243 (12.10)	131 (6.52)	79 (3.93)	84 (4.18)	59 (2.94)	50 (2.49)

*Individuals are counted each time they have a record for a first prescription of a psychotropic medication after their AN diagnosis. This means individuals may be classified under more than one medication at a time perhaps due to concurrent use.

**Coexisting psychiatric comorbidities are included in the analysis of the results, thus individuals may be classified under more than one psychiatric comorbidity at a time.

Table 13. Summary of individuals receiving any antipsychotic medication after their AN diagnosis from 1996 to 2016 (N=8,348)

Medication*	Total number (N=1,443) (%)	Female (N=1,187) (%)	Any psychiatric comorbidity (%)	Psychiatric comorbidities** (N=1,133) (%)						
				Depression	Personality disorder	Anxiety	Affective disorder	Hallucination	Psychosis	Cognitive disorder
Antipsychotics	1,443 (100)	1,187 (100)	1,133 (78.52)	928 (81.91)	340 (30.01)	81 (7.15)	157 (13.86)	117 (10.33)	123 (10.86)	36 (3.18)
Amisulpride	97 (6.72)	82 (6.91)	88 (90.72)	67 (76.14)	42 (47.73)	8 (9.09)	21 (23.86)	15 (17.05)	16 (18.18)	1 (1.14)
Aripiprazole	187 (12.96)	167 (14.07)	166 (88.77)	133 (80.12)	58 (34.94)	8 (4.82)	43 (25.90)	29 (17.47)	24 (14.46)	5 (3.01)
Olanzapine	743 (51.49)	605 (50.97)	565 (76.04)	449 (79.47)	154 (27.26)	42 (7.43)	80 (14.16)	61 (10.80)	88 (15.58)	15 (2.65)
Quetiapine	661 (45.81)	570 (48.02)	566 (85.63)	472 (83.39)	198 (34.98)	42 (7.42)	92 (16.25)	50 (8.83)	46 (8.13)	22 (3.89)
Risperidone	398 (27.58)	307 (25.86)	316 (79.40)	247 (78.16)	105 (33.23)	23 (7.28)	53 (16.77)	39 (12.34)	47 (14.87)	6 (1.90)

*Individuals are counted each time they have a record for a first prescription of a psychotropic medication after their AN diagnosis. This means individuals may be classified under more than one medication at a time perhaps due to concurrent use.

**Coexisting psychiatric comorbidities are included in the analysis of the results, thus individuals may be classified under more than one psychiatric comorbidity at a time.

7.5.2 Psychiatric comorbidities

Depression was the most common of the psychiatric comorbidities recorded for individuals with AN taking antidepressants and antipsychotics, with 93.24% and 81.91% of the cohort population respectively. Besides depression, psychiatric comorbidities in individuals with AN using antipsychotics were higher compared to individuals with AN using antidepressants. From AN individual's receiving antidepressants, the most common was fluoxetine, where in comparison to all the antidepressants, individuals had the least psychiatric comorbidities recorded (69.41%). Similarly, olanzapine was the most common antipsychotic amongst the AN population, however in comparison to other antipsychotics, individuals on olanzapine had the least psychiatric comorbidities recorded (76.04%).

7.5.3 Psychotropic drug initiation in anorexia nervosa

The rate of psychotropic medication initiated, after a diagnosis of AN, remained fairly stable throughout the study period with 3.10% initiating a first prescription in 1996, 4.91% initiating in 2006 and 3.31% initiating psychotropic medications in 2016. With a median follow-up of 8.09 years, prescription rates peaked in the first year post AN diagnosis, with 23.68% of AN individual's receiving their first prescription for an antidepressant and/or antipsychotic. Of those, 18.36% of individuals received a first prescription in the first 6 months of AN diagnosis. Within the first year of diagnosis, 18.10% were initiated on an antidepressant. After one year, this fell to 2.74% (a decrease of over 88%). Similarly, there was a decrease of 87.50% in the rate of newly initiated prescriptions for antipsychotics after 12 months to just 0.46% of individuals (Table 14).

Table 14. Summary of individuals on psychotropic medications after their AN diagnosis (N=8,348)

Duration post first AN diagnosis	Individuals on any psychotropics		Individuals on antidepressants		Individuals on antipsychotics	
	Number	%	Number	%	Number	%
6 months	1533	18.36	1511	18.10	211	2.53
6 months - 1 year	444	5.32	433	5.19	93	1.11
1 - 2 years	235	2.82	229	2.74	38	0.46
2 - 3 years	162	1.94	161	1.93	27	0.32

When antidepressant therapy initiation rates were stratified by age groups and gender, males aged 18-24 years were found to be prescribed medication more often (28.24%) compared to other age groups within the first 6 months of their AN diagnosis. Similarly, the majority of females (38.22%) that were initiated on a first prescription of antidepressants were aged 18-24 years. When antipsychotic therapy initiation rates were stratified by gender and age, it was found that in the first 6 months after AN diagnosis, more males aged 31-40 years received antipsychotics (25.81%) in comparison to other age groups. With regards to the female age groups, those aged 12-17 years were most likely to receive a first prescription (34.44%) for antipsychotics, compared to other age groups (Figure 20).

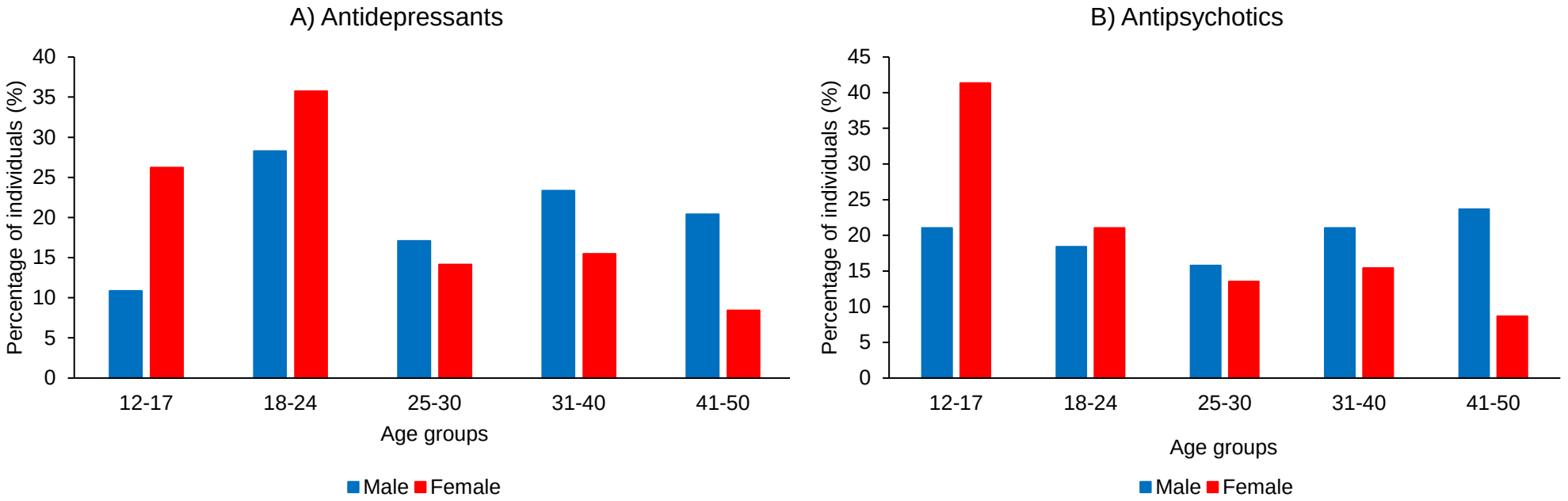

Figure 20. Proportion of individuals initiating A) antidepressants (n=8,192) or B) antipsychotics (n=1,443) medications within the first year of their AN diagnosis as recorded in THIN

7.5.3.1 Psychotropic drug initiation by gender

Females were significantly more likely to receive a prescription any time after diagnosis compared to males over time (log-rank p<0.001). At six months, 21.15% (95% CI 19.76-22.63) of males had received a prescription compared to 21.55% (95% CI 20.88-22.23) of females, by year one this was 23.90% (95% CI 22.43-25.44) and 25.69% (95% CI 24.98-26.42) and by a typical AN duration of three years, this was 42.32% (95% CI 40.49-44.21) and 51.38% (95% CI 50.50-52.27) respectively. Kaplan Meier curves representing medication initiation over time are depicted in Figure 21.

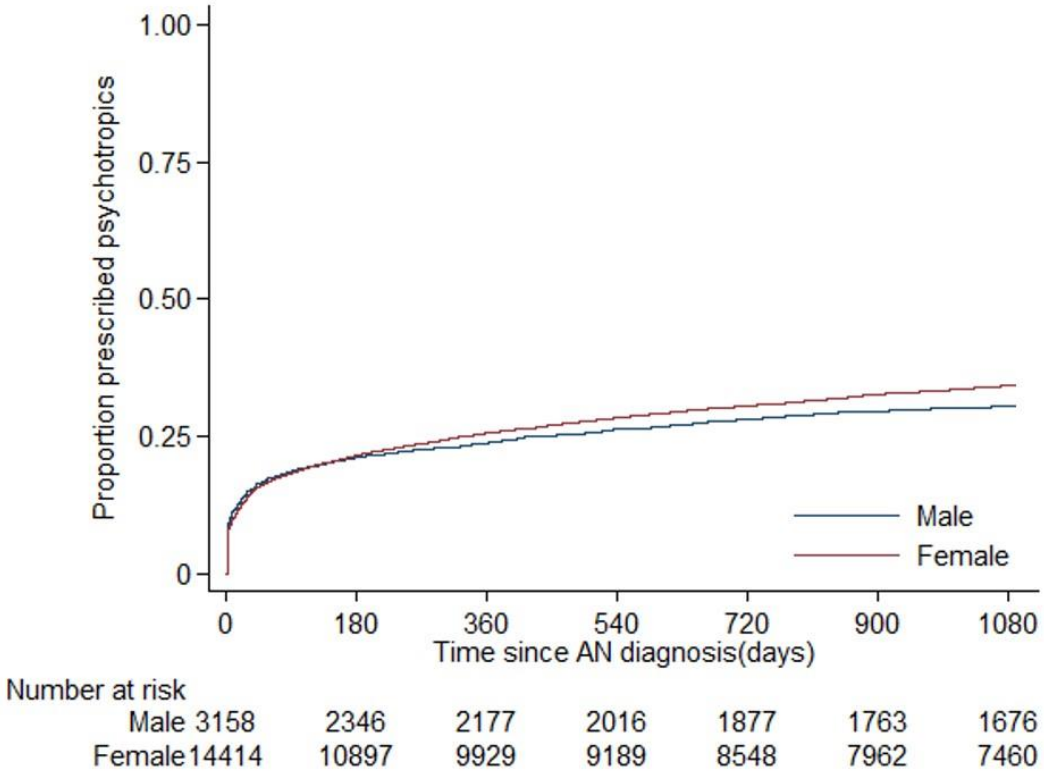

Figure 21. Survival curve for the proportion of individuals initiating psychotropic medication within three years of a first AN diagnosis, stratified by gender

7.5.3.2 Psychotropic drug initiation by age

When the results were stratified by age groups, AN diagnosed individuals aged 18-24 years were most likely to be initiated on psychotropic medications in comparison to those aged 12-17. This was particularly evident in the first six months after AN

diagnosis where only 9.54% (95% CI 8.75-10.40) of AN individuals aged 12-17 years had received a prescription for a psychotropic medication, in comparison to 22.41% (95% CI 21.30-23.57) of 18-24 year olds.

7.5.4 Psychotropic discontinuation pattern (drug cessation)

Thirty days after prescription initiation, the prevalence of males who had discontinued psychotropic medications was 29.90% (95% CI 28.19-31.70). In female individuals with AN, 25.89% had discontinued after one month (95% CI 25.04-26.76). The proportion of individuals discontinuing psychotropic medications after six months of initiating a prescription increased to 56.94% (95% CI 55.05-58.85) in males and 52.68% (95% CI 51.70-53.66) in females (Figure 22). Overall, under half of individuals (46%) initiated on a psychotropic medication continued with a psychotropic prescription after six months. When stratified by age groups, discontinuation patterns varied slightly, however there was no significant difference between the five age groups (log-rank p=0.2460).

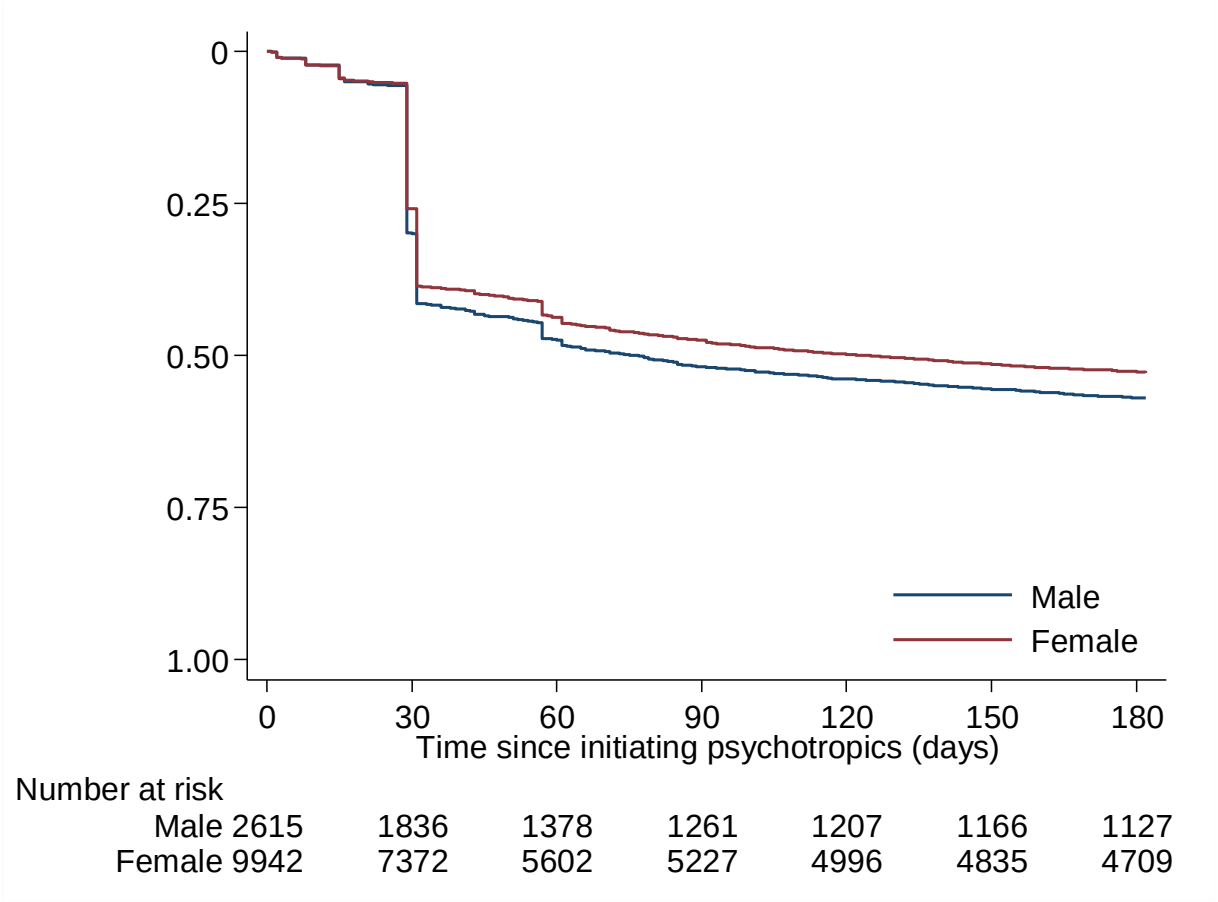

Figure 22. Kaplan Meier curve for proportion of individuals discontinuing psychotropic medications at different durations after initiating, stratified by gender

7.5.5 Adverse events in anorexia nervosa pharmacotherapy

Around 64% of individuals with AN have experienced some adverse event after a first prescription of psychotropic medication (refer to Table 15). This proportion was 40.86% and 68.31% in males and females, respectively. In females, the most common adverse events experienced were amenorrhoea (15.00%), parkinsonian (3.12%) and dystonia (2.04%). In males with AN on psychotropic medication who experienced an adverse event, the most common were erectile dysfunction (12.22%) and parkinsonian (6.96%).

Table 15. Individuals with AN with a record of an adverse event after receiving a first psychotropic medication prescription, stratified by gender

Adverse events of interest	**AN population on psychotropics**		**Gender**			
			Males		**Females**	
	Number (N=8,348)	**%**	**Number (N=1,302)**	**%**	**Number (N=7,046)**	**%**
Any adverse event within AN population	5,345	64.03	532	40.86	4,813	68.31
Adverse events	**Number (N=5,345)**	**%**	**Number (N=532)**	**%**	**Number (N=4,813)**	**%**
Parkinsonian	187	3.50	37	6.95	150	3.12
Dystonia	108	2.02	10	1.88	98	2.04
Akathisia	18	0.34	4	0.75	14	0.29
Tardive dyskinesia	14	0.26	2	0.38	12	0.25
Tachycardia	63	1.18	6	1.13	57	1.18
Arrhythmia	26	0.49	5	0.94	21	0.44
Hypotension	84	1.57	9	1.69	75	1.56
Erectile dysfunction	65	1.22	65	12.22	N/A	N/A
Amenorrhoea	722	13.51	N/A	N/A	722	15.00
Prolactin elevation	37	0.69	N/A	N/A	37	0.77

7.5.5.1 Adverse events by age

In individuals with AN who received a first psychotropic prescription, any adverse event of interest was observed most in those aged 12-17 years (71.50%). When stratified by age groups, AN individuals aged 12-17 years and 18-24 years of age had more records for any adverse event of interest, with 24.36% and 28.34%, respectively, than any of the other age groups (Table 16). Adverse events such as parkinsonian, dystonia, akathisia, tardive dyskinesia, and erectile dysfunction were more common in the older age groups of 31-40 years and 41-50 years in comparison to the younger age groups. In contrast, adverse events such as tachycardia, arrhythmia, hypotension, amenorrhoea, and prolactin elevation were common in younger age groups of 12-17 and 18-24 years of age.

Table 16. Individuals with AN with a record of an adverse event after receiving a first psychotropic medication prescription, stratified by age groups

Adverse events of interest	**12-17 years**		**18-24 years**		**25-30 years**		**31-40 years**		**41-50 years**	
	N (1,821)	**%**	**N (2,427)**	**%**	**N (1,326)**	**%**	**N (1,592)**	**%**	**N (1,182)**	**%**
Any adverse event within AN population	1,302	71.50	1,515	62.42	773	58.30	995	62.50	760	64.30
Adverse events	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Any (n=5,345)	1,302	24.36	1,515	28.34	773	14.46	995	18.62	760	14.22
Parkinsonian (n=187)	18	9.63	38	20.32	21	11.23	62	33.16	48	25.67
Dystonia (n=108)	22	20.37	32	29.63	15	13.89	28	25.93	11	10.19
Akathisia (n=18)	1	5.56	4	22.22	2	11.11	6	33.33	5	27.78
Tardive dyskinesia (n=14)	0	0	2	14.29	2	14.29	4	28.57	6	42.86
Tachycardia (n=63)	13	20.63	20	31.75	11	17.46	13	20.63	6	9.52
Arrhythmia (n=26)	6	23.08	6	23.08	1	3.85	5	19.23	8	30.77
Hypotension (n=84)	13	15.48	19	22.62	13	15.48	21	25.00	18	21.43
Erectile dysfunction (n=65)	3	4.62	9	13.85	9	13.85	21	32.31	23	35.38
Amenorrhoea (n=722)	215	29.78	227	31.44	110	15.24	126	17.45	44	6.09
Prolactin elevation (n=37)	9	24.32	12	32.43	3	8.11	10	27.03	3	8.11

Experiencing an adverse event after receiving a first psychotropic medication was evaluated at different durations for individuals with AN, as shown in Table 17.

Table 17. Duration taken for individuals with AN to experience a record of an adverse event after receiving a first psychotropic medication prescription (N=5,345)

Duration post receiving psychotropic medication	**Number of individuals experiencing any of the adverse events of interest**	**Percentage of individuals experiencing any of the adverse events of interest (%)**
Day 1 - 2 weeks	13	0.24
2 weeks - 1 month	12	0.22
1 - 3 months	64	1.20
3 - 6 months	74	1.38
6 - 9 months	66	1.23
1 year	69	1.29
2 years	194	3.63
3 years	159	2.97
Over 3 years	4,487	83.97

Within the first month of receiving a first psychotropic prescription, 0.46% of individuals with AN experienced an adverse event. As the duration of exposure to psychotropic medications increased, the percentage of individuals experiencing an adverse event also increased. At three months, six months and one year post receiving a psychotropic prescriptions, 1.66%, 3.04% and 5.56% of individuals with AN experienced an adverse event.

7.6 Discussion

To my knowledge, this is the first study to examine the pattern of medication prescription in AN in primary care within the UK. Under half (47.44%) of individuals diagnosed with AN received prescriptions for a psychotropic medication, of which the majority were antidepressants (98.13%), which is in line with a study by Fazeli et al. (2012) that showed the use of psychotropics in AN is common (Fazeli et al., 2012). A recent study by Demmler et al. (2019) has found an increase in antipsychotic and antidepressant prescriptions in eating disorders from 1990 to 2017 (Demmler et al., 2019). In the study presented in this chapter, the most common antidepressant prescribed in AN individuals was fluoxetine (60.86%) and the most common antipsychotic prescribed was olanzapine (51.49%).

A number of studies have investigated the use of fluoxetine for AN treatment and have found it to improve in weight gain and reduce the rate of relapse in AN individual's (Gwirtsman et al., 1990, Kaye et al., 2001). However, findings have been mixed (NICE, 2018), and many consider prescribing to be for comorbidities such as depression or anxiety rather than for AN itself per se. Although fluoxetine has not been recommended by NICE guidelines for the treatment of AN, it has been approved and recommended for the treatment of depression, in particular in the vulnerable age groups of children and young people. As per NICE guidelines, those aged 8-18 years have the UK marketing authorisation to be given fluoxetine in conjunction with psychotherapy (such as family therapy and individual CBT) for the treatment of moderate to severe depression (NICE, 2019a). In addition, it can be given to those with depression that is unresponsive to treatment or have recurrent depression or psychotic depression. Through clinical trials, fluoxetine has been identified as the only antidepressant for which the evidence of its benefits outweighs its risks. The use of fluoxetine, especially in younger age groups, is reflected in the results from this study, indicating a higher proportion of AN individuals on fluoxetine, compared to any other

antidepressants. Fluoxetine also appears to be the most commonly prescribed antidepressant as reported by 29% of CAED psychiatrists, shown in Chapter 5 of this thesis.

Similarly, olanzapine has been a medication of interest for many studies with regards to the treatment of AN. Most randomised controlled trials have been conducted to investigate the efficacy of olanzapine, although most have failed to demonstrate a significant difference between olanzapine and a placebo in the management of AN (Mondraty et al., 2005, Bissada et al., 2008, Brambilla et al., 2007). This is mainly due to the small sample size of these studies (n=15, 30, 34 respectively), making them difficult to generalise, interpret and detect any true differences in outcomes. A recent RCT study conducted on adult outpatients with AN has shown a modest therapeutic effect of olanzapine compared to a placebo on weight, however no significant benefit for psychological symptoms of individuals with AN (Attia E, 2019). Nonetheless, it would appear that for a number of patients with AN (less than 10%), olanzapine is considered potentially beneficial enough to justify prescribing. Further research is needed to understand the potential role of olanzapine and for which patients it may be useful adjunct to psychological treatment.

Most individuals with AN in this study were diagnosed with a psychiatric comorbidity at the time of receipt of their antidepressant (68.62%) or antipsychotic (78.52%) medications. The most common psychiatric comorbidity in AN individuals on psychotropic medications was depression. With the exception of depression, individuals with AN on antipsychotics also experienced higher psychiatric comorbidities in comparison to those individuals with AN on antidepressants. The results are reflective of literature indicating that medication approaches are often vital when a person with an eating disorder also has another type of psychiatric disorder (Flament et al., 2012). However in the case of AN, caution must be exercised as

comorbidities can mimic symptoms which may be resolved with weight gain alone (Mairs and Nicholls, 2016).

Some novel findings from this study suggests that the majority of individuals (23.68%) received a psychotropic prescription within the first year of their AN diagnosis, with the proportion decreasing annually for each year after diagnosis. For those receiving medication, under half of individuals (46%) continue treatment after 30 days, or after one receipt for a prescription for a psychotropic medication. Guidelines by NICE do not suggest enough evidence for medication use and states that first line treatment for AN is psychological interventions such as family therapy, cognitive behavioural therapy and adolescent or adult based psychotherapy (NICE, 2018). If these therapies are proving to be ineffective, medication may be prescribed in adjunct to the treatments. My analysis for the initiation of psychotropic medications was restricted to within three years of a first AN diagnosis, as I acknowledge this to be more reflective of real-life practice. It has been reported that there are discrepancies between actual treatment delivery and evidence based treatments recommended by guidelines, as most eating disorder clinicians do not adhere or occasionally deviate from evidence based treatments (Waller, 2016, Kosmerly et al., 2015). The study in this chapter supports this finding, with almost 50% of patients with AN receiving some form of psychotropic medication.

With regard to medication cessation, from those AN individuals initiated on psychotropic medications in this study, only 46% continued with a prescription after 6 months. A possible reason for cessation is the lack of robust effects of these medications in the AN population (Frank and Shott, 2016). Studies have associated long term negative outcomes when psychiatric disorders are improperly treated as a result of efficacy concerns (Wang et al., 2005, Kessler et al., 2005). Another possible reason is a lack of adherence to medications due to a) socio-demographic factors like age, educational status or employment, b) patient attitude towards medication, c)

perceived stigma of AN or medication use, or d) clinical factors (Semahegn et al., 2020). In addition, off-label psychotropic prescriptions for vulnerable populations, for example particular age groups like children and adolescents, or conditions like AN, may be risky due to differences in pharmacokinetics (Kearns and Hawley, 2014). This can result in toxicity of medications and increase the risk for side effects causing medication cessation (Frank and Shott, 2016). Although the side effect profiles of psychotropic drugs are established, its effects remain ambiguous in AN. Off-label prescribing in AN is important to inform the need for further research and education (Peggy L. O'Brien et al., 2017).

Adverse events, which are defined as temporary or permanent injuries caused by medical management that are not always due to underlying disease nor are expected outcomes of treatment, were experienced in 64% of individuals with AN in this study. In my study, amenorrhoea was the most common adverse event experienced by females with AN after a prescription for a psychotropic medication, predominantly in the 12-17 age group. Amenorrhoea is one of the diagnostic criteria of AN and in some cases precedes significant weight loss in individuals (Mitan, 2004). Previous studies have also shown that menstrual disorders are common in eating disorders like AN, particularly among adolescents (Golden and Carlson, 2008, Vale et al., 2014). (Golden and Carlson, 2008, Vale et al., 2014). A cohort study by Golden et al. (1997) has found that achieving a weight of approximately 90% of ideal body weight within 6 month was the average weight at which there was a spontaneous return to menses among the 100 adolescent females with AN (Golden et al., 1997). The most common adverse event experienced by males with AN in this study was parkinsonian, which is frequently known as a type of extrapyramidal side effect. Although the exact reasons are still unknown, some studies have suggested that males are more susceptible to develop extrapyramidal symptoms in comparison to females, perhaps due to an increased muscle mass (John Kamin et al., 2000). In my study, any adverse

event of interest was observed most in AN individuals who received a first psychotropic prescription aged 12-17 years (71.50%). Recent studies have suggested that clinicians must exercise a high level of vigilance when prescribing psychotropic drugs, especially atypical antipsychotics, as they have the potential to induce neurological symptoms effects in children and young people (Pringsheim et al., 2011a). Due to the nature of AN and the profound nutritional deprivation, those diagnosed are more likely to experience significant physiological disturbances or adverse events as a complication of treatment (Norrington et al., 2012). However this is dependent upon the individual and their severity of AN as the main factors for such adverse events are the degree of weight loss, the chronicity of the illness and the cautions associated with the psychotropic medications prescribed (Mehler and Brown, 2015). The individual risk-benefit ratio for their use for the treatment of AN has to be considered very carefully by health care professionals.

7.6.1 Strengths and limitations

This is the most recent and comprehensive study on the trends of medication prescription among individuals with AN using a large database of UK primary care records. Similar to Chapter 6, a major strength of this study includes the large sample, which is representative of the general UK population, however it is limited to patient data as recorded by GPs in primary care. The use of this database allows for exploration of the AN population prescribed psychotropic medications whom many have other psychiatric comorbidities. In comparison to RCTs where patients with comorbidities are underrepresented, community-based patient data available in observational datasets present more comorbidities, which is more reflective of real life (Hanlon et al., 2019). Similarly, I was not able to link prescriptions to underlying indications and as such, are not able to identify how many individuals received psychotropic agents for AN in comparison to other underlying health issues. I was not able to confirm whether recorded prescriptions were dispensed as a record of a

psychotropic prescription does not necessarily imply that an individual takes the medication. To handle this, the discontinuation pattern was investigated for AN individuals with repeat prescriptions of psychotropic medications (two or more), as they are more likely taking the treatment prescribed and complying with the medication on a regular basis.

7.6.2 Implications in clinical practice and future research

The findings of this study provide an insight into the psychotropic medications used by individuals with AN. Healthcare professionals need to strike a balance between effectiveness and safety when considering medication treatment options for AN. Currently, there is limited evidence on the use of any psychotropic medication for the treatment of AN. Future research should be conducted in secondary care settings to investigate the pattern of medication use in AN and its management, the rationale behind acute and long term use of psychotropics and target the reasons behind medication cessation.

Summary

- This is the first study to examine the pattern of medication prescription in individuals with AN as documented in primary care within the UK.
- The most common medications recorded on The Health Improvement Network database for this population were fluoxetine and olanzapine, which accounted for 60.86% and 51.49% of the total AN population respectively over a 20 year period.
- With the exception of depression which was the most common psychiatric comorbidity recorded for AN individual's taking antidepressants (93.24%) and antipsychotics (81.91%), psychiatric comorbidities in individuals with AN using antipsychotics were higher compared to individuals with AN using antidepressants.
- Findings of this study were prescription cessation showed just under half of individuals (46%) continued a psychotropic medication after 6 months of initiating treatment.
- Adverse events after receiving a prescription for a psychotropic medication was experienced in 64% of individuals with AN in this study, with the most common adverse event being amenorrhoea and parkinsonian in females and males, respectively.

Chapter Eight

Pharmacotherapy and weight change in adolescents with anorexia nervosa: a multisite eating disorder clinics study

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Outline

Chapters 5, 6 and 7 have demonstrated that psychotropic medications are often prescribed by health care professionals for individuals with AN, as self-proclaimed by CAED psychiatrists (Chapter 5) and documented in UK primary care data (Chapters 6 and 7). However, as AN is a condition often diagnosed in secondary care CYP EDS and under the care of specialists CAED psychiatrists, the focus of the study population in this chapter is the AN population at CYP EDS practices. The following sections describe psychotropic prescribing practices in individuals with AN in specialist secondary care services as well as describing the differences in BMI before and after pharmacotherapy, as a measure of treatment effectiveness.

8.1 Introduction

In adolescents, AN is commonly acknowledged as a chronic condition often lasting a few years, in which any one episode of care is unlikely to result in a complete cure of the psychiatric condition (Gowers et al., 2010b). It's been reported by Arcelus et al., who analysed 36 quantitative studies on eating disorders in a systematic review from 1966 to 2010, that the mortality rate of AN is higher compared to any other psychiatric disorder. The mortality rate estimated at 5.1 deaths per 1,000 people with AN per year (Arcelus et al., 2011). The first line treatment when working with adolescents with AN in the UK is Family Therapy for Anorexia Nervosa (FT-AN), as recommended in the NICE guidelines (NICE, 2018). This treatment is provided by the multidisciplinary teams in CAEDS, however 10-40% of individuals end up with poor outcomes or feeling disengaged with FT-AN (Simic et al., 2016). It has been found that a younger age of AN onset for diagnosis and longer duration of follow-up and treatment has been associated with better outcomes (Steinhausen, 2002). Next line treatment recommended by NICE is individual cognitive behavioural therapy for eating disorders (CBT-ED) or adolescent focused psychotherapy for anorexia nervosa (AFP-AN) (NICE, 2018). Based on the level of care and severity of the illness,

treatment settings can vary from inpatient care, to outpatient, partial or day care at hospitals (Hay et al., 2019) and currently no single setting is considered superior for AN treatment.

For the past decade in the UK, CAMHS have been using a four-tiered strategic framework in order to conceptualise the planning and delivery of services for young people (Health Advisory Service, 1995). Tier one provides universal services by promoting mental well-being and recognising when to refer to more specialised services. Tier two gives more targeted services to those with less severe mental health conditions on an individual health care professional level (Aggett et al., 2006). Tier three consists of specialist community CAMHS which provide a range of interventions through multi-disciplinary teams. Finally, tier four provides highly specialist services including day and inpatient services (Duffy and Skeldon, 2014).

There are many potential reasons why medications are not being selected as the primary mode of treatment in AN (Crow et al., 2009), with pharmacological adherence (compliance) being the main one as patient drop-out rates are found to be between 35% and 75% (Halmi et al., 2005). Poor medication response as a result of starvation in AN along with adverse events resulting from prescribed medications such as metabolic disruptions, extrapyramidal symptoms and sexual/reproductive events must also be considered, especially in patients with comorbid conditions (Jerrell et al., 2010). As a result of this lack of convincing evidence for drug efficacy for anorexia nervosa, no pharmacological treatment guidelines are currently in place within the England (NICE, 2018).

This study aimed to investigate the use of pharmacological treatment and the potential association with any change in BMI within a cohort of AN patients in four participating CYP EDS in England from 2015 to 2017. The results contribute quantitatively to the overall understanding of the prescribing of psychotropic medications in specialist CYP EDS in England.

8.2 Aim

The aim of this study was to describe the use of psychotropic pharmacotherapy in adolescents diagnosed with anorexia nervosa. Specifically, this study set out to measure the difference in BMI before and after treatment initiation on antipsychotic and antidepressant medications. Additionally, this study aimed to describe any comorbidities and adverse events recorded around the time of psychotropic drug initiation in individuals with anorexia nervosa.

8.3 Objectives

i. To describe a cohort of individuals diagnosed with anorexia nervosa at four CYP EDS in terms of age, gender, and any recorded psychiatric comorbidities
ii. To describe the type of treatment initiated by CAED specialists at four CYP EDS for individuals with anorexia nervosa
iii. To describe the rate and type of psychotropic agents prescribed by CAED specialists at four CYP EDS for individuals with anorexia nervosa
iv. To measure the difference in recorded BMI before and after pharmacotherapy in adolescents diagnosed with anorexia nervosa at four CYP EDS
v. To describe the adverse event profile associated with the main medications prescribed for anorexia nervosa in adolescents at four CYP EDS as found on their patient records and as experienced by individuals with anorexia nervosa.

8.4 Methods

8.4.1 Study design

This study was an analytical retrospective observational study conducted at four England based CYP EDS.

8.4.2 Data source

The present multi-site study was based on anonymised patient medical records of adolescents diagnosed with AN, from CYP EDS in England. Initially, a total of eight

collaborators from different sites had shown interest in the study and requested to collaborate, as they had also been involved in the survey study in Chapter 5. However due to time constraints and limited manpower, a total of four sites contributed to the final data for this study. For further information on the selection of these four NHS Trusts, please refer to Chapter 3.5. The included sites were:

1) Site 1: This CYP EDS site is an acute university trust that comprises of nine hospitals, located in the North West of England. They have an estimated 2,500 inpatient beds across the trust and employ over 20,000 staff (as of 2018/19). Services offered by the trust include anaesthesia, critical care, pathology, radiology, adult & paediatric ophthalmology, children's services, women's services & neonatology, and dental surgery & oral medicine.

2) Site 2: This CYP EDS is a mental health and community health services trust with university status. This CYP EDS is located in South East England and the trust operates from over 100 inpatient and community sites, of which nine are considered its main inpatient sites. It employs over 5,500 permanent staff as of 2018/19 and cares for a population total of around 750,000 people.

3) Site 3: This CYP EDS is part of the same mental health and community health services trust with university status as site 2, located in the East of England. In 2015, this site was placed under the trust to cover and broader range of geographic location and is responsible for the care needs of 630,000 people.

4) Site 4: This CYP EDS is a mental health foundation trust that provides 229 community, inpatient and outpatient services of which over 50 are specialist services in South London. These specialist services include a mother and baby unit, eating disorders, national psychosis unit and national autism unit. The trust is part of one of England's six academic health sciences centres. The site is located in South East

England with 755 inpatient beds across eight of its sites (as of 2018/19). A total of 4,800 staff members work in the trust and care for a population of 1.3 million people.

8.4.3 Study population

The study population comprises individuals who were diagnosed with AN during a three year observational window from the 1st January 2015 to 31st December 2017 with at least one year follow-up, from the four CYP EDS. Individuals that met the following inclusion criteria were selected: diagnosis of AN (F50.0/F50.1) according to ICD-10 and 13 to 18 years of age. Sample size estimations were made based on data from previous years from site 4 to make a prediction of the total sample required. The direct clinical care team at site 4 informed that the total number of patients at their CYP EDS site diagnosed with AN were 115 (52%) in 2015 and 121 (62.4%) in 2016. Of these patients, 42 (37%) and 33 (27%) were initiated on psychotropic medications for AN treatment in 2015 and 2016 respectively. Therefore, a total UK sample size estimation of 165 to 210 patients was documented on the IRAS application. However, as explained in detail in Chapter 3.4, the sample size was subsequently increased to a total UK population of 400 patients.

8.4.4 Ethical consideration

Ethical approval was obtained from the HRA in the UK with IRAS reference number 228242, due to the data being retrospective, anonymised data from NHS England sites (Appendix 11). Sponsorship was obtained from UCLH/UCL joint research office. For further detail on this, please refer to Chapter 3.4.

8.4.5 Data collection/extraction

This was a retrospective study, therefore there was no active recruitment of individuals. The lead collaborator at each site was contacted in order to facilitate the study at the sites. The individuals for the study were identified by the direct clinical care team at the four CYP EDS sites based on the listed inclusion criteria.

Demographic, medical, and psychiatric data were collected manually through retrospective case record review from December 2018 to April 2020. Diagnosis at baseline was extracted from the initial assessment form completed upon referral to the CYP EDS. For the purpose of the analyses, the first records of diagnosis and treatment were considered as the baseline. In the rare case where no diagnosis was explicitly specified, the patients' notes and correspondence histories were searched. Manual reviews of the data were carried out on-site by the direct clinical care team and transferred for analysis to the research team as a password protected Microsoft Excel file after the process of de-identification. The anonymised Excel dataset was then stored on a secure folder on an encrypted hard drive by the research team. This hard drive was stored in the UCL Research Department of Practice and Policy at the British Medical Association (BMA) Tavistock House where it was kept in a locked cabinet in the office.

As the data from each site were collected in-house and not by the same person throughout the Trusts, an audit of 10% of the extracted data was independently conducted by the lead collaborator at each site in order to ensure satisfactory reliability and quality of the data was obtained.

The type of variables and their corresponding sub-types were:

1. Demographics: gender, age at diagnosis, ethnicity & type of diagnosis
2. Psychiatric comorbidities recorded
3. All types of treatments given after AN diagnosis as recorded
4. Medications: all psychotropic medications given as recorded after AN diagnosis, with consideration of initial dosage, escalation of dose and frequency and maximum dosage of the first three psychotropic medications given

5. BMI/weight: weight & BMI at baseline, 1 month, 2 months, 3 months and 6 months after AN diagnosis as well as including the height at baseline and at 6 months
6. Psychiatric evaluations: the three evaluations used at the sites include a) the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA), b) the Children's Global Assessment Scale (CGAS) and c) the Revised Children's Anxiety and Depression Scale (RCADS). All three evaluations were assessed at baseline, 1 month, 2 months, 3 months and 6 months after AN diagnosis
7. Adverse events categorised as extrapyramidal, cardiovascular, sexual dysfunction and any other symptoms associated with psychotropic medications. The severity, causality and expectedness of the adverse events were also recorded.

8.4.6 Study schedule

Pseudonymised patient records from the participating CYP EDS sites were identified by the clinical care team and anonymised, ensuring no contacts can be made with individuals with AN for the purpose of the study. In the final dataset for the study used by the research team, all patient identifiers were removed, and the data extraction was in a completely anonymised format. No member of the research team had any access to the initial dataset nor of any patient identifiable factors, thus patient identification was not possible. There were no patient enrolment processes, follow-up or withdrawal criteria, as only retrospective data was used in this study.

The end of follow-up for each AN individual was marked if any of the following were met:

a) The patient had deceased during the study or follow-up time

b) The patient discontinued treatment at the participating CYP EDS or was discharged

c) The end date of the study (31st December 2017)

8.4.7 Main outcomes

8.4.7.1 Psychiatric comorbidities

All AN individuals with a record of psychiatric comorbidities in their medical records were identified. The psychiatric comorbidities considered were delirium, bipolar disorder, affective disorder, hallucination, OCD, depression, anxiety, generalised anxiety disorder, cognitive disorder, personality disorder, ADHD, psychosis, mania, schizophrenia, psychosexual dysfunction, schizoaffective, specific (isolated) phobias, separation anxiety disorder of childhood, hypochondriacal disorder, low mood and ASD. The proportion of individuals with AN and the aforementioned psychiatric comorbidities were calculated.

8.4.7.2 Treatments

Treatments that individuals received after a diagnosis of AN were identified based on NICE guideline recommendations. These included FT-AN, CBT-ED, AFP-AN, intensive treatment day programme (ITP), SSCM, medication therapy and individual therapy. The number of individuals on treatments for AN were counted.

8.4.7.3 Anorexia nervosa medications

All psychotropic medications prescribed in the CYP EDS sites for the treatment of AN, as listed in the BNF were identified. These medications belong to the class of antipsychotics and antidepressants (BNF chapters 4.2 & 4.3) and include amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, and sertraline. The most prevalent medications were evaluated further, and their initiation, escalation and maximum dosage and duration were calculated.

8.4.7.4 Body Mass Index (BMI)

BMI is one of the main outcomes of efficacy for treatment in AN, as it is recommended by NICE guidelines that an average weekly weight gain of 0.5kg-1kg in inpatient settings and 0.5kg in outpatient settings should be the aim (National Collaborating Centre for Mental Health, 2004). For this study, BMI recordings were assessed at baseline, 1 month, 2 months, 3 months, and 6 months after AN diagnosis. These were typically recorded at each consultation with the AN individual. As the consultation schedules varied, the baseline BMI was considered as recorded on the initial assessment and the subsequent months were considered the closest date to it with 7 days scope before and after the specified durations (1, 2, 3 & 6 months). If no BMI recordings were reported in the medical files, the weight and height of the individuals were used to calculate the BMI ($BMI=weight/height^2$) for those months.

8.4.7.5 Psychiatric evaluations

The evaluations used for assessment of psychiatric symptoms of adolescents with AN varied between the different sites (Salmond, 2020). They were also measured at various time points during the individual's care. The first psychiatric evaluation is HoNOSCA, which was used at one of the sites and focuses on general health and social functioning. It consists of a 15 item questionnaire completed by clinicians which indicate severity by rating 0-4 on each item and combining the results for a total score, with a higher score indicating more severity (Pirkis et al., 2005, Gowers et al., 1999). It includes behavioural difficulties, impairments in physical or academic functioning, social interactions and symptoms (Gowers et al., 2000). Next, CGAS evaluations were conducted by all sites. CGAS is a clinicians rating numeric scale of the overall functioning of under 18s, with scores ranging from 1 to 100 (Shaffer et al., 1983). It takes into account multiple domains such as school, home, and social settings, and also considers symptoms, where higher scores indicate better functioning. Finally, RCADS evaluations which consist of multiple subscales were assessed. Contrary to

HoNOSCA and CGAS, RCADS are self-reported symptom measures for major depression, generalised anxiety, separation anxiety, OCD, social phobia and panic disorder (Chorpita et al., 2000). The results are converted to t-scores with regards to age and gender based norms and clinical thresholds are established using normative data (Chorpita et al., 2005). The median scores of the three aforementioned evaluations were calculated and reported.

8.4.7.6 Adverse events

The adverse events associated with the use of antidepressant and antipsychotic medications that were examined were extrapyramidal symptoms (parkinsonian symptoms, dystonia, akathisia and tardive dyskinesia), cardiovascular symptoms (QT prolongation, tachycardia, arrhythmias and hypotension), and sexual dysfunction (erectile dysfunction, amenorrhea and elevated prolactin levels). The rates of individuals with AN who experienced the mentioned adverse events were calculated after a first prescription of a psychotropic medication. The sponsors of this study have a Standard Operating Procedure (SOP) for describing the recording, management and reporting of adverse events by investigators (Maidens, 2019). The SOPs are written in accordance with applicable good clinical practice requirements as outlined in Directives 2001/20/EC (Directive, 2001/20/EC) and 2005/28/EC (Directive, 2005/28/EC) (in the UK, these Directives were transposed into UK law by statutory instrument 2004/1031, statutory instrument 2006/1928) and subsequent amendments and when applicable Regulation 536/2014 and subsequent relevant statutory instruments. As per the SOP, all adverse events were assessed based on clinical severity (mild, moderate or severe, or grades 1-5). Assessment of causality is also required which as per SOP, must be done by the investigator or as in this case, by the lead collaborator at each site. To help with the decision, it is recommended to consider the following: medical history, worsening of exisiting condition, lack of effectiveness, concomitant treatments, erronous treatment with medication, protocol

related process and the evaluation of severity. The causality of the adverse event was classified as definitely, probably, possibly, unlikely, not related or not assessable. In addition, all adverse events must be assessed to see whether they meet one of the serious criteria as per the SOP definition of serious adverse event. Finally, all serious adverse reactions must be assessed for expectedness by categorising the event into expected or unexpected against the current approved reference safety information as per SOP. Further details of the protocol approved by the sponsors JRO for this study can be found in Appendix 12.

8.4.8 Statistical analysis

Descriptive analyses investigated demographic characteristics and psychiatric history for the whole sample and separately for each site. Categorical data was reported as percentages and frequencies. Prevalence of medication prescription was recorded for medication classes and each individual medication. Multilevel mixed effects linear regression analyses were used to capture any change in BMI before and after treatment while taking into account the nested nature of the data. For this particular analysis, medication 0 was defined as no psychotropic medication, medication 1 as receiving antipsychotics only and medication 2 as receiving antidepressants only. The five time points measured were baseline BMI (0), BMI at 1 month (1), BMI at 2 months (2), BMI at 3 months (3) and BMI at 6 months (4), respectively. Where appropriate, 95% CI were calculated using a significance level of 5%. All statistical procedures were performed using STATA version 14.0.

8.5 Results

Over the three year study period, a total of 373 individuals with AN were identified from the four CYP EDS (males=28, 7.51%; females=345, 92.49%). Of these, 288 (77.21%) were diagnosed with AN, 71 (19.03%) with restrictive AN and 14 (3.75%) individuals were diagnosed with binge-purge subtype AN. From the total population, 23.06% of the AN cohort was diagnosed in 2015, 32.98% in 2016 and 43.97% in

2017. The median age at diagnosis for the entire cohort was 15 years (14-16 IQR). The largest ethnicity sub-type identified was that of white British individuals who made up 82.31% of the study cohort or 307 individuals. A breakdown of the characteristics and demographic information of the cohort are provided in Table 18.

Table 18. Characteristics of individuals with AN in the participating CYP EDS sites

	Site 1	**Site 2**	**Site 3**	**Site 4**	**Total**
Number of AN individuals	10	23	88	252	373
Gender					
Females	10	22	82	231	345 (92.49%)
Males	0	1	6	21	28 (7.51%)
Diagnosis					
AN	9	8	61	210	288 (77.21%)
Atypical AN	1	15	21	34	71 (19.03%)
Binge-purge subtype	0	0	6	8	14 (3.75%)
Age at diagnosis (year)	14 (13-14)	15 (14-16)	15 (14-16)	16 (14-17)	15 (14-16)
13	3	6	22	21	52 (13.94%)
14	5	3	15	44	67 (17.96%)
15	1	6	25	55	87 (23.32%)
16	1	5	17	65	88 (23.59%)
17	0	3	9	44	56 (15.01%)
18	0	0	0	23	23 (6.17%)

Ethnicity					
White					
British	9	6	62	230	307 (82.31%)
Any other White	0	2	2	13	17 (4.56%)
Asian					
Indian	0	0	1	3	4 (1.07%)
Pakistani	0	4	2	0	6 (1.61%)
Bangladeshi	0	4	2	0	6 (1.61%)
Any other Asian	1	0	3	2	6 (1.61%)
Black British					
African	0	0	1	2	3 (0.8%)
Any other Black	0	1	0	0	1 (0.27%)
Mixed					
White & Black	0	0	1	0	1 (0. 27%)
White & Asian	0	0	1	1	2 (0.54%)
Any other Mixed	0	1	0	0	1 (0. 27%)
Other ethnic group	0	5	0	1	6 (1.61%)
Missing	0	0	13	0	13 (3.49%)

8.5.1 Comorbidities

Close to a third (n=118) of individuals with AN had a documented record for at least one other psychiatric comorbidity in their electronic health records in addition to their AN diagnosis. The most common comorbidities experienced by the cohort were depression (39.83%), followed by anxiety (33.05%) low mood (20.34%) and OCD (11.87%). Some lesser known comorbidities that were recorded were panic disorder, psychosis, Tourette syndrome (refer to Figure 23).

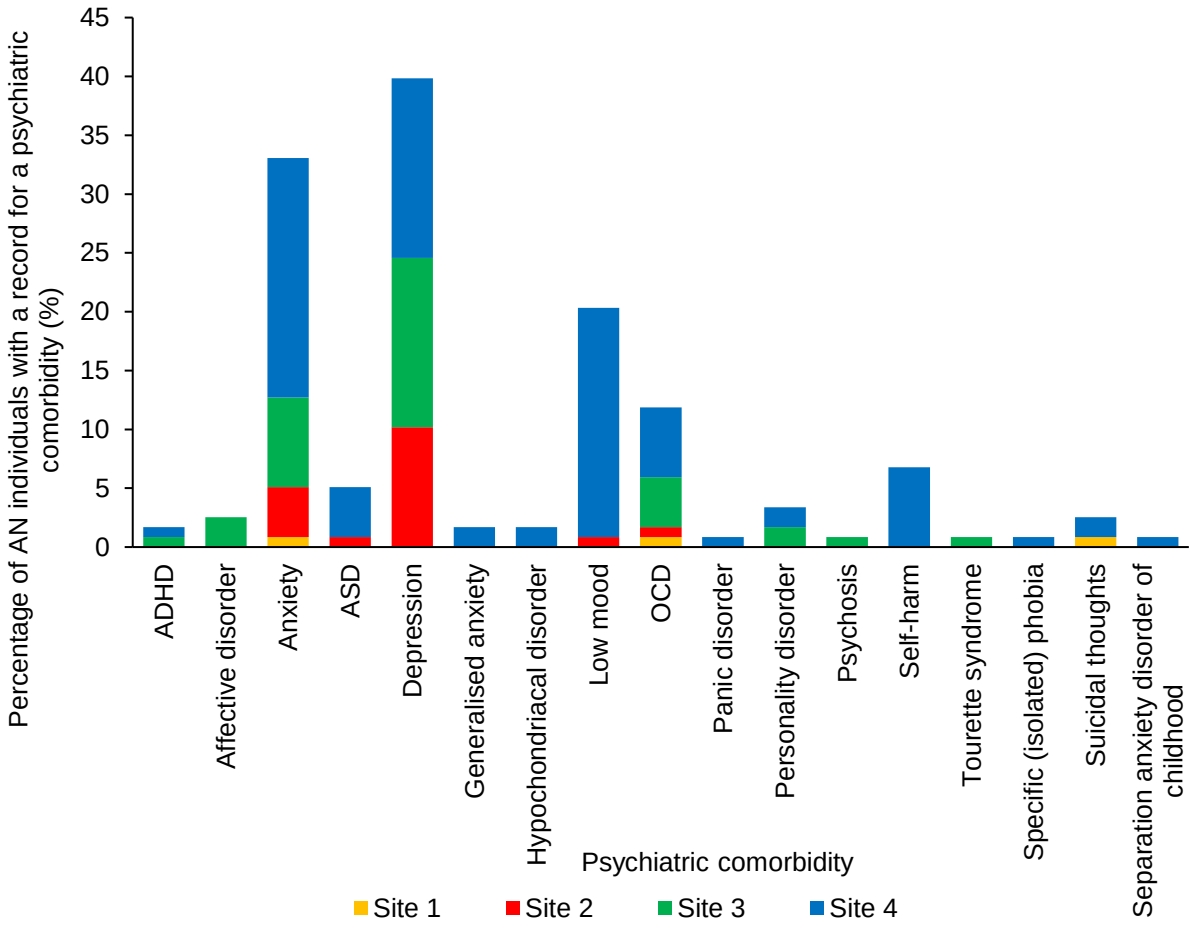

Figure 23. Psychiatric comorbidities experienced by individuals with AN in the participating CYP EDS sites

8.5.2 Treatments

Treatments that AN individuals received varied per site as policies and protocols differ based on the Trust responsible for the CYP EDS site. Overall, the most common treatment was FT-AN, as expected, with two thirds of AN individual's receiving it (66.76%). This was followed by medication therapy, which 53.62% of AN individuals had received at some point after their AN diagnosis. Other prominent therapies included individual therapy, ITP and CBT-ED, with 20.38%, 20.38% and 18.23% of individuals with AN receiving these treatments respectively (see Figure 24). When the results were analysed based on first and second line treatments received post AN diagnosis, FT-AN was the most common choice of treatment as first line treatment. For second line treatment, medication therapy was most frequently given for AN treatment.

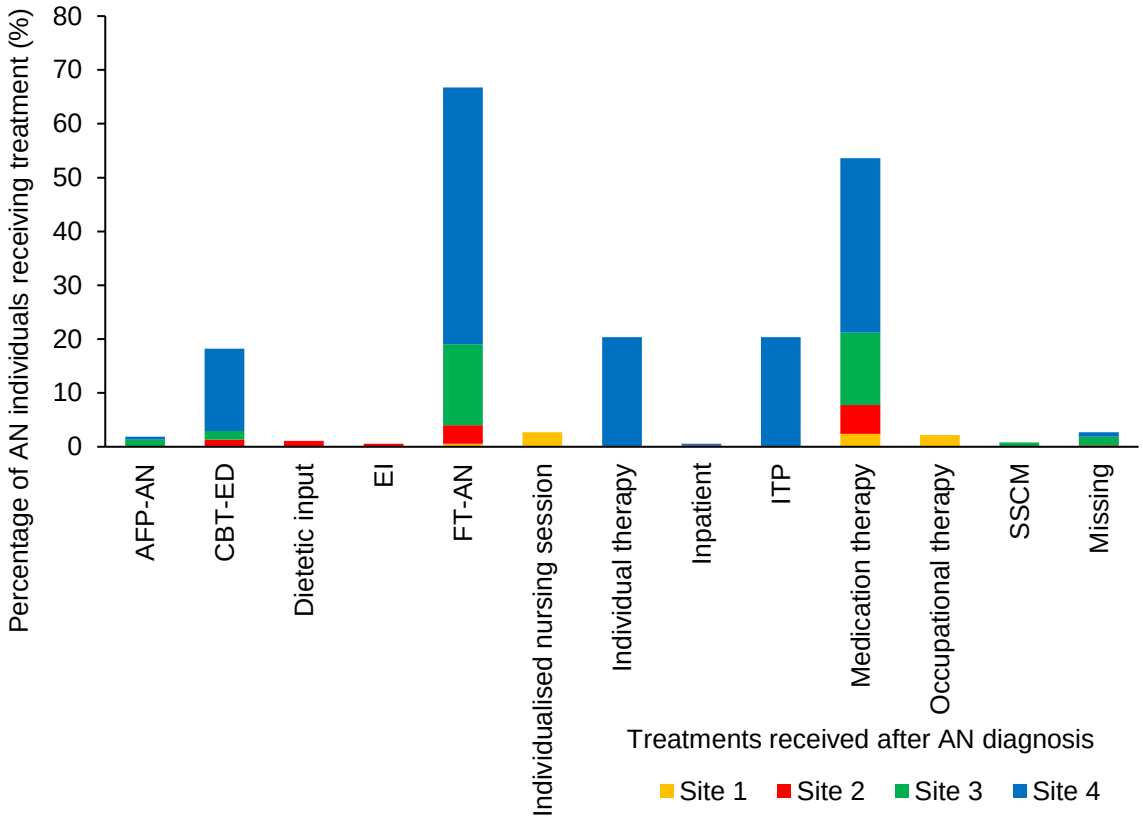

Figure 24. All treatments received for AN in the participating CYP EDS sites for individuals diagnosed with AN

Medication treatment was primarily initiated either on the same day as other therapies, or was the only form of treatment that was given to individuals with AN. It was found that only a fifth of individuals (20%) were initiated on medication after their diagnosis date.

8.5.3 Medications

A total 200 individuals with AN (53.62%) received medication therapy at some point after their AN diagnosis (median of 202 days (IQR 106-278.5 days)). The two most common psychotropic medications prescribed to individuals with AN were olanzapine and fluoxetine, accounting for 41.50% and 40.50% of the total individuals receiving medications respectively. Other frequently prescribed psychotropic medications for AN in the cohort were sertraline (25.50%) and citalopram (14.00%). In some cases, other class of medications that were notably prescribed for AN included promethazine hydrochloride, melatonin and lamotrigine (refer to Figure 25).

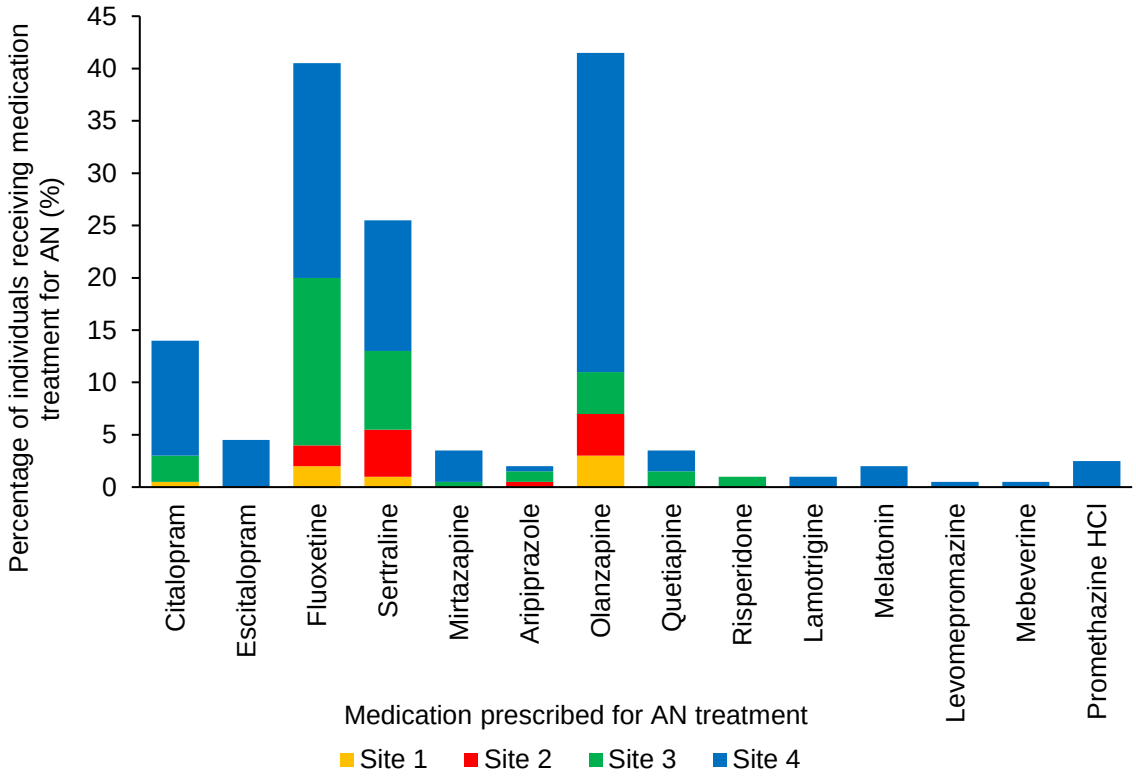

Figure 25. Pharmacotherapy received for AN in the participating CYP EDS sites for individuals diagnosed with AN

The main medications prescribed for individuals with AN were further broken down to evaluate their dosages.

8.5.3.1 Olanzapine dosage

The most common initiation dose recorded for olanzapine was 2.5mg/day (36.14%), followed by 1.25mg/day (28.92%) and 5mg/day (18.07%). Some individuals with AN did receive olanzapine at lower or higher doses than 1.25-5mg/day, however numbers were small. Majority of the records showed that olanzapine was escalated at increments of 1.25 to 2.5mg. The maximum olanzapine dose to have been recorded for individuals with AN was 2.5mg/day (25.30%), followed closely by 5mg/day (24.10%).

8.5.3.2 Fluoxetine dosage

Fluoxetine was mainly initiated at a dose of 10mg/day or 20mg/day by 40.74% and 32.10% of those receiving the medication, respectively. The escalation dose of fluoxetine was predominately in increments of 10mg increase (28.40%). The maximum fluoxetine dose recorded in individuals with AN were 20mg/day (37.04%) and 40mg/day (22.22%).

8.5.3.3 Sertraline dosage

Following olanzapine and fluoxetine, sertraline was found to be commonly initiated at a dose of up to 50mg/day in individuals with AN (62.75%). The dosage was escalated at increments of 50mg and would be given at a maximum dose of 150-200mg/day (25.49-43.14%) in the total AN cohort.

8.5.4 Body Mass Index and pharmacotherapy

To assess the BMI of AN individuals with regards to the pharmacotherapy they received, repeated measures analysis was conducted to measure the median BMI and IQR at five different time points after initiation (Table 19). Result outputs can be found under Appendix 13.

Table 19. The median and interquartile range of AN cohort receiving treatment at five time points

Treatment	**Baseline BMI (kg/m^2)**	**1 month BMI (kg/m^2)**	**2 months BMI (kg/m^2)**	**3 months BMI (kg/m^2)**	**6 months BMI (kg/m^2)**
No psychotropic medication	*n=173*	*n=143*	*n=119*	*n=80*	*n=51*
Median	16.92	17.68	18.10	18.17	18.56
Lower IQR	15.74	16.69	17.28	17.58	17.72
Upper IQR	18.45	18.94	19.24	19.27	19.08
Any psychotropic combination*	*n=50*	*n=43*	*n=39*	*n=35*	*n=25*
Median	17.10	17.30	17.57	17.69	18.30
Lower IQR	15.50	16.24	16.55	17.04	17.90
Upper IQR	17.90	18.17	18.73	18.86	19.73
Antipsychotics only	*n=40*	*n=34*	*n=31*	*n=27*	*n=21*
Median	15.01	16.02	17.00	17.46	18.41
Lower IQR	13.71	14.48	15.44	16.12	16.89
Upper IQR	16.85	17.10	17.94	19.06	19.30
Antidepressants only	*n=100*	*n=75*	*n=67*	*n=59*	*n=41*
Median	17.35	17.91	18.37	18.42	18.55
Lower IQR	16.32	16.76	17.22	17.64	18.11
Upper IQR	18.83	19.49	19.57	19.55	19.54

*****This can be 1) antipsychotic + antidepressant, 2) antipsychotic + antipsychotic, or 3) antidepressant + antidepressant

Table 19 shows that the median BMI at baseline was much lower in individuals with AN receiving only antipsychotics (15.01 IQR 13.71-16.85) compared to those on antidepressants (17.35 IQR 16.32-18.83), any psychotropic drug combination (17.10 IQR 15.50-17.90) or no psychotropic medication treatment at all (16.92 IQR 15.74-18.45). However, by six months, the median BMI of those on only antidepressants and no psychotropic medication reached similar values, however AN individuals treated with antipsychotics only reached a median BMI of 18.41. This is visually represented in Figure 26 as a profile plot.

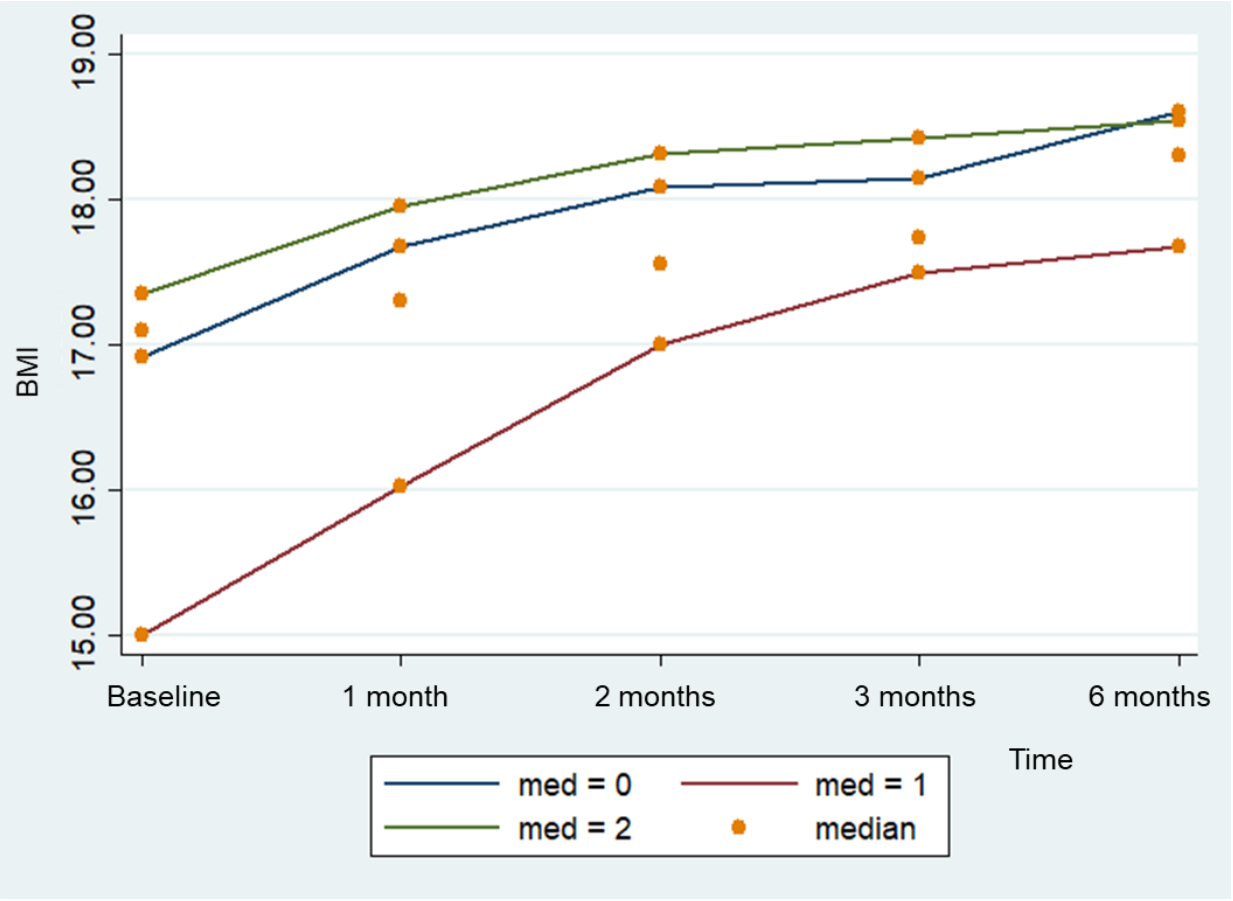

Figure 26. Profile plot of the median BMI of AN individuals at five time points

The sample mean BMI (thick black line) which is an estimate of the fixed part of the model for BMI was found to be 17.82 and the estimate of the sample standard

deviation equalled to 2.08. This was plotted at each time point with regards to the BMI for individuals with AN as shown in Figure 27.

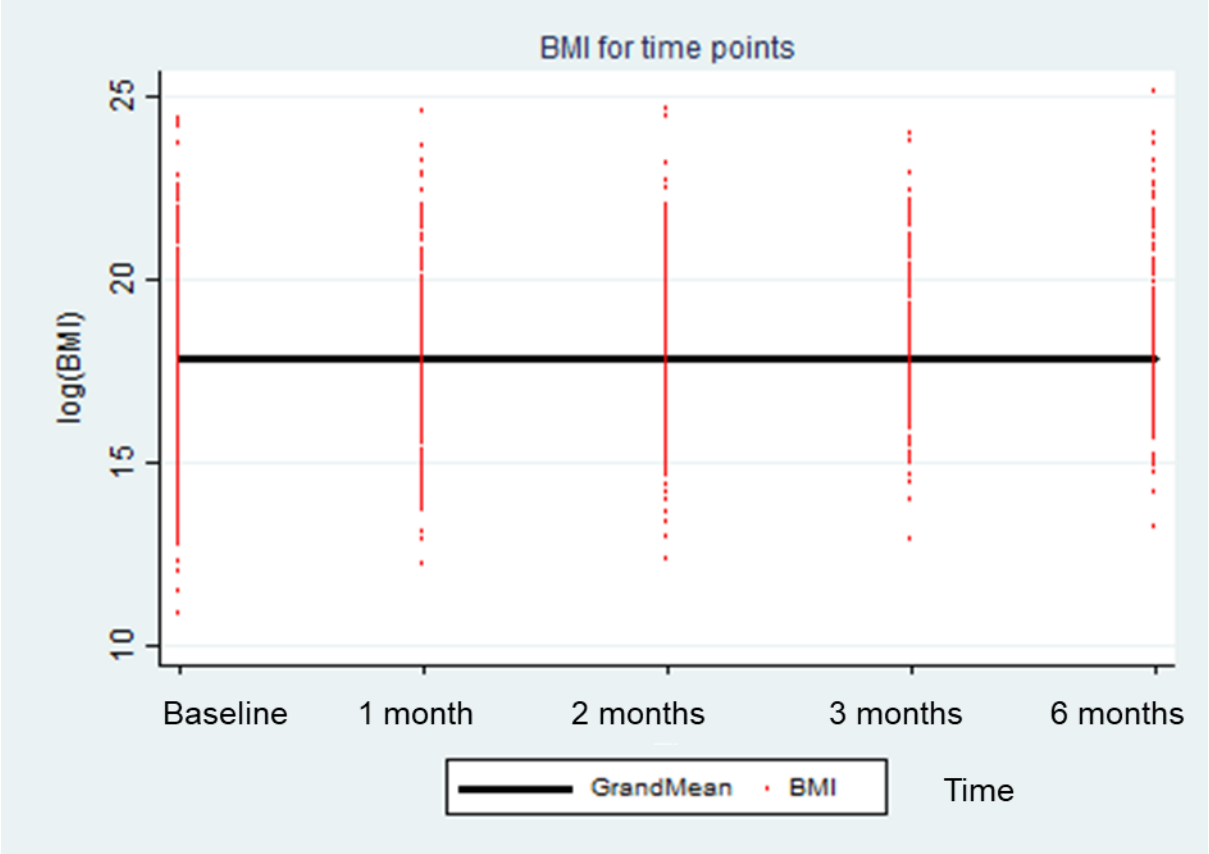

Figure 27. Two-way plot of BMI residuals at five time points with estimate of fixed part of model for BMI

To evaluate the BMI of all individuals who had received no psychotropic medication, antipsychotics or antidepressants, a two-way line plot depicting the BMI of all individuals with AN at five time points (Figure 28) was plotted.

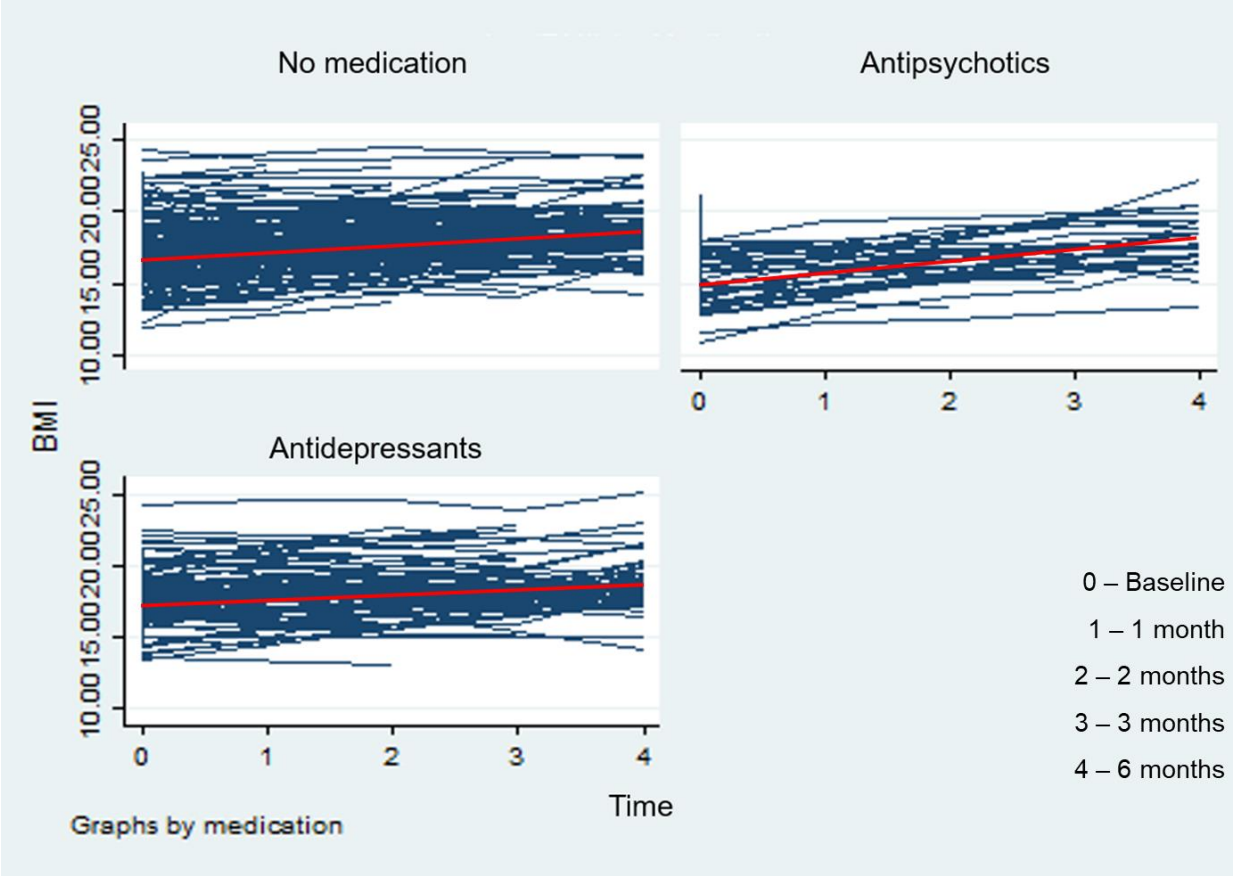

Figure 28. Two-way plot of the BMI of all AN individual's receiving no pharmacotherapy, antipsychotics or antidepressants at five time points with slope

The estimates of the fixed and random effects of the multilevel linear regression are shown in Table 20 below. At baseline, there was a significant difference in AN individuals receiving no medication treatment and those on antipsychotics ($p<0.001$). However there was a small non-significant difference between no medication treatment and antidepressants at baseline, $p=0.125$.

For AN individuals on no psychotropic medication, BMI increased by 0.68 (95% CI 0.54-0.82) at one month after AN diagnosis and by 1.90 (95% CI 1.60-2.20) at six months ($p<0.001$) compared to baseline. When time was considered as a continuous variable rather than the five categorical time points selected, for a one month increase after AN diagnosis, there was a BMI increase of 0.36 (95% CI 0.30-0.42) for individuals not on medication ($p<0.001$).

For individuals on antipsychotics, BMI increased significantly by 0.69 (95% CI 0.40-0.98) at one month after AN diagnosis and by 2.53 (95% CI 1.97-3.09) at six months ($p<0.001$) compared to baseline. When time was considered as a continuous, for a one month increase after AN diagnosis, there was a BMI increase of 0.45 (95% CI 0.34-0.56) for individuals on antipsychotics ($p<0.001$).

For individuals on antidepressants, BMI increased by 0.35 (95% CI 0.16-0.54) at one month after AN diagnosis and by 1.27 (95% CI 0.90-1.63) at six months ($p<0.001$) compared to baseline. When time was considered as a continuous, for a one month increase after AN diagnosis, there was a BMI increase of 0.22 (95% CI 0.14-0.29) for individuals on antidepressants ($p<0.001$).

There were no significant differences in the BMI change from baseline to one month by type of medication treatment, though there was a possible trend towards a slightly larger difference between those on no medication and those on antidepressants, with those on no medications having a slightly larger increase ($p=0.097$). This possible trend for a larger difference was also evident between individuals on antipsychotics and those on antidepressants, with antipsychotics having a larger increase from baseline to one month, although this was found to not be statistically significant ($p=0.199$).

At six months, BMI change compared to baseline was greater in those individuals on antipsychotics compared to those not on medication [0.57 (95% CI -0.01-1.14)], although this just missed statistical significance ($p=0.052$). When compared to individuals on antidepressants, those on antipsychotics had a much greater difference in BMI change at six months [1.29 (95% CI 0.69-1.90)], which was found to be statistically significant ($p<0.001$). When individuals on no medication and those on antidepressants were compared from baseline to six months, BMI change was statistically greater in those not on medication [0.73 (95% CI 0.30-1.15) $p=0.001$].

Table 20. Multilevel linear regression model to evaluate the effects of the number of medication groups and time points in BMI change in individuals with AN

Independent variables	**Estimates**	**SE***	**P-value**
Fixed factors effects			
Intercept	17.824	0.056	<0.001
Medication groups			
No medication	0	-	-
Antipsychotics (AP)	-2.012	0.361	<0.001
Antidepressants (AD)	0.396	0.258	0.125
Time points			
Baseline	0	-	-
1 month	0.679	0.071	<0.001
2 months	1.127	0.099	<0.001
3 months	1.534	0.126	<0.001
6 months	1.900	0.151	<0.001
Medication groups x time points			
No vs AP at baseline	0	-	-
No vs AP at 1 month	0.048	0.274	0.862
No vs AP at 6 months	0.566	0.291	0.052
No vs AD at baseline	0	-	-
No vs AD at 1 month	-0.331	0.199	0.097
No vs AD at 6 months	-0.725	0.216	0.001

AP vs AD at baseline	0	-	-
AP vs AD at 1 month	-0.378	0.294	0.199
AP vs AD at 6 months	1.291	0.308	<0.001
Random factor effects			
Residual (Within-subject variance)	2.077	0.039	<0.001
Intercept (Between-subjects variance)	0.861	0.131	<0.001
Total variance	2.938	-	-

*SE = Standard error

8.5.5 Psychiatric evaluations

HoNOSCA evaluations were only conducted by one site out of the four, initially at baseline and up to two months after AN diagnosis. The median score at baseline was found to be 20, which decreased to 18.5 at one month post AN diagnosis and 18 at two months after diagnosis. However it was difficult to interpret the results as the four key aspects of the scoring criteria must be taken into account.

CGAS evaluations were conducted in all of the participating sites. The median score at baseline for CGAS was 52 which can be interpreted as individuals functioning with sporadic difficulties or symptoms in several but not all social areas. At this level it is often the case that the service provision for the care of AN individuals is that of specialist mental health services. By six months after AN diagnosis, this score reached 76.5 which meant no more than slight impairments in functioning were evaluated in AN individuals and the service provision would be primary health care services.

RCADS evaluations of low mood, total anxiety and OCD subscales were conducted by site one and the low mood subscale RCADS was also conducted by site three. At

baseline, the median RCADS for low mood subscale was 64.5 which was classified as borderline clinically significant. By six months, this value was found to be 59, which is interpreted as not clinically significant. With regards to the results for both the total anxiety and OCD subscale, the results were found to be clinically not significant from baseline to six months.

8.5.6 Adverse events

The adverse events recorded in the medical records were limited. With the consideration of categorising adverse events to extrapyramidal, cardiovascular, sexual dysfunction and other symptoms, only nine individuals had a record for experiencing an adverse event. The only extrapyramidal symptom experienced was dystonia, which one AN individual had experienced during their time at the CYP EDS whilst on treatment with olanzapine at a maximum dose of 7.5mg/day. No cardiovascular adverse events were experienced. For sexual dysfunction, one individual on olanzapine at a maximum dose of 5mg/day had a record for prolactin elevation, which resulted in their dose being reduced to 2.5mg/day to rectify this. Two individuals on treatment with both sertraline (maximum dose of 200mg/day) and olanzapine (maximum dose of 5mg/day) experienced drownisess. Sedation was recorded in the medical records of one individual who received multi-drug treatment with mirtazapine at a maximum dose of 7.5mg/day, olanzapine at a maximum dose of 2.5mg/day and sertraline at a maximum dose of 50mg/day. Two individuals had experienced feeling sick whilst on fluoxetine (maximum dose 20mg/day), of which one individual was also on olanzapine at a maximum dose of 2.5mg/day, which resulted in the cessation of fluoxetine and initiation of escitalopram at a dose of 10mg/day. The few adverse events reported and recorded were of events that were expected, meaning they were consistent with the information in the summary of product characteristics (SPC), manual of operation and the BNF. In addition, none of the adverse events were classified as serious with regards to severity.

8.6 Discussion

In this chapter the results of a multisite retrospective data describing psychotropic pharmacotherapy and the difference in BMI before and after medication treatment in adolescents diagnosed with AN were presented. To my knowledge, this was the largest study to describe a population diagnosed with AN in specialist CYP EDS in England, and to assess any BMI differences before and after pharmacotherapy in this population to date. In this study, I identified a cohort of 373 individuals diagnosed with AN from 2015 to 2017, with at least one year of follow-up. In this cohort of primarily females (92.49%), the median age of AN diagnosis was found to be 15 years old (IQR 14-16). Although AN can emerge at any age, it is commonly agreed by most studies that the typical age of AN onset is early to mid adolescence (Herpertz-Dahlmann, 2009).

Psychiatric comorbidities were recorded in over 31% of AN individuals in this cohort during the study period. Studies have shown that around half of AN adolescents meet the criteria for at lease one other comorbid psychiatric illness (Bühren et al., 2014). The study in this chapter has found depression (39.83%), anxiety (33.05%) and low mood (20.34%) to be the most commonly experienced psychiatric comorbidity among AN individuals as recorded in medical records. Multiple studies and reviews have reported up to three quarters of AN individuals have a lifetime history of mood disorders, most commonly major depressive disorder, or anxiety disorders, which often precede their AN diagnosis (Fernandez-Aranda et al., 2007, Raney et al., 2008, Swinbourne and Touyz, 2007). In my study, OCD was recorded in around 12% of the AN cohort, which was closely in line with a study conducted in AN adolescents which reported that OCD occurs in 15-29% of individuals (Salbach-Andrae et al., 2008).

The most common treatment given at the CYP EDS sites was family therapy for AN (FT-AN), with over two thirds of individuals receiving this treatment. This was in line with first line treatment as recommended by NICE guidelines (NICE, 2018).

Surprisingly however, medication therapy was observed in this study for over half of individuals following their diagnosis of AN. Despite the limited evidence based recommendations by NICE, one study found nearly 90% of adults in an adult partial hospitalisation programme and over 78% of adolescents in a residential adolescent treatment programme were prescribed psychotropics, specifically antidepressants (Garner et al., 2016). The most widely prescribed medication for individuals diagnosed with AN in my cohort was found to be olanzapine (41.50%), fluoxetine (40.50%) and sertraline (25.50%). The findings of this chapter are in line with the findings of a study by Gowers et al (2010), who found that of the 26 different drugs that may be prescribed in CAED services for AN treatment, fluoxetine and olanzapine were the most common (Gowers et al., 2010a, Harrington et al., 2015). The maximum doses of these medications were 2.5-5mg/day for olanzapine, 20mg/day for fluoxetine and 150-200mg/day for sertraline. With the consideration of the limited RCT studies on medication use in AN, my findings were in line with previous studies. In particular, the study in Chapter 5 of this thesis, which also found that CAED psychiatrists reported to prescribe a maximum daily dose of 5mg for olanzapine treatment in AN (Y Beykloo et al., 2019). Compared to the studies included in the systematic review of Chapter 4 of this thesis, this study is of a much greater sample size (n=373) conducted in the UK. This chapter demonstrated a head to head comparison of antipsychotics, antidepressants and no medication in conjunction with psychotherapy for the treatment of AN as opposed to the studies included in the systematic review, where drugs were compared either to a placebo or to no medication at all.

This study found that despite individuals with AN receiving antipsychotics starting at a lower median BMI of 15.01kg/m^2 compared to antidepressants (17.35kg/m^2) or no medications (16.92kg/m^2), by six months, this increase in BMI resulted in a median BMI of 18.41kg/m^2 for those on antipsychotics. Antidepressants had the least change in BMI over time. A possible mechanism was proposed by Uher et al (2009) stating individuals with higher BMI may have decreased efficacy due to a larger distribution

volume of lipophilic antidepressants which can lead to inadequate plasma levels (Uher et al., 2009), although studies prior to this provided no evidence for such a relationship between antidepressant plasma concentration and clinical response (Amsterdam et al., 1997, Norman et al., 1993).

Although there was no significant difference in BMI change from baseline to one month post AN diagnosis, there was a possible trend towards a slightly larger difference between those not on medication and those receiving antidepressants, and individuals on antipsychotics and those on antidepressants. By six months, BMI change from baseline was greatest in those using antipsychotics compared to those using antidepressants (1.29kg/m^2, $p<0.001$). There was also a statistically significant greater change in BMI in those receiving no medication compared to those receiving antidepressants at six months (0.73kg/m^2). However, when the change in BMI was compared between those using antipsychotics and those receiving no medication, despite a change in BMI of 0.57kg/m^2 from baseline to six months, there was marginal statistical significance ($p=0.052$). Although the sample size of those still receiving antipsychotics at 6 months was small and the findings show marginal significance, its been reported that borderline significance does not necessarily mean that the results are ineffective. Rather, it is important to emphasise that CI's are a better indicator of likelihood of an effect and its size, thus the true effect is more likely to lie around the middle of the confidence interval than at either end (Hackshaw and Kirkwood, 2011). Two studies presented in the systematic review chapter of this thesis (Chapter 4) reflect similar results. First, Kafantaris et al. (2011) found that although the mean percentage of mean body weight improved in both olanzapine and placebo groups within the 10 weeks, there was no further increases in the olanzapine group at any time point in comparison to the placebo. Second, Norris et al. (2011) found the rate of weekly weight gain and BMI at discharge was greater in the 43 patients in the olanzapine group in comparison to the 43 matched control patients not on olanzapine treatment, despite not being statistically significant. In this chapter, my study has

shown that at six months (24 months), increase in BMI was significantly greater in the antipsychotic group compared to those on antidepressants and marginally significant to those not on medication. The large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study conducted in 57 US sites on individuals with chronic schizophrenia found significant differences in the proportion of individuals gaining weight of ≥7% from their baseline weight when comparing olanzapine (30%), quetiapine (16%) and risperidone (14%) among other antipsychotics over an 18 months duration (Lieberman et al., 2005). Olanzapine has also been found to have the highest weight gain among antipsychotics in the Schizophrenia Outpatient Health Outcomes (SOHO) database with a mean of 4.2kg reaching a peak in the first 6-12 months and not plateauing (Bushe et al., 2012). Several meta-analyses on children and adolescents have also been conducted which report the risk of olanzapine inducing more weight gain than any other atypical antipsychotic, with results of 3.45kg (De Hert et al., 2011), 3.99kg (Cohen et al., 2012) and 7.2kg (Almandil et al., 2013) reported in individuals with antipsychotics experiencing adverse effects and 3.8-16.2kg in young people with psychotic and bipolar disorders (Maayan and Correll, 2011). On the contrary to some studies that have shown other psychiatric conditions such as schizophrenia and bipolar disorder being given antipsychotics as treatment and witnessing weight gain as a common side effect, this is not persistantly reflected so in AN individuals (McKnight and Park, 2010, Chwastiak et al., 2009, Hay and Claudino, 2012). A cross sectional study on weight gain in individuals using antidepressants found that sertraline, paroxetine, citalopram, escitalopram, mirtazapine, venlafaxine and duloxetine were associated with significant weight gain, however this was not the case for fluoxetine as it had no effect on body weight ($p=0.893$) (Uguz et al., 2015). One of the most recent population based cohort studies using CPRD evaluated the long term association between antidepressant prescribing and body weight and found mirtazapine to be associated with the greatest adjusted rate ratio (1.50) of weight gain between the antidepressants, despite it being

infrequently prescribed. They also reported that the use of antidepressants for less than one year appeared to not be associated with weight gain (Gafoor et al., 2018). Similarly, a large US database study evaluating weight change after atypical antidepressant use over two years found that when compared to fluoxetine, individuals using sertraline gained an average of 5.9lbs (equivalent to 4.8kg) in weight compared to 4.6lbs (2.1kg) (Arterburn et al., 2016). Contrary to this, some older studies have found that SSRIs may lead to improvements in weight over short term use in children and adolescents however not in long term use (Nilsson et al., 2004, Emslie et al., 2004). A study by Blumenthal et al (2014) using electronic health records reported that SSRIs were similar in rate of weight gain when compared to citalopram over a duration of 12 months, however less weight gain was observed with fluoxetine (Blumenthal et al., 2014).

Psychiatric evaluations varied between different sites as not all used the same ones. Documentation of these evaluations were found to be poor in this study. Most of the individuals with AN had a record for some form of psychiatric evaluation upon initial assessment, however records for further assessments of these evaluations were few in numbers. This is despite other studies reporting that the therapeutic use of psychiatric evaluations like HoNOSCA for conditions such as AN look promising and individuals with AN might be encouraged to gain weight and evaluate improvements or deterioration in their recovery (Gowers et al., 2002).

With regards to adverse events experienced in this AN cohort, it was sparsely reported based on the data identified from patient records. None of the adverse events were classified as serious and they were deemed as expected based on information from SPC and BNF. Summarised in Chapter 4, Kafantaris et al. (2011) also highlighted in their study that they observed no immediate safety concerns with olanzapine use in the 10 weeks duration of their however suggested close monitoring for long term use. Besides feelings of drowsiness, feeling sick and low mood, the adverse event of prolactin elevation experienced by one AN individual on olanzapine

was of interest. The findings of this study were consistent with other published studies that have found atypical antipsychotics such as olanzapine to increase the likelihood of prolactin levels in the younger populations (Pringsheim et al., 2011b, Spettigue et al., 2018).

8.6.1 Strengths and limitations

To my knowledge, this was the largest study comprising an adolescent AN population using UK secondary care data, where diagnoses, treatment and management often occur, to date. One of the main strengths of this study was the data size and likely generalisibility of this cohort as I used multiple sites that provide near monopoly coverage of the geographical areas and cover ethnically diverse populations within England. In addition, the data for this study was from medical notes of AN patients in four secondary mental health care providers in England, which are in line with other national and international data, ensuring the data was more generalisable to other services and areas. However the study was limited to and only accounted for individuals receiving secondary care, thus lacks cases that were managed exclusively in primary care. In addition, as the source of data was secondary care services, there may be an underestimation of AN cases because not all those experiencing psychiatric conditions will be referred by GPs or self referred to secondary care. Another strength of this study was the use of full clinical care records, which ensured that high level of detailed clinical data was collected. In particular, data on medication therapy and repeated measure of BMI was more detailed than in many previous observational studies which were often limited by sample size. However, it is important to consider that the quality of the clinical data was primarily dependant on the comprehensiveness and accuracy of the data completed by clinicians and other health care professionals recording data and thus may have had some missing data.

8.6.2 Conclusion

In conclusion, medication treatment was a common form of therapy for AN treatment in children and adolescents that were under the care of the participating specialist CYP EDS sites. Treatment with antipsychotics appears to have a significant increase in median BMI of the cohort from AN diagnosis until six months, in comparison to antidepressant treatment. The adverse events experienced with psychotropics are few in this cohort and suggests a favourable safety profile for its use in the treatment of AN.

8.6.2.1 Recommendations for future research

The results of this study and the lack of available literature on pharmacotherapy in AN emphasise the need for future research to be conducted on a larger scale. Considering the recent increase in specialist CAMHS like CYP EDS in England and the referral of patients to these services, studies can evaluate treatment in the adolescent AN population in more recent years, covering larger populations. In addition, evidence based methodological studies can be designed for evaluating the effectiveness and safety of psychotropic medications in adolescent AN populations with large sample sizes, in order to provide guidance for updates in the NICE guidelines for pharmacotherapy in AN.

8.6.2.2 Implications for clinical practice

The findings of this study provide an insight into the psychotropic medications prescribed in the adolescent AN population in specialist CYP EDS and its potential impact on BMI as an outcome measure of the effectiveness of treatment. Psychotropic prescription given as AN therapy appears to be common in CYP EDS in England, however a lack of clear guidelines on its prescription is of particular concern. It is essential that healthcare professionals consider the benefits and harms of these medications in vulnerable cohorts such as AN adolescents in order to provide the best care. It also helps emphasise the necessity for comprehensive and accurate documentation of clinical data in secondary care, which can help in conducting observational studies for understudies conditions like AN.

Summary

- This is the largest study on the adolescent AN population using UK secondary care data, where diagnoses, treatment and management often occur.
- This study found that over half of adolescents diagnosed with AN in CYP EDS are prescribed psychotropic medications for pharmacotherapy.
- Findings show that from baseline to six months after AN diagnosis, BMI difference was significantly greater in antipsychotics groups compared to antidepressants by 1.29kg/m^2 ($p<0.001$). This was also evident in those receiving no medication compared to those receiving antidepressants by 0.73kg/m^2 ($p=0.001$).
- Adverse events experienced in the AN cohort were sparsely reported and none were classified as serious adverse events.

Chapter Nine

Discussion and conclusion of thesis

Outline

In this chapter, the main findings from the previous chapters are drawn together to summarise the key information and implications of the results. As this thesis explored pharmacotherapy in individuals with AN through 1) the perspective of health care professionals and prescribers in England, 2) primary health care setting, and 3) within multisite specialised secondary health care settings, the findings provide a holistic summary. This chapter evaluates the strengths and limitations of the studies prior to a conclusion.

9.1 Medications

Concerns have been raised about the use of psychotropic medications for the treatment of individuals with AN. A detailed summary of studies conducted on medication treatment in AN can be found in Chapter 1.6.2. Despite not being the first line treatment recommendation as per NICE guidelines, they are still prescribed as adjuncts to psychological therapies. Previous publications have been conducted reviewing the current scientific evidence for medication use in eating disorders like AN (Flament et al., 2012, Claudino et al., 2006, Mitchell et al., 2013, McKnight and Park, 2010). However most conclude there is still a lack in large scale, well designed trials which evaluate individuals seen in clinical settings, with comorbid conditions, in order to assess long term outcomes.

In this thesis, the use of medications in individuals with AN was investigated in multiple ways. First, a systematic review was set out to perform an extensive literature search on the safety and efficacy of psychotropic drugs in adolescents with AN. Following the review, the use of psychotropics was explored in prescribing health care professionals in both primary care and secondary health care settings.

9.1.1 Summary of the research

The most important findings were:

- The survey in Chapter 5 asking CAED psychiatrists to estimate the percentage of their patients on medication therapy for AN found that the majority of CAED psychiatrists estimated under 10% of their patients were on psychotropic medication in their service. The results from primary care in Chapter 7 using THIN found that nearly half of AN individual's (47.44%) from 1996 to 2016 had a record for a psychotropic medication. This was also reflected in the secondary care data in Chapter 8 where just over half of the AN cohort (53.62%) had been prescribed psychotropic medications for the treatment of AN.
- The most common medications prescribed for AN were the same in the studies conducted for this thesis. Chapter 5 found that the two most common medications CAED psychiatrists self-reported prescribing were olanzapine (38%) followed by fluoxetine (29%). This was reflected in the primary care data in Chapter 7. However, the difference was in the order of most common medication, as a record for fluoxetine prescription was observed in 60.86% of the AN primary care population on antidepressants, followed by olanzapine in 51.49% of AN individuals on antipsychotics. Similar to the results in Chapter 5, the secondary care data in Chapter 7 found olanzapine was the most common medication prescribed (41.50%) for AN treatment, closely followed by fluoxetine (40.50%) in the AN population. It is notable that the most common psychotropic medications that the studies of this thesis have identified are olanzapine and fluoxetine, which fits in line with previously published studies in this area.
- The prescribing of olanzapine was described in Chapters 5 and 8 by studies based on self-reporting of CAED psychiatrists and the recorded secondary care medical data, respectively. The results from both chapters showed the most common initiation dose of olanzapine as 2.5mg/day. Chapter 5 shows

that self-reported increase in dosage was done in increments of 2.5mg, whereas the secondary care data in Chapter 8 showed dosage increments of 1.25 to 2.5 mg. The maximum dosage prescribed for olanzapine as reported by CAED psychiatrists was 5mg/day (53%) for a total duration of less than six months. This was in line with results from Chapter 8 where 25.30% were prescribed a maximum dosage of 2.5mg/day and 24.10% were prescribed a maximum dosage of 5mg/day in the AN population.

Figure 29 is a summary of the main findings of the chapters in this thesis with regards to medication use in AN.

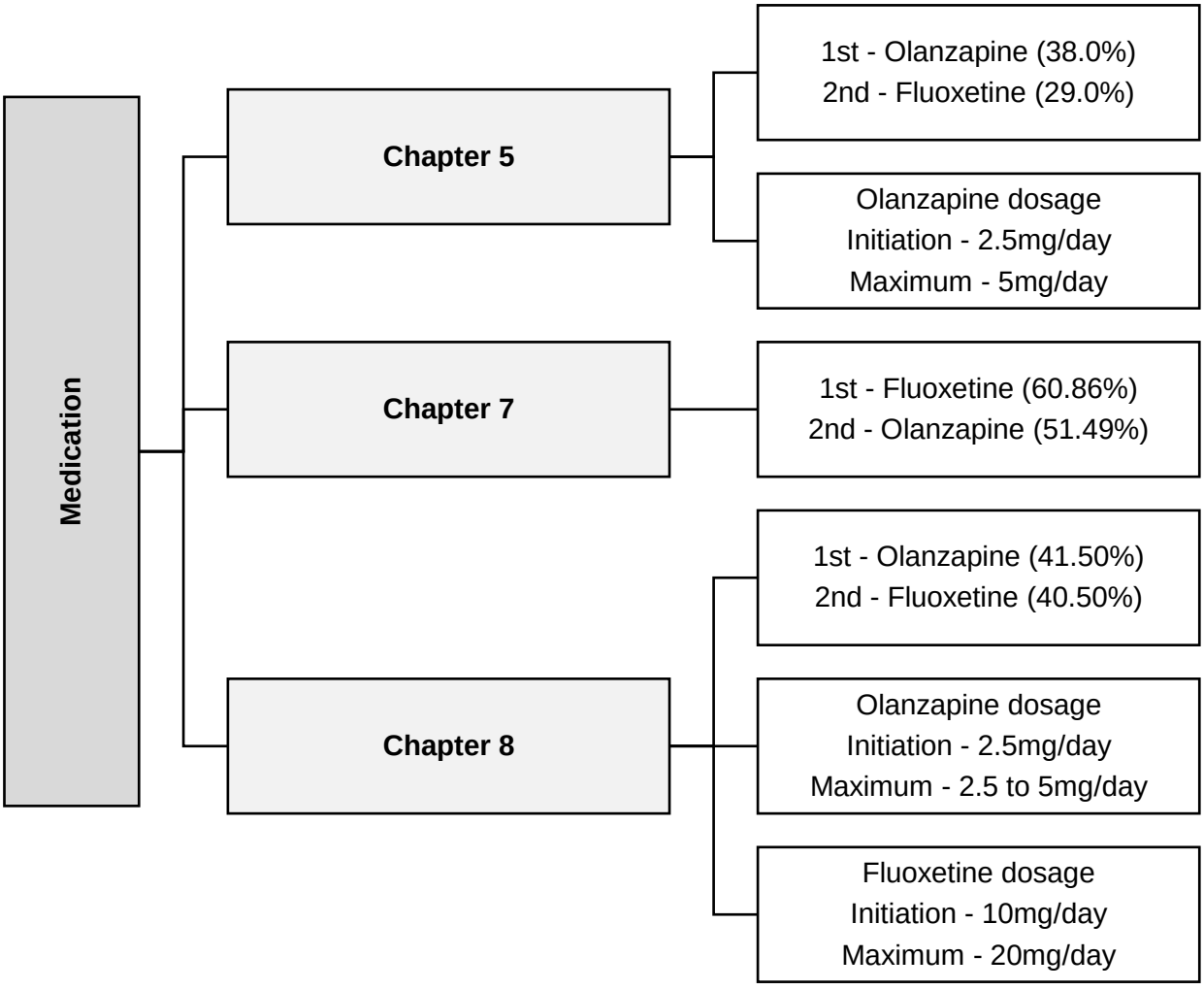

Figure 29. Summary of the main findings of medication use in AN

9.2 Comorbidities

In clinical populations, comorbidity studies have been conducted which have suggested strong associations between eating disorders like AN and other psychiatric comorbidities (Gadalla, 2008). A few of the most common psychiatric conditions associated with AN include anxiety disorders, major depressive disorders and OCD (O'Brien and Vincent, 2003a, Woodside and Staab, 2006, Godart et al., 2002, Godart et al., 2007).

For this thesis, initially all comorbidities associated with AN based on existing literature were explored in the primary care database. Following on from that, psychiatric comorbidities were explored further with regards to psychotropic prescriptions in individuals with AN. Similarly, psychiatric comorbidities were also explored in secondary care data.

9.2.1 Summary of the research

The most important findings were:

- Within the primary care database (Chapter 6), comorbidities were recorded in 62.74% of the population with AN. The most common comorbidity in individuals with AN was psychiatric comorbidities (45.64%), of which 84.14% of them were females. This was followed by reproductive (26.46%), nutrient and mineral imbalances (9.49%), bone (6.24%) and cardiac (2.68%) comorbidities. When results were evaluated in time periods before and after a record for an AN diagnosis, 20.96% had a record for any comorbidity within the one year leading to their AN and 30.55% received a comorbidity diagnosis up to one year after they had already received their AN diagnosis.
- As described in Chapter 6, psychiatric comorbidities are the most prevalent in individuals with AN. The most common psychiatric comorbidity was depression (91.32%), followed by personality disorders (10.06%) and anxiety

(6.13%) in AN individuals. Similarly, in Chapter 7, amongst AN individuals with records of psychotropic medications, depression was identified as the most common of the psychiatric comorbidities recorded for those taking antidepressants (93.24%) and antipsychotics (81.91%).

- In Chapter 8, psychiatric comorbidities were recorded in 31.64% of the individuals with AN in the secondary care data. As reflected in the primary care database, secondary care data also found the most common of the psychiatric comorbidities to be depression (39.83%), anxiety (33.05%), and low mood (20.34%).

Figure 30 is a summary of the main findings of the chapters in this thesis with regards to comorbidities in AN.

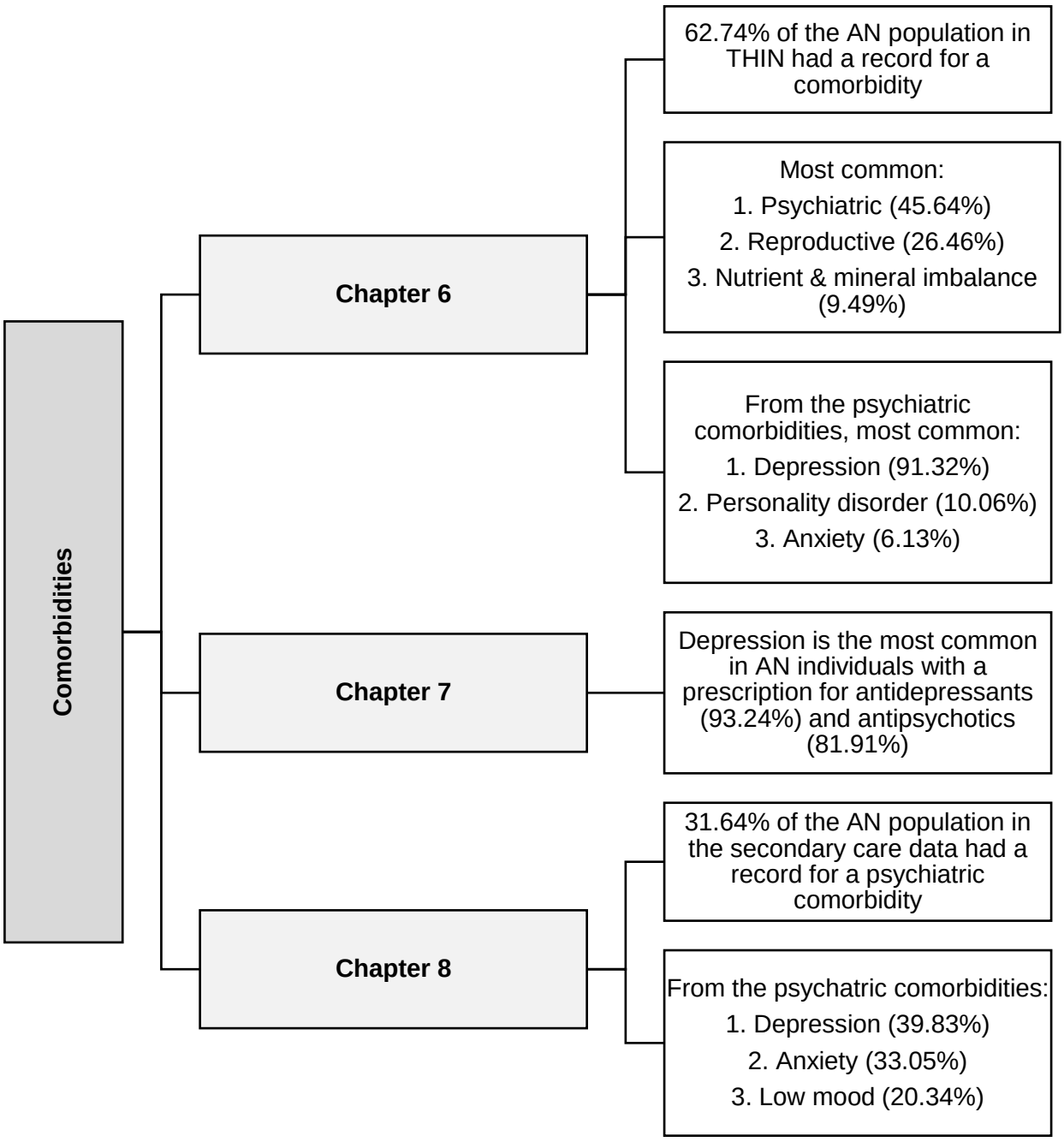

Figure 30. Summary of the main findings of comorbidities in AN population

9.3 Weight change

Treatment objectives in AN include weight gain, prevention of weight loss, a change in eating behaviour, reduction of associated psychopathologies and treatment of associated conditions (Aigner et al., 2011). Studies evaluating the effectiveness of pharmacotherapy in AN often use weight as an outcome measure (refer to Chapter 4), which is a crucial part of recovery and enables the correction of other somatic functional conditions.

In this thesis, an outcome for measuring effectiveness of psychotropic medications in AN was weight change. Due to the nature of AN, an increase in weight can be a useful outcome to ensure the treatments have been proven to be beneficial, as one of the main goals of treatment in AN includes restoring the individual to a healthy weight. In secondary care data analysis, the difference in BMI between individuals that were prescribed different psychotropic drug classes was described as shown in Chapter 8.

9.3.1 Summary of the research

The most important findings were:

- From the preliminary step of exploring BMI data in THIN, I identified over half (N=4,712, 56.44%) of the total AN population in the primary care data (Chapter 6 and 7) had a BMI reading close to their first prescription of a psychotropic medication. Of these, only half (N=2,441) continued to have BMI measurements recorded in primary care in THIN after a first psychotropic prescription. Contrary to this and as expected, BMI was well recorded and thorough in secondary care data (Chapter 8), as all the individuals with AN had a minimum of one recorded BMI value upon AN diagnosis.
- The preliminary analysis of the primary care database informed me that the majority (65.42%) of the AN individuals were classified during the analysis as having a normal BMI (18.5-25 kg/m^2) on or after their first psychotropic

medication prescription. In addition, based on the definition of AN diagnosis with regards to BMI, individuals with BMI classifications of underweight (17.75-18.5 kg/m^2), mild anorexia (17.75-17.0 kg/m^2) and moderate anorexia (16.0-17.0 kg/m^2) were at similar proportions, with 26.51%, 27.65% and 24.95% of the AN population, respectively. Under a third of AN individuals had a BMI record which classified as severe (15.0-16.0 kg/m^2) or extreme anorexia (under 15 kg/m^2) at some point during the study period in the primary care database. The average BMI for the total AN secondary care cohort in Chapter 8 was calculated as 17.82 kg/m^2 (SD 2.08), which was classified as underweight.

- In Chapter 8, the median BMI values for different treatments in the AN secondary care cohort were described at baseline upon AN diagnosis. These were found to be 15.01 kg/m^2 (IQR 13.71-16.85) for those on antipsychotics only, 17.35 kg/m^2 (IQR 16.32-18.83) for those only on antidepressants and for AN individual's not on medication treatment, the median was 16.92 kg/m^2 (IQR 15.74-18.45). At six months after AN diagnosis, the median BMI for those on antipsychotics only was 18.41 kg/m^2 (IQR 16.89-19.30), those on antidepressants only was 18.55 kg/m^2 (IQR 18.11-19.54) and those not on any psychotropic medications for AN treatment had a median BMI of 18.56 kg/m^2 (IQR 17.72-19.08).
- The results from Chapter 8 showed there were no significant differences in the BMI change from baseline to one month after AN diagnosis by type of medication treatment, however at six months, differences between treatments were observed. BMI change compared to baseline was greater in those receiving antipsychotics compared to those on no medication [0.57 (95% CI -0.01-1.14)], although this just missed statistical significance (p=0.052). When compared to those on antidepressants, individuals on antipsychotics had a much greater difference in BMI change at six months [1.29 (95% CI 0.69-

1.90)], which was also found to be statistically significant (p<0.001). When no medication and antidepressants were compared from baseline to six months, BMI change was statistically greater in those individuals not on medication [0.73 (95% CI 0.30-1.15) p=0.001].

Figure 31 is a summary of the main findings of the chapters in this thesis with regards to weight change in the AN population on psychotropic medications.

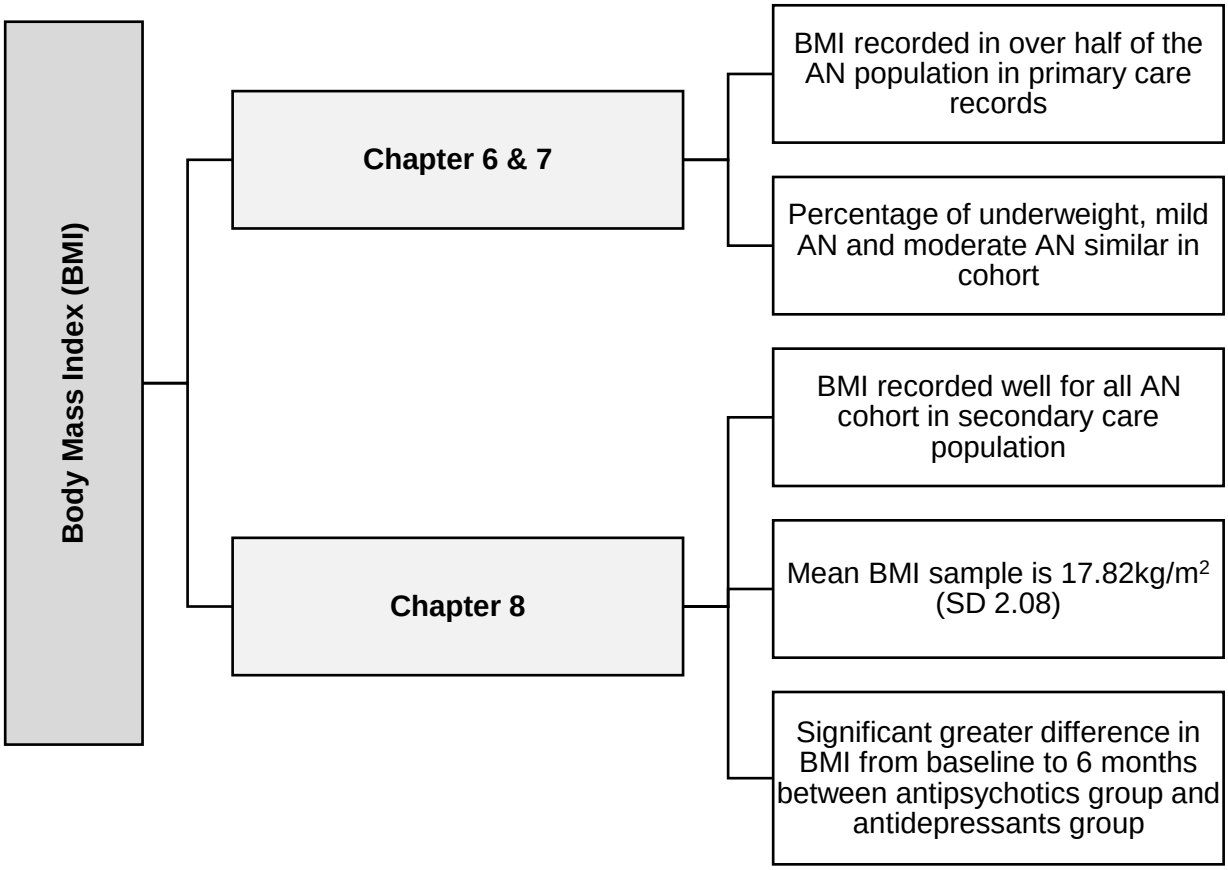

Figure 31. Summary of the main findings of weight in AN population on psychotropic medications. SD = standard deviation

9.4 Adverse events

The majority of medications used for AN treatment are used off-label (Aigner et al., 2011). They are widely prescribed, however not in compliance with national or international guidelines, thus can be potentially unsafe for individuals with AN (Garner et al., 2016). In addition, the peak onset of AN is in adolescents, who are classified as a vulnerable group, which raises questions about the use of psychotropic drugs like antipsychotics, in this group.

For this thesis, the safety profile of psychotropic medications was explored in the systematic review (Chapter 4), in primary care database (Chapter 7) and in secondary care setting (Chapter 8). The systematic review assessed the safety of psychotropic drugs in AN by measurements of adverse events through various assessment scales, reported side effects, safety measurements such as ECG and laboratory test results and finally, death. In the primary care analysis in Chapter 7, the rates of adverse events defined as serious were of extrapyramidal, cardiovascular, and sexual dysfunction nature were calculated after a prescription for psychotropic medications. Similarly, rates of adverse events were also calculated in Chapter 8 based on secondary care data, in addition to assessing severity and causality of the event.

9.4.1 Summary of the research

The most important findings were:

- Two studies were identified in the review in Chapter 4 reporting adverse events. One study reported sedation as the most common side effect of olanzapine, and the other reported significantly higher results in depressive symptoms and psychopathology scores in SSRI groups within a 10 week study period. Similar results were reflected in secondary care (Chapter 8) where sedation was recorded in the medical records of one individual and drowsiness was experienced by two individuals with AN.

- The results of Chapter 7 presented amenorrhoea as the most common adverse event recorded in primary care database. This was followed by parkinsonian (3.50%), dystonia (2.02%), and hypotension (1.57%). However, in the secondary care AN cohort, drowsiness, feeling sick, prolactin elevation, dystonia and sedation were the only adverse events reported, and at very low frequencies.
- In Chapter 8, a few adverse events were reported and upon assessment for severity and causality, presented to be not of a serious adverse event nature. The limited information on adverse events indicates that psychotropic use is not a serious risk and gives reassurance for their prescription in AN population.

Figure 32 is a summary of the main findings of the chapters in this thesis with regards to adverse events in the AN population on psychotropic medications.

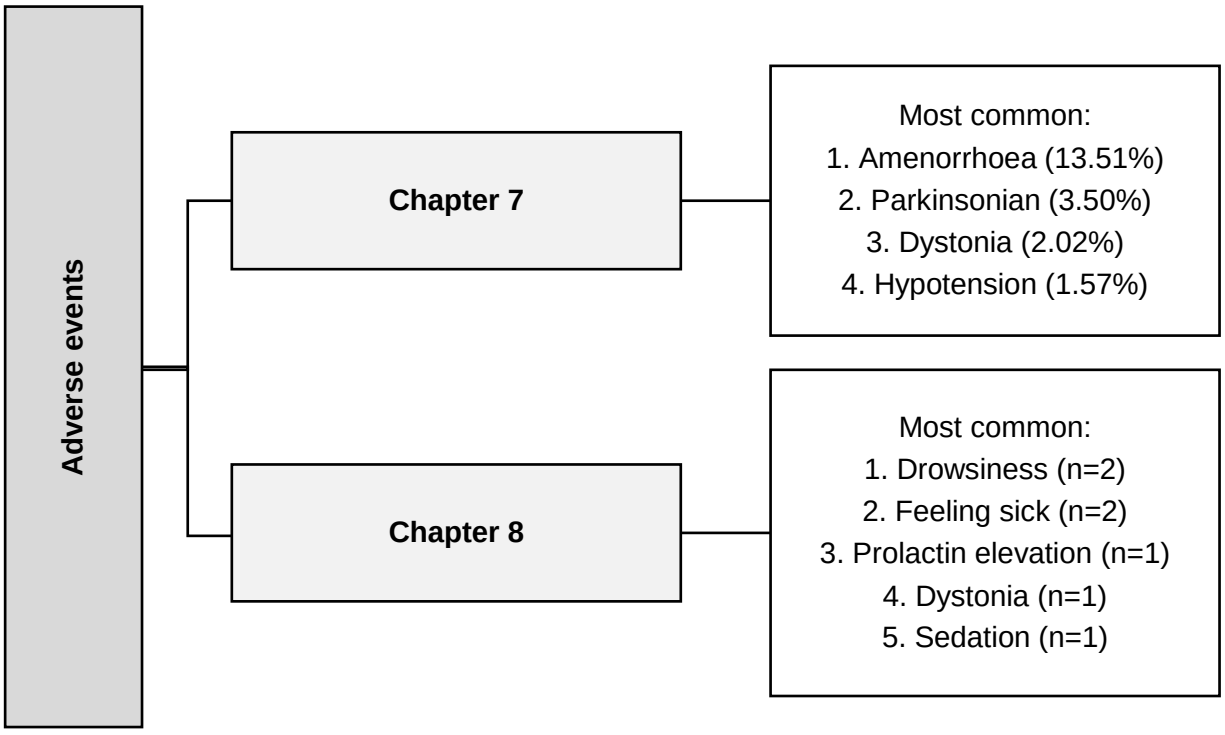

Figure 32. Summary of the main findings of adverse events in AN population on psychotropic medications

9.5 Strengths and limitations

In this thesis, psychotropic drug use in individuals with AN was investigated and described in both primary and secondary care, as well as from the perspective of prescribers.

Systematic reviews are important to summarise the results of existing clinical research studies and provide high level evidence on the effectiveness of healthcare interventions. Essentially, they enable researchers to assess the evidence for any benefits or harms from treatments in healthcare. Yet one major limitation of systematic reviews is publication bias (Sutton et al., 2000), where studies with significant findings are more likely to be published compared to studies with negative findings or non-significant results (Hopewell et al., 2009). In order to combat this, a statistical method called funnel plot can be used to graphically detect the existence of publication bias, by plotting intervention effect estimates from each study against the measure of each study size (Cochrane, 2017). However due to the small sample size in the RCTs in my systematic review, I was unable to assess publication bias using this method. In my review, three RCT studies were included which assessed the effectiveness of psychotropic medications and adverse events of these medications in adolescents with AN (Hagman et al., 2011, Kafantaris et al., 2011, Weizman et al., 1985). RCT study designs are considered the gold standard for the investigation of drug efficacy, however, it is likely that some severe adverse drug reactions will not be detected during the trial period (Hariton and Locascio, 2018). This may be due to many factors, including a small sample size which would make it hard to detect a rare effect, short duration of study follow-up time, and the strict inclusion and exclusion criteria for study participants. Nevertheless, the Cochrane's risk of bias assessment tool was still used to investigate bias in the three RCTs of the review in Chapter 4 (Higgins et al., 2011). In addition, quality assessment for the seven observational studies was also evaluated using the modified NOS.

As established, RCTs are only able to provide evidence of treatment effect under strict, protocol controlled conditions for a defined period of treatment in a selected group of participants (Klungel et al., 2004). An important strength of observational studies is that they typically involve large and diverse populations of patients in real world setting and determine the effectiveness of drug treatment in routine clinical practice (Nallamothu et al., 2008). They also allow for stratification of results into subgroups of patients on the basis of characterisation in order to reduce confounding bias. The rise of confounding or selection bias in determining drug effect is often due to an absence of randomisation in observational designs, which makes it difficult to compare the treated and untreated populations (Nallamothu et al., 2008). The benefit of observational studies for my studies in Chapters 6, 7 and 8 was that it enabled examination of uncommon diseases like AN and detection of rare complication or minor treatment effects, in a relatively inexpensive and rapid manner in large populations.

9.6 Implications for practice and future research

AN continues to be a problem in the UK and worldwide. It is important to examine how health care professionals are addressing this critical issue in order to identify the need for further training and services in clinical practice. This thesis provides a timely and useful update of primary and secondary care practice on prescribing medication for AN treatment in children and young people. Results of this thesis can help generate recommendations for clinical practice in the management of AN, which may further inform policy guidelines. Despite the current NICE guidelines, we have seen that clinical practitioners support the development of a prescribing guide on AN treatment in children and young people. In addition, health care professionals, in particular CAED psychiatrists, should be offered further training and support on the appropriate psychotropic drug to prescribe based on evidence-based practice. Below are suggestions for future research.

The first beneficial area for further research that was identified would be to explore the perceptions and concerns of individuals with AN and their families on psychotropic drug use for AN management and the reasons and possible factors for continuation or cessation of treatment through qualitative research. In-depth, semi structured face-to-face interviews with adolescents and their parents/carers can be conducted. In this thesis, it was not possible to investigate the views due to the complexity of obtaining ethical approval for such a vulnerable group in the time restraints of a PhD.

A second area of work identified for future research should be to develop a collaborative, prospective, AN pharmacotherapy management network for children and adolescents across CYP EDS in England. Although the findings of Chapter 8 reported in this thesis came from four specialist sites, they cannot be generalised to other specialist sites across the UK. This could examine the psychotropic prescribing pattern along with NICE guideline approved psychological interventions for the management of AN, in order to monitor the effectiveness of pharmacotherapy in clinical practice in a much larger population.

The final area of further research would be the long-term effectiveness and safety of psychotropics, particularly olanzapine and fluoxetine, for AN treatment. The long-term efficacy and known adverse drug reactions after treatment with psychotropic drugs in young people with AN remains unknown to date. Some studies have been conducted in adults investigating efficacy of psychotropics for AN treatment, however it is not appropriate to extrapolate adult data to children and adolescents due to the differences in physiological responses in particular in a condition such as AN. The ideal standard for investigating therapeutic effect is an RCT, but it is not ideal in all situations because of its cost and time complications and difficulty to generalise to routine clinical practice. Therefore, an observational study may be considered with appropriate statistical techniques in order to assess psychotropic drug treatment in

AN at a population level which will in turn minimise the cost and time of conducting the study in comparison to a RCT.

9.7 Conclusion

The findings from this thesis advanced our understanding of the effectiveness, prescribing patterns, and safety of psychotropic medication treatment in individuals with AN, in particular children and adolescents, in different clinical settings. The efficacy of psychotropic drugs from previous literature and published RCTs have shown that fluoxetine and olanzapine are the most common antidepressants and antipsychotics, respectively, to be given for pharmacotherapy in AN. However, results on their effectiveness and safety are conflicting. The questionnaire survey study in Chapter 5 suggested that under 10% of patients under the care of CAED psychiatrists receive psychotropic medications for AN treatment, of which olanzapine is the most common drug prescribed.

In the primary care data used in this thesis, the prescribing of psychotropic medications was observed in around half of the AN population between 1996 and 2016 but from those, only 46% continued with a psychotropic prescription after 6 months of initiation. This may indicate that these drugs were perhaps not effective or were poorly tolerated or adhered to.

As AN diagnosis and initiation of treatment, including pharmacotherapy, is often instigated in secondary care, this thesis also explored prescribing and effectiveness of treatment in secondary care settings for children and young people, between 2015 to 2017. The most common medications prescribed in this study were olanzapine and fluoxetine. Frequently reported adverse events were mainly of gastrointestinal problems and no serious adverse drug reactions were reported in any of the individuals with AN within the studied sites.

To date, research on the long-term effectiveness and safety of psychotropic medications, specifically olanzapine and fluoxetine, as treatment for AN is required, as currently they are not licensed nor have been recommended as pharmacological treatment in existing NICE guidelines for AN treatment in either children or adolescents. As studies in this thesis have shown, there is an increased use of psychotropic medications in AN treatment, with around half of individuals in the primary care and secondary care study having a record for psychotropic prescriptions. Thus, it is important clinicians use the most up-to-date evidence when prescribing psychotropics for AN treatment in children and adolescents. The findings from this thesis have increased our knowledge of psychotropics drugs in both primary care and secondary care, specifically for children and adolescents. This knowledge should enable healthcare professionals, in particular CAED psychiatrists, to offer more effective pharmacological interventions in clinical practice, as pharmacotherapy has been essential in conjunction with psychotherapy evidence-based guidance provided by NICE for AN treatment.

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Research profile

Collaboration and data sharing

All the analyses performed for this thesis were done so by the PhD researcher (myself). Statistical analyses were double checked by supervisors, in particular Dr Ruth Brauer, and statistical consultations were made with Amy Kirkwood, senior statistician at UCL cancer trials centre. Supervisors also supported with refining the research questions of the thesis, the analysis plan and interpretation of the data for all the studies.

For Chapter 2, the technique for conducting a systematic review and identifying databases for the search was taught by a librarian at UCL's School of Pharmacy. The studies selected were consulted with a second reviewer (Abdallah Naser) and the studies to include in the review and extract data for were discussed with the supervisors.

With regards to studies in Chapter 5, 6, 7 and 8, two consultant CAED psychiatrists in clinical practice were appointed as clinical advisors for the PhD thesis (Dr Dasha Nicholls and Dr Mima Simic). They were essential in ensuring the interpretation of data and results for the studies were clinically correct and advised on possible justifications of results. For the data in Chapter 5, they helped in reviewing the questionnaire draft, distributing the questionnaire to the target population and collecting the questionnaire back so it can be interpreted by the PhD researcher.

Software

As described in the relevant chapters of this thesis, the statistical software used for analysis was primarily Stata (version 14.0). Review Manager (version 5.0) was used for bias analysis in Chapter 2. All the tables, graphs and figures included in this thesis were produced either using Stata or Microsoft Excel.

Publications as first author

Publication resulting from the findings of Chapter 5 in this PhD thesis:

M, Y. Beykloo., Nicholls, D., Simic, M., Brauer, R., Mills, E. & Wong, I. C. K. 2019. Survey on self-reported psychotropic drug prescribing practices of eating disorder psychiatrists for the treatment of young people with anorexia nervosa. *BMJ Open,* 9**,** e031707.

Manuscripts for Chapter 2 and Chapters 6 and 7 have been written, which will be submitted to relevant journals for publication. Similarly, findings of Chapter 8 have been drafted into a manuscript and will be sent to all co-authors for review, prior to journal submission.

Publications as co-author

1. Naser, A. Y., Wong, I. C. K., Whittlesea, C., **Beykloo, M. Y**., Man, K. K. C., Lau, W. C. Y., Hyassat, D. A. & Wei, L. 2018. Use of multiple antidiabetic medications in patients with diabetes and its association with hypoglycaemic events: a case-crossover study in Jordan. *BMJ Open,* 8**,** e024909.
2. Mohsin-Shaikh, S., Furniss, D., Blandford, A., Mcleod, M., Ma, T., **Beykloo, M. Y**. & Franklin, B. D. 2019. The impact of electronic prescribing systems on healthcare professionals' working practices in the hospital setting: a systematic review and narrative synthesis. *BMC Health Serv Res,* 19**,** 742.
3. Naser, A. Y., Wong, I. C. K., Whittlesea, C., Alwafi, H., Abuirmeileh, A., Alsairafi, Z. K., Turkistani, F. M., Bokhari, N. S., **Beykloo, M. Y**., Al-Taweel, D., Almane, M. B. & Wei, L. 2019. Attitudes and perceptions towards hypoglycaemia in patients with diabetes mellitus: A multinational cross-sectional study. *PLoS One,* 14**,** e0222275.

Conference presentations

Parts of this thesis have been presented at local, national, and international conferences. A breakdown of this can be found below.

- Oral presentation of Chapter 5 was presented at the Eating Disorders International Conference (EDIC) in London, UK (2018)
- Poster presentation of Chapter 5 was presented at the Royal College of Psychiatrists (RCPsych) International Congress in Birmingham, UK (2018)
- Oral presentation of parts of Chapter 6 was presented at the Asian Conference on Clinical Pharmacy (ACCP) in Tehran, Iran (2018)
- Poster presentations of Chapters 2 and 5 were presented at the International Society of Pharmacoepidemiology (ISPE) annual conference in Prague, Czech Republic (2018)
- Poster presentation of Chapter 5 was presented at UCL's School of Pharmacy PhD research day in London, UK (2018)
- Poster presentation of part of Chapter 6 was presented at RCPsych Faculty of Eating Disorders Annual Conference in London, UK (2019)
- Poster presentation of parts of Chapters 6 and 7 were presented at UCL's Doctoral School Research Poster Competition in London, UK (2020)
- Poster presentation of parts of Chapters 6 and 7 were presented at the Health Services Research & Pharmacy Practice (HSRPP) Conference in Cardiff, UK (2020)
- Oral presentation was given to UCL's Eating Disorders and Clinical Nutrition MSc students on parts of Chapters 7 and 8 under the guidance of Dr Erica Cini.

Awards won

As a result of the poster and oral presentations, prizes were won for the parts of the findings in this thesis, as mentioned below.

1. Winner for the RCPsych Best psychopharmacology poster at the International RCPsych Congress 2018
2. Winner of the Faculty of Eating Disorders Psychiatry Poster prize at the 2020 annual conference

Appendices

Appendix 1

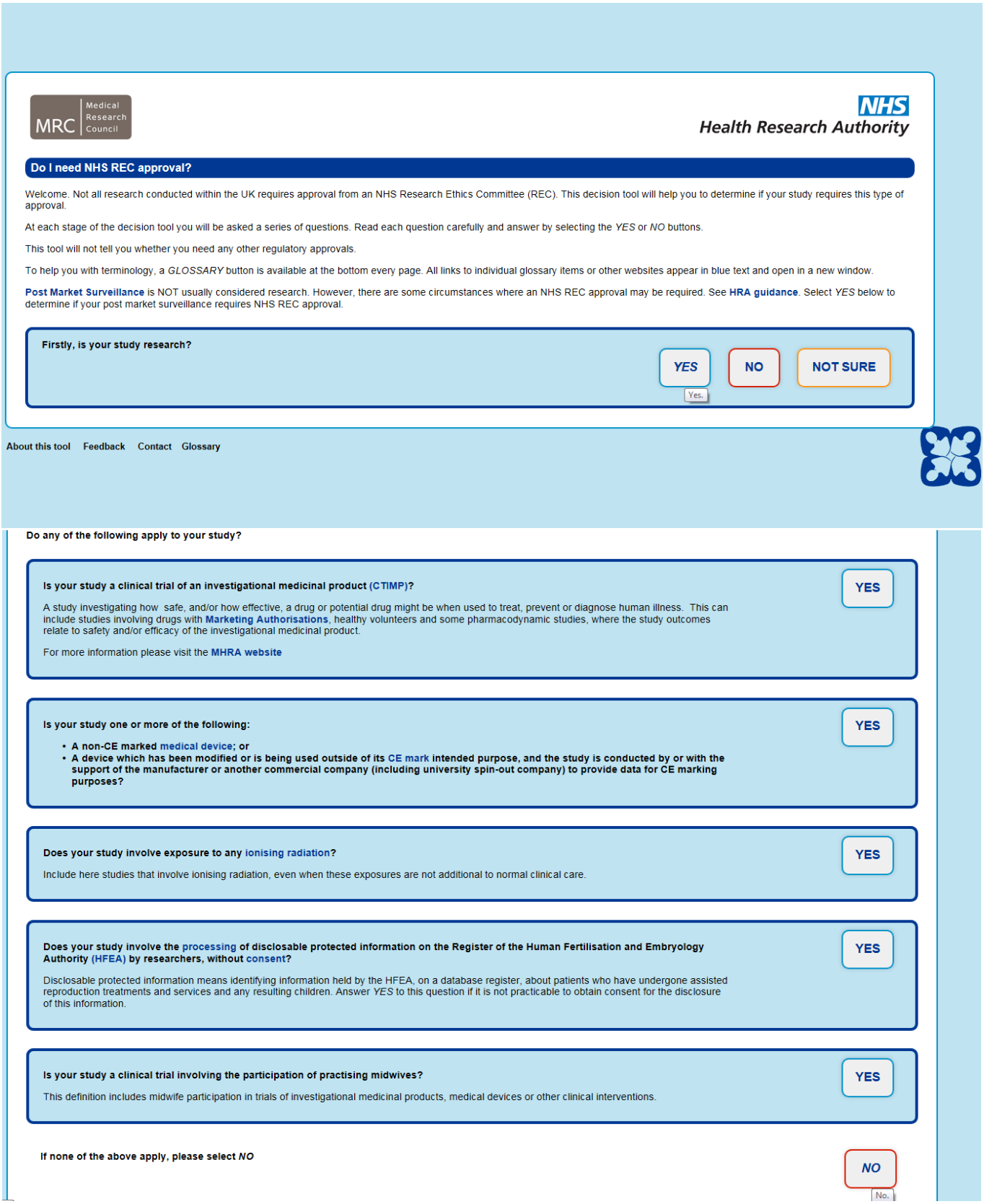
Code lists

Anorexia nervosa

Read code	Description
R030z00	[D]Anorexia NOS
ZR1O.00	Anorexic attitudes questionnaire
ZR1O.11	AAQ - Anorexia attitudes questionnaire
ZR1P.00	Anorexic behaviour scales
ZR1P.11	ABS - Anorexic behaviour scales
1467.00	H/O: anorexia nervosa
1612.00	Appetite loss - anorexia
1612.11	Anorexia symptom
E271.00	Anorexia nervosa
Eu50000	[X]Anorexia nervosa
Eu50100	[X]Atypical anorexia nervosa
R030.00	[D]Anorexia

Appendix 2

HRA decision tool


MRC Medical Research Council
NHS Health Research Authority
Do I need NHS REC approval?
Welcome. Not all research conducted within the UK requires approval from an NHS Research Ethics Committee (REC). This decision tool will help you to determine if your study requires this type of approval.
At each stage of the decision tool you will be asked a series of questions. Read each question carefully and answer by selecting the YES or NO buttons.
This tool will not tell you whether you need any other regulatory approvals.
To help you with terminology, a GLOSSARY button is available at the bottom every page. All links to individual glossary items or other websites appear in blue text and open in a new window.
Post Market Surveillance is NOT usually considered research. However, there are some circumstances where an NHS REC approval may be required. See HRA guidance. Select YES below to determine if your post market surveillance requires NHS REC approval.
Firstly, is your study research?
YES
NO
NOT SURE
Yes.
About this tool
Feedback
Contact
Glossary
Do any of the following apply to your study?
Is your study a clinical trial of an investigational medicinal product (CTIMP)?
A study investigating how safe, and/or how effective, a drug or potential drug might be when used to treat, prevent or diagnose human illness. This can include studies involving drugs with Marketing Authorisations, healthy volunteers and some pharmacodynamic studies, where the study outcomes relate to safety and/or efficacy of the investigational medicinal product.
For more information please visit the MHRA website
YES
Is your study one or more of the following:
A non-CE marked medical device; or
A device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
YES
Does your study involve exposure to any ionising radiation?
Include here studies that involve ionising radiation, even when these exposures are not additional to normal clinical care.
YES
Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority (HFEA) by researchers, without consent?
Disclosable protected information means identifying information held by the HFEA, on a database register, about patients who have undergone assisted reproduction treatments and services and any resulting children. Answer YES to this question if it is not practicable to obtain consent for the disclosure of this information.
YES
Is your study a clinical trial involving the participation of practising midwives?
This definition includes midwife participation in trials of investigational medicinal products, medical devices or other clinical interventions.
YES
If none of the above apply, please select NO
NO
No.

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

Where are you conducting your study?

To continue select the area of the map where you are conducting your study. This is the study location itself not the location of the **Chief Investigator** (if different).

If your study is **taking place in more than one country** within the UK then you should check your answers for each country in turn. You will be able to navigate back to this map at the end of each country's set of questions by selecting the *'OTHER UK COUNTRIES'* button.

Follow this link to start again.

About this tool Feedback Contact Glossary

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

My study location: England

Will your study involve research participants identified from, or because of their past or present use of services (adult and children's healthcare within the NHS and adult social care), for which the UK health departments are responsible (including services provided under contract with the private or voluntary sectors), including participants recruited through these services as healthy controls?	YES
Will your research involve collection of tissue or information from any users of these services (adult and children's healthcare within the NHS and adult social care)? This may include users who have died within the last 100 years.	YES
Will your research involve the use of previously collected tissue or information from which the research team could identify individual past or present users of these services (adult and children's healthcare within the NHS and adult social care), either directly from that tissue or information, or from its combination with other tissue or information likely to come into their possession?	YES
Will your research involve research participants identified because of their status as relatives or carers of past or present users of these services (adult and children's healthcare within the NHS and adult social care)?	YES
If none of the above apply, please select *NO*	NO

Follow this link to start again.

About this tool Feedback Contact Glossary

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Pharmacotherapy and weight change in adolescents with anorexia nervosa within eating disorder clinics

IRAS Project ID (if available):

Your answers to the following questions indicate that **you need NHS REC approval for sites in England and you may also need other approvals**:

You have answered ***'YES'*** to: Is your study research?

Question Set 1
You answered ***'NO'*** to all of these questions:

- Is your study a clinical trial of an investigational medicinal product?
- Is your study one or more of the following: A non-CE marked medical device, or a device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
- Does your study involve exposure to any ionising radiation?
- Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority by researchers, without consent?
- Is your study a clinical trial involving the participation of practising midwives?

You answered ***'England'*** to: Where is your study taking place?

Question Set 2

You have answered ***'YES'*** to: Will your research involve the use of previously collected tissue or information from which the research team could identify individual past or present users of these services (adult and children's healthcare within the NHS and adult social care), either directly from that tissue or information, or from its combination with other tissue or information likely to come into their possession?

Applications must be made using the **Integrated Research Application System (IRAS)**.

To understand the reasons why your research requires NHS REC review, please visit the **HRA algorithm**.

Appendix 3

Honorary contract

Honorary contract 1

South London and Maudsley NHS
NHS Foundation Trust

Human Resources Department
Employee Services
Lower Ground Floor
Denmark Hill
London SE5 8AZ
Telephone: 0203 228 5371
Fax: 0203 228 5369

14 July 2017

Private & Confidential

Miss Maedeh Yakhchi Beykloo

Dear Miss Yakhchi Beykloo,

Re: Honorary Research Assistant

I am pleased to confirm the arrangements for you to carry out your Honorary Attachment under the supervision of **Dr Mima Simic** within:

Michael Rutter Centre for Children and Young People, Maudsley Hospital
De Crespigny Park
London SE5 8AZ
CAMHS CAG

South London and Maudsley NHS Foundation Trust with effect from:

1st September 2017 – 1st September 2018

(Extension requests to be submitted one month before expiry date - 1 year maximum)

You will have a formal number of clinical sessions with the Trust. You will also have access to patient data.

Your supervisor/manager will ensure that you are familiar with all relevant HR and Operational Policies and Procedures of the Trust, that you work in accordance with these, and conduct your work to the standards of behaviour and performance required by the Trust. Please also read the 'Conditions of Attachment' enclosed.

If you agree to accept this clinical placement, please could you sign both copies of this letter, returning one copy to me as your acceptance of these arrangements and retaining the second for your own information.

I hope you enjoy your placement.

Marta Subocz
Employee Services Assistant
020 3228 5357

I hereby accept the offer of an Honorary Attachment as set out in the Terms and Conditions, which accompany this letter.

Signed

Dated

Managers' sign

THE SOUTH LONDON & MAUDSLEY NHS TRUST
HONORARY ATTACHMENT – CONDITIONS OF ATTACHMENT

1. The Attachment will be without remuneration from the Trust. Travelling expenses etc., will not be met by the Trust unless prior formal approval has been given

2. The Trust will not be responsible for the reimbursement of course, lecture or examination fees unless prior application has been made for a refund of such expenses and formal approval has been given.

3. The Trust has an obligation under the Health and Safety at Work Act 1974 to provide safe and healthy working conditions and methods. You are required to co-operate with Management in discharging its responsibilities under the Act and to take reasonable care for the health and safety of yourself and others.

4. During the course of the Attachment you may have access to see or hear information of a confidential nature and you are required to undertake not to disclose such information to any unauthorised persons. Breach of confidentiality may result in the termination of the Attachment.

5. Any event of misconduct or poor performance may result in the termination of your Honorary Attachment. In cases of alleged serious misconduct you will be required to leave Trust premises pending investigation.

6. Your Honorary Attachment to the Trust does not constitute employment per se and you will not be entitled to any form of payment on its cessation. Employment with the Trust is not guaranteed in any way or conferred by this letter.

7. If, for any reason e.g. sickness, you are unable to attend for the purpose of your Attachment, you should inform your immediate superior as soon as possible.

8. Whilst on an Honorary Attachment to the Trust you will comply with its policies and procedures as prescribed.

9. The Trust does not normally accept responsibility for articles lost or damaged on NHS property.

10. Copies of the Trust's disciplinary policy and rules (relating to summary dismissal offences), grievance procedure and Health and Safety documents can be viewed in the Personnel Department. Although applicable to employees, the principles of both the Health and Safety documents and the disciplinary rules may be applied directly to the terms of your Attachment. The grievance procedure and disciplinary policy should also be interpreted as referring to your Honorary Attachment wherever there is a reference to 'employee' or 'service' although your rights of appeal cannot extend beyond the Trust, i.e. as far as possible the policies and procedures applicable to you shall mirror those of the Trust's employees.

11. The Trust indemnified you against any legal claims arising from the proper execution of your recognised duties on Trust or other authorised premises.

Honorary contract 2

South London and Maudsley NHS
NHS Foundation Trust

Human Resources Department
HR Support Services
6th Floor, Jeanette Wallace House
1 Edridge Road, Croydon
Surrey CR0 1FE
Tel: 0203 228 5371
Fax: 0203 228 4899

05 December 2018

Private & Confidential

Miss Maedeh Yakhchi Beykloo

EXTENSION

Dear Miss Yakhchi Beykloo,

Re: Honorary Research Assistant

I am pleased to confirm the arrangements for you to carry out your Honorary Attachment under the supervision of **Dr Mima Simic** within:

Michael Rutter Centre for Children and Young People, Maudsley Hospital
De Crespigny Park
London SE5 8AZ
CAMHS CAG

South London and Maudsley NHS Foundation Trust with effect from:

1st September 2018 – 1st September 2019

(Extension requests to be submitted one month before expiry date - 1 year maximum)

You will have a formal number of clinical sessions with the Trust. You will also have access to patient data.

Your supervisor/manager will ensure that you are familiar with all relevant HR and Operational Policies and Procedures of the Trust, that you work in accordance with these, and conduct your work to the standards of behaviour and performance required by the Trust. Please also read the 'Conditions of Attachment' enclosed.

If you agree to accept this clinical placement, please could you sign both copies of this letter, returning one copy to me as your acceptance of these arrangements and retaining the second for your own information.

I hope you enjoy your placement.

Marta Subocz
HR Support Services Administrator
South London and Maudsley NHS Foundation Trust

Appendix 4

Systematic search strategy

EMBASE

04/08/2019

1. adolescent/

2. adolescen*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

3. 1 or 2

4. exp anorexia nervosa/ or exp anorexia/ or anorexia.mp.

5. (anorexia nervosa*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

6. 4 or 5

7. psychotropic drugs.mp. or exp psychotropic agent/

8. (psychoactive agent* or psychoactive drug* or psychodynamic agent* or psychopharmaceutic agent* or psychotropic drug* or (psychotropic adj2 treatment*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

9. 7 or 8

10. antipsychotics.mp. or exp neuroleptic agent/

11. (antipsychotic agent* or (butyrophenone adj2 antipsychotic agent*) or (phenothiazine adj2 antipsychotic agent*) or antipsychotic drug* or antipsychotic* or

(butyrophenone adj2 tranquilizer*) or classical antipsychotic* or classical antipsychotic agent* or classical antipsychotic drug* or (long acting adj2 neuroleptic*) or major tranquilizer* or neuroleptic* or neuroleptic drug* or neurolepticum or (phenothiazine adj2 tranquilizer*) or major tranquilizing agent* or typical antipsychotic* or typical antipsychotic agent* or typical antipsychotic drug* or typical neuroleptic* or typical neuroleptic agent* or typical neuroleptic drug* or olanzapine or atypical antipsychotic* or atypical antipsychotic agent* or atypical antipsychotic drug* or (first generation adj2 antipsychotic*) or (second generation adj2 antipsychotic*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

12. 10 or 11

13. exp body weight/ or exp weight change/ or exp weight/ or weight.mp.

14. (thinness or total body weight* or body weight* or body weight change* or body weight disorder* or (weight adj2 change*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

15. 13 or 14

16. exp weight/ or exp body mass/ or BMI.mp. or exp body weight/

17. (BMI or body mass index or quetelet index or thinness or (total body adj2 weight*) or body weight*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

18. 16 or 17

19. 9 or 12

20. 15 or 18

21. 3 and 6 and 19 and 20

Total articles: 703

MEDLINE

04/08/2019

1. adolescents.mp. or exp Adolescent/

2. (adolescen* or female adolescen* or male adolescen* or teen* or youth*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. anorexia nervosa.mp. or exp Anorexia Nervosa/

5. (anorexia nervosa*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. 4 or 5

7. psychotropic drugs.mp. or exp Psychotropic Drugs/

8. (psychotropic drug* or psychoactive agent* or psychoactive drug* or psychopharmaceutic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9. 7 or 8

10. antipsychotics.mp. or exp Antipsychotic Agents/

11. (antipsychotic* or antipsychotic agent* or antipsychotic drug* or antipsychotic effect* or (major adj2 tranquilizer*) or (major adj2 tranquilizing agent*) or neuroleptic agent* or neuroleptic drug* or neuroleptic* or (first generation adj2 antipsychotic*) or (second generation adj2 antipsychotic*) or typical antipsychotic* or atypical antipsychotic* or olanzapine).mp. [mp=title, abstract, original title, name of substance word, sub

ject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12. 10 or 11

13. 9 or 12

14. body weight.mp. or exp Body Weight/

15. body weight*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16. 14 or 15

17. exp Body Mass Index/ or bmi.mp.

18. (body mass index or quetelet index or bmi).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

19. 17 or 18

20. 16 or 19

21. 3 and 6 and 13 and 20

Total articles: 111

PSYCINFO

04/08/2019

1. exp ADOLESCENT PSYCHIATRY/ or exp ADOLESCENT PSYCHOPATHOLOGY/ or exp ADOLESCENT PSYCHOLOGY/ or adolescents.mp.

2. (adolescen* or adolescen* psychiatry or adolescen* psychology or adolescen* psychotherapy).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

3. 1 or 2

4. anorexia nervosa.mp. or exp Anorexia Nervosa/

5. (anorexia nervosa*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

6. 4 or 5

7. exp Antidepressant Drugs/ or exp Neuroleptic Drugs/ or psychotropics.mp.

8. ((psychotropic adj2 drug*) or (antidepressant adj2 drug*) or antidepressant* or (neuroleptic adj2 drug*) or neuroleptic* or psychotropic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

9. 7 or 8

10. exp Olanzapine/ or exp Neuroleptic Drugs/ or antipsychotics.mp.

11. (antipsychotic* or (neuroleptic adj2 drug*) or neuroleptic* or olanzapine or (first generation adj2 antipsychotic*) or (second generation adj2 antipsychotic*) or typical

antipsychotic* or atypical antipsychotic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

12. 10 or 11

13. 9 or 12

14. exp BODY WEIGHT/ or exp WEIGHT GAIN/ or weight.mp. or exp WEIGHT LOSS/

15. (weight* or (body adj2 weight*) or (weight adj2 gain) or (weight adj2 loss) or (body weight adj2 change*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

16. 14 or 15

17. exp Body Mass Index/ or exp Body Weight/ or bmi.mp. or exp Eating Behavior/

18. (bmi or (body mass adj2 index) or (body adj2 weight) or (eating adj2 disorder*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

19. 17 or 18

20. 16 or 19

21. 3 and 6 and 13 and 20

Total articles: 172

Appendix 5

Risk of bias assessment tool

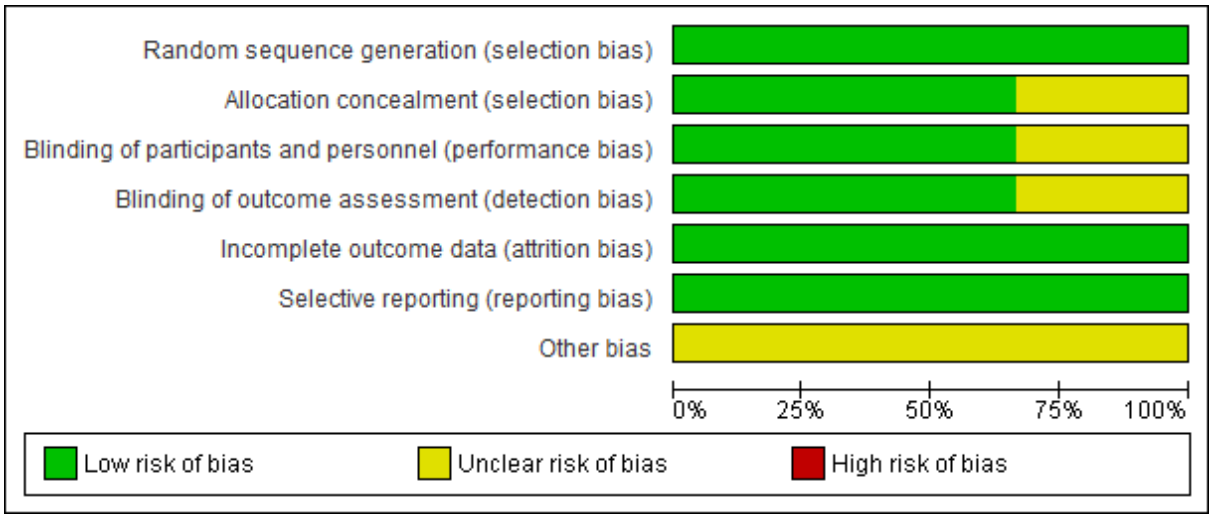


Figure 1. Risk of bias graph for RCT studies

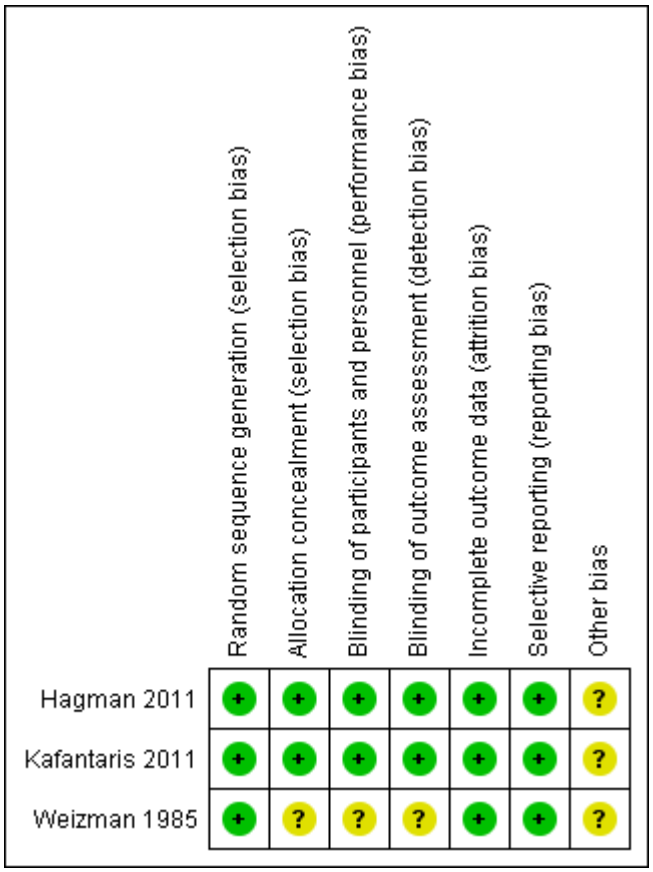


Figure 2. Risk of bias summary for RCT studies

Appendix 6

Survey questionnaire

Feedback form on medication use in Anorexia Nervosa

1. **How frequently, on average, do you see your patients with anorexia nervosa within the first 18 weeks of treatment initiation to review medication? (Please specify specific schedule below.)**
   Once a week [ ] Once every two weeks [ ]
   Once a month [ ] Other schedule [ ];
   please specify _____

2. **Please estimate what proportion of your young patients with anorexia are prescribed psychotropic medications?**
   Less than 10% of patients [ ] 10 – 20% [ ] 20 – 30% [ ] 30 – 40% [ ] 40 – 50% [ ] 50 – 60% [ ] 60 – 70% [ ] 70 – 80% [ ] 80 – 90% [ ] 90 – 100% [ ]

3. **What are the top two psychotropic medications you are most likely to prescribe for someone with anorexia nervosa?**
   Most common: _____
   2nd most common: _____

4. **We are specifically interested in the prescribing of olanzapine;**

a) **What dosage and duration is olanzapine typically initiated?**

   _____ mg for _____ week(s)

b) **How do you escalate the dose?**
   _____ mg increment every _____ week(s)

5. **On average, how long and at what maximum dose do you prescribe olanzapine for?**

   _____

6. **Is there a protocol for monitoring olanzapine side effects in patients? If so, what is monitored?**

   _____

   _____

7. **Do you inform the GP about the olanzapine treatment procedures undertaken?**
   Yes / No

8. **Do you prescribe from your service when initiating olanzapine treatment?**
   Yes / No

9. **Do you pass on the prescribing of olanzapine to the GP to continue? (If so, please specify when.)**

10. Would you be willing to participate in future research on the use of Olanzapine in young people on anorexia nervosa? If yes, please fill out the details below.

Yes / No

Team: **Name:**

Email:

Appendix 7

Ethical approval for Chapters 6 and 7

SRC Feedback

Researcher Name: Maedeh Yakhchi Beykloo

Organisation: UCL School of Pharmacy

SRC Reference Number: 17THIN063

Date: 4th September 2017

Study title: Pharmacotherapy in patients with anorexia nervosa: a population based descriptive study based on The Health Improvement Network Database

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Advice (General advice for the researchers as information only)
A) The study population described on page 3 should also include people without a diagnosis of anorexia nervosa in order to calculate incidence and prevalence rates. Will there be any inclusion/ exclusion criteria for this deominator population?
B) In order to differentiate between incident and prevalent cases consider including a minium time between registration data and anorexia diagnosis for the incidednce analysis.
C) This study will provied information on the incidence and prevalence of anorexia recorded in primary care medical records. The wording is therefore important to acknowledge the limitation of missing diagnoses from secondary care or non-recorded cases.
E) The adverse events associated with anitpsychotic drugs are likely to be under-repored by patients and under-recorded by clinicians. Therefore, how meaningful will the findings of aim 4 be?
F) Consider calulating incidence per 1000 person years at risk (PYAR)

Approved documents:

Approved document	Version	Date
SRC_Protocol_17THIN063_v1.0_05-07-2017	1	05/07/2017

We are pleased to inform that you can proceed with the study as this is now approved. QuintilesIMS will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform QuintilesIMS in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words “The Health Improvement Network (THIN)” within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla

Consultant

Appendix 8

Code list

Psychiatric comorbidities

Read codes	Description
E010.00	Alcohol withdrawal delirium
E010.11	DTs - delirium tremens
E010.12	Delirium tremens
E02y000	Drug-induced delirium
E030.11	Delirium - acute organic
E031.11	Delirium - subacute organic
Eu04.00	[X]Delirium, not induced by alcohol+other psychoactive subs
Eu04y00	[X]Other delirium
Eu04y11	[X]Delirium of mixed origin
Eu04z00	[X]Delirium, unspecified
Eu10400	[X]Men & behav dis due alcohl: withdrawl state with delirium
Eu10411	[X]Delirium tremens, alcohol induced
Eu11400	[X]Men & behaviour dis due opioid: withdrawal state with delirium
Eu12400	[X]Men & beh dis due cannabinds: withdrawal state with delirium
Eu13400	[X]Men & beh dis due seds/hypns: withdrawal state with delirium
Eu14400	[X]Men & behav dis due cocaine: withdrawal state with delirium
Eu15400	[X]Mnt/bh dis oth stims inc caffne: withdrawal state with delirium
Eu16400	[X]Men & beh dis due hallucngns: withdrawal state with delirium
Eu17400	[X]Men & behav dis due tobacco: withdrawal state with delirium
Eu18400	[X]Men & beh dis vol solvents: withdrawal state with delirium
Eu1A400	[X]Ment behav dis due crack cocaine: withdraw state delirium

Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Eu22.00	[X]Persistent delusional disorders
Eu22000	[X]Delusional disorder
Eu22y00	[X]Other persistent delusional disorders
Eu22z00	[X]Persistent delusional disorder, unspecified
Eu24.00	[X]Induced delusional disorder
212V.00	Bipolar affective disorder resolved
E114.00	Bipolar affective disorder, currently manic
E114000	Bipolar affective disorder, currently manic, unspecified
E114100	Bipolar affective disorder, currently manic, mild
E114200	Bipolar affective disorder, currently manic, moderate
E114300	Bipolar affect disord, currently manic, severe, no psychosis
E114400	Bipolar affect disord, currently manic,severe with psychosis
E114500	Bipolar affect disord, currently manic, part/unspec remission
E114600	Bipolar affective disorder, currently manic, full remission
E114z00	Bipolar affective disorder, currently manic, NOS
E115.00	Bipolar affective disorder, currently depressed
E115000	Bipolar affective disorder, currently depressed, unspecified
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115300	Bipolar affect disord, now depressed, severe, no psychosis

E115400	Bipolar affect disord, now depressed, severe with psychosis
E115500	Bipolar affect disord, now depressed, part/unspec remission
E115600	Bipolar affective disorder, now depressed, in full remission
E115z00	Bipolar affective disorder, currently depressed, NOS
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified
E116100	Mixed bipolar affective disorder, mild
E116200	Mixed bipolar affective disorder, moderate
E116300	Mixed bipolar affective disorder, severe, without psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E116500	Mixed bipolar affective disorder, partial/unspec remission
E116600	Mixed bipolar affective disorder, in full remission
E116z00	Mixed bipolar affective disorder, NOS
E117.00	Unspecified bipolar affective disorder
E117000	Unspecified bipolar affective disorder, unspecified
E117100	Unspecified bipolar affective disorder, mild
E117200	Unspecified bipolar affective disorder, moderate
E117300	Unspecified bipolar affective disorder, severe, no psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E117500	Unspecified bipolar affect disord, partial/unspec remission
E117600	Unspecified bipolar affective disorder, in full remission
E117z00	Unspecified bipolar affective disorder, NOS

E118.00	Seasonal affective disorder
Eu06y11	[X]Right hemispheric organic affective disorder
Eu25.00	[X]Schizoaffective disorders
Eu25000	[X]Schizoaffective disorder, manic type
Eu25100	[X]Schizoaffective disorder, depressive type
Eu25200	[X]Schizoaffective disorder, mixed type
Eu25y00	[X]Other schizoaffective disorders
Eu25z00	[X]Schizoaffective disorder, unspecified
Eu3..00	[X]Mood - affective disorders
Eu31.00	[X]Bipolar affective disorder
Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31600	[X]Bipolar affective disorder, current episode mixed
Eu31700	[X]Bipolar affective disorder, currently in remission
Eu31800	[X]Bipolar affective disorder type I
Eu31900	[X]Bipolar affective disorder type II
Eu31y00	[X]Other bipolar affective disorders
Eu31z00	[X]Bipolar affective disorder, unspecified
Eu33.15	[X]SAD - Seasonal affective disorder
Eu34.00	[X]Persistent mood affective disorders
Eu34y00	[X]Other persistent mood affective disorders
Eu34z00	[X]Persistent mood affective disorder, unspecified

Eu3y.00	[X]Other mood affective disorders
Eu3y000	[X]Other single mood affective disorders
Eu3y100	[X]Other recurrent mood affective disorders
Eu3yy00	[X]Other specified mood affective disorders
Eu3z.00	[X]Unspecified mood affective disorder
ZV11100	[V]Personal history of affective disorder
1B1c.00	Alcohol induced hallucinations
1B1d.00	Hypnagogic hallucination
1B1E.00	Hallucinations
1B1e.00	Hypnopompic hallucination
1B1g.00	No hallucinations
38P0600	HoNOSCA item 7 - hallucinations and delusions
F481K00	Visual hallucinations
R001.00	[D]Hallucinations
R001000	[D]Hallucinations, auditory
R001100	[D]Hallucinations, gustatory
R001200	[D]Hallucinations, olfactory
R001300	[D]Hallucinations, tactile
R001400	[D]Visual hallucinations
R001z00	[D]Hallucinations NOS
Ryu5300	[X]Other hallucinations
Z4K3.00	Interpretation of hallucinations
Z4K4.00	Clarification of hallucinations
Z4K4.11	Analysing hallucinations
Z4K5.00	Avoiding positive reinforcement of hallucinations
Z4K5100	Avoiding listening to patient talking about hallucinations
Z4K6.00	Allowing patient to talk about hallucinations
Z4K7.00	Allowing patient to explore hallucinations
388w.00	Generalised anxiety disorder 7 item score
38QN.00	Generalised anxiety disorder 2 scale
8IH8.00	GAD-7 (Generalized Anxiety Disorder 7) scale declined

E200200	Generalised anxiety disorder
E292000	Separation anxiety disorder
Eu05400	[X]Organic anxiety disorder
Eu40.00	[X]Phobic anxiety disorders
Eu40y00	[X]Other phobic anxiety disorders
Eu40z00	[X]Phobic anxiety disorder, unspecified
Eu41.00	[X]Other anxiety disorders
Eu41100	[X]Generalized anxiety disorder
Eu41300	[X]Other mixed anxiety disorders
Eu41y00	[X]Other specified anxiety disorders
Eu41z00	[X]Anxiety disorder, unspecified
Eu51511	[X]Dream anxiety disorder
Eu93000	[X]Separation anxiety disorder of childhood
Eu93100	[X]Phobic anxiety disorder of childhood
Eu93200	[X]Social anxiety disorder of childhood
Eu43.00	[X]Reaction to severe stress, and adjustment disorders
Eu43200	[X]Adjustment disorders
Eu05500	[X]Organic dissociative disorder
E205.00	Neurasthenia - nervous debility
Eu46000	[X]Neurasthenia
Eu05700	[X]Mild cognitive disorder
Eu05800	[X]Cognitive communication disorder
ZS3..00	Language-related cognitive disorder
ZRku.00	Structured interview for DSM-III personality disorders
E02y400	Drug-induced personality disorder
E21..00	Personality disorders
E21..11	Neurotic personality disorder
E210.00	Paranoid personality disorder
E211.00	Affective personality disorder
E211000	Unspecified affective personality disorder
E211100	Hypomanic personality disorder
E211200	Depressive personality disorder
E211300	Cyclothymic personality disorder

E211z00	Affective personality disorder NOS
E212.00	Schizoid personality disorder
E212000	Unspecified schizoid personality disorder
E212z00	Schizoid personality disorder NOS
E213.00	Explosive personality disorder
E214.00	Compulsive personality disorders
E214z00	Compulsive personality disorder NOS
E215.00	Histrionic personality disorders
E215.11	Hysterical personality disorders
E215000	Unspecified histrionic personality disorder
E215z00	Histrionic personality disorder NOS
E216.00	Inadequate personality disorder
E217.00	Antisocial or sociopathic personality disorder
E21y.00	Other personality disorders
E21y000	Narcissistic personality disorder
E21y100	Avoidant personality disorder
E21y200	Borderline personality disorder
E21y300	Passive-aggressive personality disorder
E21y400	Eccentric personality disorder
E21y500	Immature personality disorder
E21y600	Masochistic personality disorder
E21y700	Psychoneurotic personality disorder
E21yz00	Other personality disorder NOS
E21z.00	Personality disorder NOS
Eu06000	[X]Organic personality disorder
Eu21.18	[X]Schizotypal personality disorder
Eu34011	[X]Affective personality disorder
Eu34112	[X]Depressive personality disorder
Eu60.00	[X]Specific personality disorders
Eu60000	[X]Paranoid personality disorder
Eu60011	[X]Expansive paranoid personality disorder
Eu60012	[X]Fanatic paranoid personality disorder
Eu60013	[X]Querulant personality disorder
Eu60014	[X]Sensitive paranoid personality disorder
Eu60100	[X]Schizoid personality disorder

Eu60200	[X]Dissocial personality disorder
Eu60211	[X]Amoral personality disorder
Eu60212	[X]Antisocial personality disorder
Eu60213	[X]Asocial personality disorder
Eu60214	[X]Psychopathic personality disorder
Eu60215	[X]Sociopathic personality disorder
Eu60300	[X]Emotionally unstable personality disorder
Eu60311	[X]Aggressive personality disorder
Eu60312	[X]Borderline personality disorder
Eu60313	[X]Explosive personality disorder
Eu60400	[X]Histrionic personality disorder
Eu60411	[X]Hysterical personality disorder
Eu60412	[X]Psychoinfantile personality disorder
Eu60500	[X]Anankastic personality disorder
Eu60511	[X]Compulsive personality disorder
Eu60512	[X]Obsessional personality disorder
Eu60513	[X]Obsessive-compulsive personality disorder
Eu60600	[X]Anxious [avoidant] personality disorder
Eu60700	[X]Dependent personality disorder
Eu60711	[X]Asthenic personality disorder
Eu60712	[X]Inadequate personality disorder
Eu60713	[X]Passive personality disorder
Eu60714	[X]Self defeating personality disorder
Eu60800	[X]Addictive personality
Eu60y00	[X]Other specific personality disorders
Eu60y11	[X]Eccentric personality disorder
Eu60y12	[X]Haltlose type personality disorder
Eu60y13	[X]Immature personality disorder
Eu60y14	[X]Narcissistic personality disorder
Eu60y15	[X]Passive-aggressive personality disorder
Eu60y16	[X]Psychoneurotic personality disorder
Eu60z00	[X]Personality disorder, unspecified
Eu61.00	[X]Mixed and other personality disorders
Eu84013	[X]Infantile psychosis
Eu84111	[X]Atypical childhood psychosis

Eu84312	[X]Disintegrative psychosis
Eu84314	[X]Symbiotic psychosis
R20..00	[D]Senility, without mention of psychosis
R20z.00	[D]Senility, without psychosis NOS
ZV11111	[V]Personal history of manic-depressive psychosis
ZV11112	[V]Personal history of manic-depressive psychosis
212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
212X.00	Psychosis resolved
2229.13	O/E - senility - no psychosis
8G13100	CBTp - cognitive behavioural therapy for psychosis
8HHs.00	Referral to psychosis early intervention service
E00y.11	Presbyophrenic psychosis
E011000	Korsakov's alcoholic psychosis
E011100	Korsakov's alcoholic psychosis with peripheral neuritis
E01y.00	Other alcoholic psychosis
E01yz00	Other alcoholic psychosis NOS
E01z.00	Alcoholic psychosis NOS
E02z.00	Drug psychosis NOS
E03y300	Unspecified puerperal psychosis
E040.11	Korsakoff's non-alcoholic psychosis
E04z.00	Chronic organic psychosis NOS
E110300	Single manic episode, severe without mention of psychosis
E110400	Single manic episode, severe, with psychosis
E111300	Recurrent manic episodes, severe without mention psychosis
E111400	Recurrent manic episodes, severe, with psychosis
E112300	Single major depressive episode, severe, without psychosis

E112400	Single major depressive episode, severe, with psychosis
E113300	Recurrent major depressive episodes, severe, no psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E114300	Bipolar affect disord, currently manic, severe, no psychosis
E114400	Bipolar affect disord, currently manic,severe with psychosis
E115300	Bipolar affect disord, now depressed, severe, no psychosis
E115400	Bipolar affect disord, now depressed, severe with psychosis
E116300	Mixed bipolar affective disorder, severe, without psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E117300	Unspecified bipolar affective disorder, severe, no psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E11zz00	Other affective psychosis NOS
E121.00	Chronic paranoid psychosis
E12z.00	Paranoid psychosis NOS
E130.00	Reactive depressive psychosis
E131.00	Acute hysterical psychosis
E13y100	Brief reactive psychosis
E13z.00	Nonorganic psychosis NOS
E141.00	Disintegrative psychosis
E141z00	Disintegrative psychosis NOS
E14y100	Borderline psychosis of childhood
E14z.00	Child psychosis NOS
E1z..00	Non-organic psychosis NOS
Eu02z12	[X] Presenile psychosis NOS
Eu02z15	[X] Senile psychosis NOS

Eu03.11	[X]Korsakov's psychosis, nonalcoholic
Eu04.13	[X]Acute / subacute infective psychosis
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu05y11	[X]Epileptic psychosis NOS
Eu0z.11	[X]Organic psychosis NOS
Eu0z.12	[X]Symptomatic psychosis NOS
Eu10514	[X]Alcoholic psychosis NOS
Eu10611	[X]Korsakov's psychosis, alcohol induced
Eu22011	[X]Paranoid psychosis
Eu23012	[X]Cycloid psychosis
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Eu23312	[X]Psychogenic paranoid psychosis
Eu23z11	[X]Brief reactive psychosis NOS
Eu23z12	[X]Reactive psychosis
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25012	[X]Schizophreniform psychosis, manic type
Eu25111	[X]Schizoaffective psychosis, depressive type
Eu25112	[X]Schizophreniform psychosis, depressive type
Eu25212	[X]Mixed schizophrenic and affective psychosis
Eu25z11	[X]Schizoaffective psychosis NOS
Eu26.00	[X]Nonorganic psychosis in remission
Eu2y.11	[X]Chronic hallucinatory psychosis
Eu2z.00	[X]Unspecified nonorganic psychosis
Eu2z.11	[X]Psychosis NOS
Eu31.12	[X]Manic-depressive psychosis
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32314	[X]Single episode of reactive depressive psychosis
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms

Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu3z.11	[X]Affective psychosis NOS
Eu44.14	[X]Hysterical psychosis
Eu53111	[X]Puerperal psychosis NOS
Eu30000	[X]Hypomania
Eu30100	[X]Mania without psychotic symptoms
Eu30200	[X]Mania with psychotic symptoms
Eu30211	[X]Mania with mood-congruent psychotic symptoms
Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Eu30z11	[X]Mania NOS
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32314	[X]Single episode of reactive depressive psychosis
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms

Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32900	[X]Single major depr ep, severe with psych, psych in remiss
Eu32A00	[X]Recurr major depr ep, severe with psych, psych in remiss
Eu32B00	[X]Antenatal depression
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32y12	[X]Single episode of masked depression NOS
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS
Eu32z12	[X]Depressive disorder NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms

Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu41211	[X]Mild anxiety depression
Eu53011	[X]Postnatal depression NOS
Eu53012	[X]Postpartum depression NOS
PE03.00	Depressions in skull
Q018.00	Fetus or neonate affected by maternal postnatal depression
Q482000	Newborn cerebral depression
R007z13	[D]Postoperative depression
ZR2A.00	Beck depression inventory
ZR2A.11	BDI - Beck depression inventory
ZR2h.00	Brief depression rating scale
ZR2h.11	BDRS - Brief depression rating scale
ZR3L.00	Child depression scale
ZR3L.11	CDS - Child depression scale
ZR3L100	Child depression scale, second research edition
ZR7..00	Depression anxiety scale
ZR8..00	Depression self rating scale
ZR8..11	DSRS - Depression self rating scale
ZRBY.00	Edinburgh postnatal depression scale

ZRBY.11	EPDS - Edinburgh postnatal depression scale
ZRL6.00	Geriatric depression scale
ZRL6.11	GDS - Geriatric depression scale
ZRL6.12	Geriatric depression score
ZRLr.00	Hospital anxiety and depression scale
ZRLr.11	HAD - Hospital anxiety and depression scale
ZRLr.12	HADS - Hospital anxiety and depression scale
ZRLU.00	Hamilton rating scale for depression
ZRLU.11	HAMD - Hamilton rating scale for depression
ZRLU.12	HRSD - Hamilton rating scale for depression
ZRrc.00	Zung self-rating depression scale
ZRrc.11	SDS - Zung self-rating depression scale
ZRrI.00	Wakefield self-assessment depression inventory
ZRrY.00	WHO depression scale
ZRVM.00	Leeds scale for the self-assessment of anxiety & depression
ZV79000	[V]Screening for depression
12K8.00	Maternal postnatal depression
13Y3.00	Manic-depression association member
1B1U.00	Symptoms of depression
1JJ..00	Suspected depression
212S.00	Depression resolved
32E4.00	ECG: S-T depression
3885	Edinburgh postnatal depression scale
388a.00	Depression anxiety stress scales stress score
388b.00	Depression anxiety stress scales anxiety score
388g.00	Beck depression inventory second edition score
388J.00	Hospital anxiety and depression scale
388K.00	Geriatric depression scale
388l.00	BASDEC - Brief Assessment Schedule Depression Cards score

388P.00	HAD scale: depression score
388Z.00	Depression anxiety stress scales depression score
38Dp.00	HAMD - Hamilton rating scale for depression
38Dp.11	HRSD - Hamilton rating scale for depression
38Dq.00	MADRS - Montgomery-Asberg depression rating scale
38GJ000	EuroQol five dimension five level anxiety depression score
62T1.00	Puerperal depression
6891	Depression screen
6891000	Assessment using Whooley depression screen
6896	Depression screening using questions
6G00.00	Postnatal depression counselling
8BK0.00	Depression management programme
8HHq.00	Referral for guided self-help for depression
8I3F.00	Edinburgh postnatal depression scale at 8 months declined
8I3G.00	Edinburgh postnatal depression scale declined
8ID..00	Postnatal depression not discussed
8ID..00	Postnatal depression not discussed
8IH3100	Depression screening declined
8IH5200	Referral for guided self-help for depression declined
9H90.00	Depression annual review
9H91.00	Depression medication review
9H92.00	Depression interim review
9HA0.00	On depression register
9HA1.00	Removed from depression register
9hC..00	Exception reporting: depression quality indicators
9hC0.00	Excepted from depression quality indicators: Patient unsuita

9hC1.00	Excepted from depression quality indicators: Informed dissen
9k4..00	Depression - enhanced services administration
9k40.00	Depression - enhanced service completed
9kQ..00	On full dose long term treatment depression - enh serv admin
9kQ..11	On full dose long term treatment for depression
9Ov..00	Depression monitoring administration
9Ov0.00	Depression monitoring first letter
9Ov1.00	Depression monitoring second letter
9Ov2.00	Depression monitoring third letter
9Ov3.00	Depression monitoring verbal invite
9Ov4.00	Depression monitoring telephone invite
E113700	Recurrent depression
E11z200	Masked depression
E130.11	Psychotic reactive depression
E135.00	Agitated depression
E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E204.11	Postnatal depression
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu20400	[X]Post-schizophrenic depression
Eu42y00	[X]Other obsessive-compulsive disorders
Eu42z00	[X]Obsessive-compulsive disorder, unspecified
E203.00	Obsessive-compulsive disorders
E203z00	Obsessive-compulsive disorder NOS
Eu25.00	[X]Schizoaffective disorders
Eu25000	[X]Schizoaffective disorder, manic type
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25012	[X]Schizophreniform psychosis, manic type
Eu25100	[X]Schizoaffective disorder, depressive type

Eu25111	[X]Schizoaffective psychosis, depressive type
Eu25200	[X]Schizoaffective disorder, mixed type
Eu25y00	[X]Other schizoaffective disorders
Eu25z00	[X]Schizoaffective disorder, unspecified
Eu21.00	[X]Schizotypal disorder
E227.00	Psychosexual dysfunction
E227000	Unspecified psychosexual dysfunction
E227z00	Psychosexual dysfunction NOS
Z4Q..00	Sexual dysfunction counselling
Z4Q..11	Counselling for sexual dysfunction
ZG43200	Advice for sexual dysfunction
ZV11000	[V]Personal history of schizophrenia
13Y2.00	Schizophrenia association member
212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
212W.00	Schizophrenia resolved
E100.00	Simple schizophrenia
E100.11	Schizophrenia simplex
E100000	Unspecified schizophrenia
E100100	Subchronic schizophrenia
E100200	Chronic schizophrenic
E100300	Acute exacerbation of subchronic schizophrenia
E100400	Acute exacerbation of chronic schizophrenia
E100500	Schizophrenia in remission
E100z00	Simple schizophrenia NOS
E101.00	Hebephrenic schizophrenia
E101000	Unspecified hebephrenic schizophrenia
E101100	Subchronic hebephrenic schizophrenia
E101200	Chronic hebephrenic schizophrenia
E101300	Acute exacerbation of subchronic hebephrenic schizophrenia
E101400	Acute exacerbation of chronic hebephrenic schizophrenia
E101500	Hebephrenic schizophrenia in remission

E101z00	Hebephrenic schizophrenia NOS
E102.00	Catatonic schizophrenia
E102000	Unspecified catatonic schizophrenia
E102100	Subchronic catatonic schizophrenia
E102200	Chronic catatonic schizophrenia
E102300	Acute exacerbation of subchronic catatonic schizophrenia
E102400	Acute exacerbation of chronic catatonic schizophrenia
E102500	Catatonic schizophrenia in remission
E102z00	Catatonic schizophrenia NOS
E103.00	Paranoid schizophrenia
E103000	Unspecified paranoid schizophrenia
E103100	Subchronic paranoid schizophrenia
E103200	Chronic paranoid schizophrenia
E103300	Acute exacerbation of subchronic paranoid schizophrenia
E103400	Acute exacerbation of chronic paranoid schizophrenia
E103500	Paranoid schizophrenia in remission
E103z00	Paranoid schizophrenia NOS
E104.00	Acute schizophrenic episode
E105.00	Latent schizophrenia
E105000	Unspecified latent schizophrenia
E105100	Subchronic latent schizophrenia
E105200	Chronic latent schizophrenia
E105300	Acute exacerbation of subchronic latent schizophrenia
E105400	Acute exacerbation of chronic latent schizophrenia
E105500	Latent schizophrenia in remission
E105z00	Latent schizophrenia NOS
E106.00	Residual schizophrenia
E106.11	Restzustand - schizophrenia
E107.00	Schizo-affective schizophrenia

E107.11	Cyclic schizophrenia
E107000	Unspecified schizo-affective schizophrenia
E107100	Subchronic schizo-affective schizophrenia
E107200	Chronic schizo-affective schizophrenia
E107300	Acute exacerbation subchronic schizo-affective schizophrenia
E107400	Acute exacerbation of chronic schizo-affective schizophrenia
E107500	Schizo-affective schizophrenia in remission
E107z00	Schizo-affective schizophrenia NOS
E10y.00	Other schizophrenia
E10y.11	Cenesthopathic schizophrenia
E10y000	Atypical schizophrenia
E10y100	Coenesthopathic schizophrenia
E10yz00	Other schizophrenia NOS
E10z.00	Schizophrenia NOS
E14z.11	Childhood schizophrenia NOS
Eu05200	[X]Organic delusional [schizophrenia-like] disorder
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Eu20.00	[X]Schizophrenia
Eu20000	[X]Paranoid schizophrenia
Eu20011	[X]Paraphrenic schizophrenia
Eu20100	[X]Hebephrenic schizophrenia
Eu20111	[X]Disorganised schizophrenia
Eu20200	[X]Catatonic schizophrenia
Eu20212	[X]Schizophrenic catalepsy
Eu20213	[X]Schizophrenic catatonia
Eu20214	[X]Schizophrenic flexibilatis cerea
Eu20300	[X]Undifferentiated schizophrenia
Eu20311	[X]Atypical schizophrenia
Eu20400	[X]Post-schizophrenic depression
Eu20500	[X]Residual schizophrenia

Eu20511	[X]Chronic undifferentiated schizophrenia
Eu20512	[X]Restzustand schizophrenic
Eu20600	[X]Simple schizophrenia
Eu20y00	[X]Other schizophrenia
Eu20y11	[X]Cenesthopathic schizophrenia
Eu20z00	[X]Schizophrenia, unspecified
Eu21.11	[X]Latent schizophrenic reaction
Eu21.12	[X]Borderline schizophrenia
Eu21.13	[X]Latent schizophrenia
Eu21.14	[X]Prepsychotic schizophrenia
Eu21.15	[X]Prodromal schizophrenia
Eu21.16	[X]Pseudoneurotic schizophrenia
Eu21.17	[X]Pseudopsychopathic schizophrenia
Eu23111	[X]Bouffee delirante with symptoms of schizophrenia
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Eu23200	[X]Acute schizophrenia-like psychotic disorder
Eu25211	[X]Cyclic schizophrenia

Cardiac comorbidities

Read code	**Description**
A364100	Meningococcal pericarditis
A742100	Coxsackie pericarditis
A93y000	Syphilitic pericarditis
A98y200	Gonococcal pericarditis
AB40300	Histoplasma capsulatum with pericarditis
AB41300	Histoplasma duboisii with pericarditis
AB4z300	Histoplasmosis with pericarditis
G010.00	Acute rheumatic pericarditis
G10..00	Chronic rheumatic pericarditis
G101.00	Chronic rheumatic mediastinopericarditis
G102.00	Chronic rheumatic myopericarditis

G10z.00	Chronic rheumatic pericarditis NOS
G50..00	Acute pericarditis
G500.00	Acute pericarditis in diseases EC
G500000	Acute pericarditis - coxsackie
G500100	Acute pericarditis - meningococcal
G500200	Acute pericarditis - syphilitic
G500300	Acute pericarditis - tuberculous
G500311	TB - acute pericarditis
G500400	Acute pericarditis - uraemic
G500500	Acute pericarditis - gonococcal
G500z00	Acute pericarditis in diseases EC NOS
G501.00	Post infarction pericarditis
G50z.00	Other and unspecified acute pericarditis
G50z000	Acute pericarditis - unspecified
G50z100	Acute idiopathic pericarditis
G50z111	Viral pericarditis NOS
G50z200	Acute pericarditis - pneumococcal
G50z300	Acute pericarditis - staphylococcal
G50z400	Acute pericarditis - streptococcal
G50z500	Acute purulent pericarditis unspecified
G50zz00	Acute pericarditis NOS
G531.00	Adhesive pericarditis
G531z00	Adhesive pericarditis NOS
G532.00	Constrictive pericarditis
G532z00	Constrictive pericarditis NOS
G53yz11	Chronic pericarditis
Gyu5000	[X]Other forms of acute pericarditis
Gyu5100	[X]Other specified diseases of pericardium
Gyu5200	[X]Pericarditis in bacterial diseases classified elsewhere
Gyu5300	[X]Pericarditis in other infectious+parasitic diseases CE
Gyu5400	[X]Pericarditis in other diseases classified elsewhere

N000400	Systemic lupus erythematosus with pericarditis
A32y100	Diphtheritic myocarditis
A364300	Meningococcal myocarditis
A742300	Coxsackie myocarditis
A93y100	Syphilitic myocarditis
AD03.00	Toxoplasma myocarditis
G012.00	Acute rheumatic myocarditis
G1y0.00	Rheumatic myocarditis
G52..00	Acute myocarditis
G520.00	Acute myocarditis in diseases EC
G520000	Acute aseptic myocarditis of the newborn
G520100	Acute myocarditis - coxsackie
G520200	Acute myocarditis - diphtheritic
G520300	Acute myocarditis - influenzal
G520400	Acute myocarditis - syphilitic
G520500	Acute myocarditis - toxoplasmosis
G520600	Acute myocarditis - tuberculous
G520700	Acute myocarditis - meningococcal
G520z00	Acute myocarditis in diseases EC, NOS
G52y.00	Other acute myocarditis
G52y000	Acute myocarditis, unspecified
G52y100	Isolated (Fiedler's) myocarditis
G52y111	Giant cell myocarditis
G52y200	Idiopathic myocarditis NOS
G52y300	Septic myocarditis - pneumococcal
G52y400	Septic myocarditis - staphylococcal
G52y500	Septic myocarditis - streptococcal
G52y600	Septic myocarditis NOS
G52y700	Toxic myocarditis
G52yz00	Other acute myocarditis NOS
G52z.00	Acute myocarditis NOS
G5y0.00	Myocarditis NOS
G5y7.00	Sarcoid myocarditis
G5y8.00	Rheumatoid myocarditis

Gyu5F00	[X]Other acute myocarditis
Gyu5G00	[X]Acute myocarditis, unspecified
Gyu5H00	[X]Myocarditis in bacterial diseases classified elsewhere
Gyu5J00	[X]Myocarditis in viral diseases classified elsewhere
Gyu5K00	[X]Myocarditis in other infectious+parasitic diseases CE
Gyu5L00	[X]Myocarditis in other diseases classified elsewhere
F391B00	Cardiomyopathy in Duchenne muscular dystrophy
G343.00	Ischaemic cardiomyopathy
G55..00	Cardiomyopathy
G551.00	Hypertrophic obstructive cardiomyopathy
G552.00	Obscure African cardiomyopathy
G554000	Congestive cardiomyopathy
G554011	Congestive obstructive cardiomyopathy
G554100	Constrictive cardiomyopathy
G554200	Familial cardiomyopathy
G554300	Hypertrophic non-obstructive cardiomyopathy
G554400	Primary dilated cardiomyopathy
G554500	Takotsubo cardiomyopathy
G554511	Stress cardiomyopathy
G554z00	Other primary cardiomyopathy NOS
G555.00	Alcoholic cardiomyopathy
G556.00	Cardiomyopathy in Chagas's disease
G557.00	Nutritional and metabolic cardiomyopathies
G557400	Mucopolysaccharidosis cardiomyopathy
G557z00	Nutritional and metabolic cardiomyopathy NOS
G558.00	Cardiomyopathy in disease EC
G558000	Cardiomyopathy in Friedreich's ataxia
G558100	Cardiomyopathy in myotonic dystrophy
G558200	Dystrophic cardiomyopathy

G558400	Amyloid cardiomyopathy
G558z00	Cardiomyopathy in diseases EC, NOS
G559.00	Arrhythmogenic right ventricular cardiomyopathy
G55A.00	Tachycardiomyopathy
G55A.11	Tachycardia-induced cardiomyopathy
G55y.00	Secondary cardiomyopathy NOS
G55y.11	Secondary dilated cardiomyopathy
G55y000	Cardiomyopathy due to drugs and other external agents
G55z.00	Cardiomyopathy NOS
Gyu5M00	[X]Other hypertrophic cardiomyopathy
Gyu5N00	[X]Other restrictive cardiomyopathy
Gyu5P00	[X]Other cardiomyopathies
Gyu5Q00	[X]Cardiomyopathy in infectious+parasitic diseases CE
Gyu5R00	[X]Cardiomyopathy in metabolic diseases CE
Gyu5S00	[X]Cardiomyopathy in nutritional diseases CE
Gyu5T00	[X]Cardiomyopathy in other diseases classified elsewhere
L186500	Cardiomyopathy in the puerperium
G560.00	Complete atrioventricular block
G560.11	Third degree atrioventricular block
G561.00	Partial atrioventricular block
G561000	Atrioventricular block unspecified
G561100	First degree atrioventricular block
G561200	Mobitz type II atrioventricular block
G561300	Mobitz type I (Wenckebach) atrioventricular block
G561311	Mobitz type 1 second degree atrioventricular block
G561400	Second degree atrioventricular block
G561z00	Atrioventricular block NOS
Gyu5U00	[X]Other and unspecified atrioventricular block

329A.00	ECG: left bundle branch block
G562.11	Left bundle branch block
G56..00	Conduction disorders
G56..11	Conduction disorders of heart
G56y.00	Other conduction disorders
G56yz00	Other conduction disorders NOS
G56z.00	Conduction disorders unspecified
G56zz00	Conduction disorders NOS
Gyu5Y00	[X]Other specified conduction disorders
2241.00	O/E - collapse -cardiac arrest
G574011	Cardiac arrest-ventricular fibrillation
G575.00	Cardiac arrest
G575000	Cardiac arrest with successful resuscitation
G575z00	Cardiac arrest, unspecified
L09y100	Cardiac arrest following abortive pregnancy
SP11000	Cardiac arrest as a complication of care
G572.00	Paroxysmal tachycardia unspecified
G572000	Essential paroxysmal tachycardia
G572z00	Paroxysmal tachycardia NOS
G573.00	Atrial fibrillation and flutter
G573000	Atrial fibrillation
G573100	Atrial flutter
G573200	Paroxysmal atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G573400	Permanent atrial fibrillation
G573500	Persistent atrial fibrillation
G573600	Paroxysmal atrial flutter
G573700	Chronic atrial fibrillation
G573800	Typical atrial flutter
G573900	Atypical atrial flutter
G573z00	Atrial fibrillation and flutter NOS
14O7100	At risk of atrial fibrillation
14O7200	High risk of atrial fibrillatn
1I12.00	Atrial fibrillation excluded
212R.00	Atrial fibrillation resolved

3272.00	ECG: atrial fibrillation
3273.00	ECG: atrial flutter
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
7936A00	Implant intravenous pacemaker for atrial fibrillation
8CMW200	Atrial fibrillation care pathway
8HTy.00	Referral to atrial fibrillation clinic
8OAD.00	Provision of written information about atrial fibrillation
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
793M100	Perc transluminal ablation of atrial wall for atrial flutter
793M300	Perc translum ablat conduct sys heart for atrial flutter NEC
G57..11	Cardiac arrhythmias
Gyu5a00	[X]Other specified cardiac arrhythmias
1J62.00	Suspected arrhythmia
327..00	ECG: supraventricular arrhythmia
3271.00	ECG: no supraventric. arryth.
328..00	ECG: ventricular arrhythmia
3281.00	ECG: no ventricular arrhythmia
328Z.00	ECG: ventricular arrhythmia NOS
F256000	Hypsarrhythmia
G577.00	Sinus arrhythmia
G57yA00	Re-entry ventricular arrhythmia

1I10.00	Heart failure excluded
1J60.00	Suspected heart failure
1O1..00	Heart failure confirmed
2126400	Heart failure resolved
2JZ..00	On optimal heart failure therapy
388D.00	New York Heart Assoc classification heart failure symptoms
661M500	Heart failure self-management plan agreed
661N500	Heart failure self-management plan review
662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
679W100	Education about deteriorating heart failure
679X.00	Heart failure education
67D4.00	Heart failure information given to patient
68B6.00	Heart failure screen
8CeC.00	Preferred place of care for next exacerbation heart failure
8CL3.00	Heart failure care plan discussed with patient
8CMK.00	Has heart failure management plan
8CMW800	Heart failure clinical pathway
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8Hg8.00	Discharge from practice nurse heart failure clinic
8HgD.00	Discharge from heart failure nurse service
8HHb.00	Referral to heart failure nurse
8HHz.00	Referral to heart failure exercise programme
8Hk0.00	Referred to heart failure education group
8HTL.00	Referral to heart failure clinic
8HTL000	Referral to rapid access heart failure clinic
8I98.00	Heart failure rehabilitation programme not available
8IE0.00	Referral to heart failure education group declined

8IE1.00	Referral to heart failure exercise programme declined
9hH..00	Exception reporting: heart failure quality indicators
9hH0.00	Excepted heart failure quality indicators: Patient unsuitable
9hH1.00	Excepted heart failure quality indicators: Informed dissent
9m5..00	High risk of heart failure screening invitation
9N0k.00	Seen in heart failure clinic
9N2p.00	Seen by community heart failure nurse
9N4s.00	Did not attend practice nurse heart failure clinic
9N4w.00	Did not attend heart failure clinic
9N6T.00	Referred by heart failure nurse specialist
9Or..00	Heart failure monitoring administration
9Or0.00	Heart failure review completed
9Or1.00	Heart failure monitoring telephone invite
9Or2.00	Heart failure monitoring verbal invite
9Or3.00	Heart failure monitoring first letter
9Or4.00	Heart failure monitoring second letter
9Or5.00	Heart failure monitoring third letter
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G58..00	Heart failure
G580.00	Congestive heart failure
G580.12	Right heart failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580400	Congestive heart failure due to valvular disease
G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction

G58z.00	Heart failure NOS
G5y4z00	Post cardiac operation heart failure NOS
SP11111	Heart failure as a complication of care
ZRad.00	New York Heart Assoc classification heart failure symptoms
8B29.00	Cardiac failure therapy
G58..11	Cardiac failure
G580.11	Congestive cardiac failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G58z.12	Cardiac failure NOS
L09y200	Cardiac failure following abortive pregnancy
Q48y100	Congenital cardiac failure
Q490.00	Neonatal cardiac failure
Q48C.00	Neonatal hypotension
8624.00	Hypothermia with hypotension
F130300	Parkinsonism with orthostatic hypotension
F287.00	Idiopathic intracranial hypotension
F291000	Intracranial hypotension following ventricular shunting
G87..00	Hypotension
G870.00	Orthostatic hypotension
G870.11	Postural hypotension
G871.00	Chronic hypotension
G872.00	Idiopathic hypotension
G873.00	Hypotension due to drugs
G87z.00	Hypotension NOS
Gyu9000	[X]Other hypotension
L392.00	Maternal hypotension syndrome
L392000	Maternal hypotension syndrome unspecified
L392100	Maternal hypotension syndrome - delivered
L392200	Maternal hypotension syndrome - delivered with p/n problem
L392300	Maternal hypotension syndrome with antenatal problem

L392400	Maternal hypotension syndrome with postnatal problem
L392z00	Maternal hypotension syndrome NOS
R1y3.00	[D]Low blood pressure reading

Bone comorbidities

Read code	Description
14O9.00	At risk of osteoporosis
2126500	Osteoporosis resolved
66a..00	Osteoporosis monitoring
66a0.00	Initial osteoporosis assessment
66a1.00	Follow-up osteoporosis assessment
66a2.00	Osteoporosis treatment started
66a3.00	Osteoporosis treatment stopped
66a4.00	Osteoporosis treatment changed
66a5.00	Osteoporosis - no treatment
66a6.00	Osteoporosis - dietary advice
66a7.00	Osteoporosis - dietary assessment
66a8.00	Osteoporosis - exercise advice
66a9.00	Osteoporosis - falls prevention
66aA.00	Osteoporosis - treatment response
66aB.00	Osteoporosis - no treatment response
66aE.00	Refer to osteoporosis specialist
679F.00	Health education - osteoporosis
8B31E00	Osteoporosis medication compliance review
8B6b.00	Osteoporosis medication prophylaxis
8HTS.00	Referral to osteoporosis clinic
8I6c.00	Osteoporosis treatment not indicated
9hP..00	Exception reporting: osteoporosis quality indicators
9hP0.00	Excepted osteoporosis quality indicators: patient unsuitable
9hP1.00	Excepted osteoporosis quality indicators: informed dissent

9kj..00	Osteoporosis - enhanced services administration
9kj0.00	Bone sparing drug treatment offered for osteoporosis - ESA
9N0h.00	Seen in osteoporosis clinic
9Od..00	Osteoporosis monitoring administration
9Od0.00	Attends osteoporosis monitoring
9Od1.00	Refuses osteoporosis monitoring
9Od2.00	Osteoporosis monitoring default
9Od3.00	Osteoporosis monitoring first letter
9Od4.00	Osteoporosis monitoring second letter
9Od5.00	Osteoporosis monitoring third letter
9Od6.00	Osteoporosis monitoring verbal invitation
9Od7.00	Osteoporosis monitoring telephone invitation
9Od8.00	Osteoporosis monitoring deleted
9Od9.00	Osteoporosis monitoring check done
9OdA.00	Osteoporosis risk assessment done
9OdB.00	Osteoporosis risk assessment refused
9OdC.00	Osteoporosis risk assessment defaulted
N330.00	Osteoporosis
N330000	Osteoporosis, unspecified
N330100	Senile osteoporosis
N330200	Postmenopausal osteoporosis
N330300	Idiopathic osteoporosis
N330400	Dissuse osteoporosis
N330500	Drug-induced osteoporosis
N330600	Postoophorectomy osteoporosis
N330700	Postsurgical malabsorption osteoporosis
N330800	Localized osteoporosis - Lequesne
N330900	Osteoporosis in multiple myelomatosis
N330A00	Osteoporosis in endocrine disorders
N330B00	Vertebral osteoporosis
N330C00	Osteoporosis localized to spine
N330D00	Osteoporosis due to corticosteroids
N330z00	Osteoporosis NOS

N331200	Postoophorectomy osteoporosis with pathological fracture
N331300	Osteoporosis of disuse with pathological fracture
N331400	Postsurgical malabsorption osteoporosis with path fracture
N331500	Drug-induced osteoporosis with pathological fracture
N331600	Idiopathic osteoporosis with pathological fracture
N331800	Osteoporosis + pathological fracture lumbar vertebrae
N331900	Osteoporosis + pathological fracture thoracic vertebrae
N331A00	Osteoporosis + pathological fracture cervical vertebrae
N331B00	Postmenopausal osteoporosis with pathological fracture
N331H00	Collapse of cervical vertebra due to osteoporosis
N331J00	Collapse of lumbar vertebra due to osteoporosis
N331K00	Collapse of thoracic vertebra due to osteoporosis
N331L00	Collapse of vertebra due to osteoporosis NOS
N331M00	Fragility fracture due to unspecified osteoporosis
N331M11	Minimal trauma fracture due to unspecified osteoporosis
NyuB000	[X]Other osteoporosis with pathological fracture
NyuB100	[X]Other osteoporosis
NyuB200	[X]Osteoporosis in other disorders classified elsewhere

NyuB800	[X]Unspecified osteoporosis with pathological fracture
NyuB300	[X]Other drug-induced osteomalacia in adults
NyuB400	[X]Other adult osteomalacia
NyuB900	[X]Adult osteomalacia, unspecified
C28..11	Osteomalacia
C282.00	Osteomalacia unspecified
C283.00	Puerperal osteomalacia
C284.00	Senile osteomalacia
C285.00	Adult osteomalacia due to malabsorption
C286.00	Adult osteomalacia due to malnutrition
C28B.00	Aluminium-related osteomalacia
N331.00	Pathological fracture
N331000	Pathological fracture of thoracic vertebra
N331100	Pathological fracture of lumbar vertebra
N331200	Postoophorectomy osteoporosis with pathological fracture
N331300	Osteoporosis of disuse with pathological fracture
N331400	Postsurgical malabsorption osteoporosis with path fracture
N331500	Drug-induced osteoporosis with pathological fracture
N331600	Idiopathic osteoporosis with pathological fracture
N331800	Osteoporosis + pathological fracture lumbar vertebrae
N331900	Osteoporosis + pathological fracture thoracic vertebrae
N331A00	Osteoporosis + pathological fracture cervical vertebrae
N331B00	Postmenopausal osteoporosis with pathological fracture
N331C00	Pathological fracture of cervical vertebra
N331y00	Other specified pathological fracture
N331z00	Pathological fracture NOS

NyuB000	[X]Other osteoporosis with pathological fracture
NyuB800	[X]Unspecified osteoporosis with pathological fracture
B585000	Pathological fracture due to metastatic bone disease
S00..11	Frontal bone fracture
S00..12	Parietal bone fracture
S01..15	Occiput bone fracture
S01..18	Sphenoid bone fracture
S01..19	Temporal bone fracture
S20..11	Collar bone fracture
S35..11	Metatarsal bone fracture
S35..12	Tarsal bone fracture
S350.11	Heel bone fracture
7K1Gy11	Primary open reduction of bone fracture & external fixation
7K1Jy00	Closed reduction of bone fracture and internal fixation OS
7K1Jz00	Closed reduction of bone fracture and internal fixation NOS
7K1Ky00	Closed reduction of bone fracture and external fixation OS
7K1Kz00	Closed reduction of bone fracture and external fixation NOS
N334900	Osteonecrosis due to drugs
N334A00	Osteonecrosis due to previous trauma
N334B00	Osteonecrosis in caisson disease
N334C00	Osteonecrosis due to haemoglobinopathy
NyuC400	[X]Other secondary osteonecrosis
NyuC500	[X]Other osteonecrosis
NyuCB00	[X]Osteonecrosis due to haemoglobinopathy CE
NyuCC00	[X]Osteonecrosis in other diseases classified elsewhere
N33z100	Epiphyseal arrest

N33z800	Complete epiphyseal arrest
N33z900	Partial epiphyseal arrest
NyuCA00	[X]Osteopathy in other infectious diseases CE
NyuCF00	[X]Osteopathy in other diseases classified elsewhere
82D2.00	Osteopathy
C287.11	Aluminium-related osteopathy
N3...00	Osteopathy/chondropathy/acquired musculoskeletal deformity
N307.00	Osteopathy from poliomyelitis
N307000	Poliomyelitis osteopathy of unspecified site
N307100	Poliomyelitis osteopathy of the shoulder region
N307200	Poliomyelitis osteopathy of the upper arm
N307300	Poliomyelitis osteopathy of the forearm
N307400	Poliomyelitis osteopathy of the hand
N307500	Poliomyelitis osteopathy of the pelvic region and thigh
N307600	Poliomyelitis osteopathy of the lower leg
N307700	Poliomyelitis osteopathy of the ankle and foot
N307800	Poliomyelitis osteopathy of other specified sites
N307900	Poliomyelitis osteopathy of multiple sites
N307z00	Poliomyelitis osteopathy NOS
N324.00	Juvenile osteochondrosis of the leg
N324000	Juvenile osteochondrosis of the leg, unspecified
N324100	Kohler's disease - osteochondrosis of primary patella centre
N324111	Juvenile osteochondrosis of the primary patellar centre
N324200	Blount's disease - osteochondrosis of proximal tibia
N324300	Juvenile osteochondrosis of the secondary patellar centre

N324311	Sinding-Larsen's dis - osteochondrosis second patella centre
N324400	Osgood-Schlatter's dis - osteochondrosis of tibial tubercle
N324411	Tibial tubercle juvenile osteochondritis
N324z00	Juvenile osteochondrosis of the leg, NOS
N325.00	Juvenile osteochondrosis of the foot
N325000	Juvenile osteochondrosis of the foot, unspecified
N325100	Diaz's disease - osteochondrosis of astragalus
N325200	Sever's disease - osteochondrosis of calcaneum
N325300	Freiberg's disease - osteochondrosis of second metatarsal
N325400	Iselin's disease - osteochondrosis of fifth metatarsal
N325500	Haglund's disease - osteochondrosis of os tibiale externum
N325600	Kohler's disease - osteochondrosis of tarsal navicular
N325z00	Juvenile osteochondrosis of the foot NOS
N326.00	Other juvenile osteochondroses
N326300	Juvenile osteochondrosis NOS
N328.00	Juvenile osteochondrosis of spine
N32y000	Adult osteochondrosis of spine
N32z300	Osteochondrosis NOS
Nyu5B00	[X]Spinal osteochondrosis, unspecified
NyuD000	[X]Other juvenile osteochondrosis of hip and pelvis
NyuD100	[X]Other juvenile osteochondrosis of upper limb
NyuD200	[X]Other specified juvenile osteochondrosis

Reproductive comorbidities

Read code	Description
3189000	Female infertility test normal
3189100	Female infertility test abnormal
3195.00	Male infertility testing
8C82.00	Female infertility therapy
8C83.00	Male infertility therapy
K26..00	Male infertility
K26z.00	Male infertility NOS
K5B0.00	Female infertility of anovulatory origin
K5B0z00	Female infertility of anovulatory origin NOS
K5B1.00	Female infertility of pituitary - hypothalamic origin
K5B1z00	Female infertility of pituitary - hypothalamic cause NOS
K5B2.00	Female infertility of tubal origin
K5B2z00	Female infertility of tubal origin NOS
K5B3.00	Female infertility of uterine origin
K5B3z00	Female infertility of uterine origin NOS
K5B4.00	Female infertility of cervical origin
K5B4z00	Female infertility of cervical origin NOS
K5B5.00	Female infertility of vaginal origin
K5B5z00	Female infertility of vaginal origin NOS
K5B6.00	Female infertility associated with male factors
K5B7.00	Female infertility due to diminished ovarian reserve
K5By.00	Other female infertility
K5Byz00	Other female infertility NOS
K5Bz.00	Female infertility NOS
Kyu9G00	[X]Female infertility of other origin
K314.00	Atrophy of breast
7E0D800	Laparoscopic laser destruction of endometriosis
BBL1.11	[M]Stromal endometriosis
K50..00	Endometriosis
K500.00	Endometriosis of uterus

K500000	Internal endometriosis
K500100	Endometriosis of myometrium
K500200	Endometriosis of cervix
K500z00	Endometriosis of uterus NOS
K501.00	Endometriosis of ovary
K502.00	Endometriosis of the fallopian tube
K503.00	Endometriosis of the pelvic peritoneum
K503000	Endometriosis of the broad ligament
K503100	Endometriosis of the pouch of Douglas
K503200	Endometriosis of the parametrium
K503300	Endometriosis of the round ligament
K503z00	Endometriosis of the pelvic peritoneum NOS
K504.00	Endometriosis of the rectovaginal septum and vagina
K504000	Endometriosis of the rectovaginal septum
K504100	Endometriosis of the vagina
K504z00	Endometriosis of the rectovaginal septum and vagina NOS
K505.00	Endometriosis of the intestine
K505000	Endometriosis of the appendix
K505100	Endometriosis of the colon
K505200	Endometriosis of the rectum
K505z00	Endometriosis of the intestine NOS
K506.00	Endometriosis in scar of skin
K50y.00	Other endometriosis
K50y000	Endometriosis of the bladder
K50y100	Endometriosis of the lung
K50y200	Endometriosis of the umbilicus
K50y300	Endometriosis of the vulva
K50yz00	Other endometriosis NOS
K50z.00	Endometriosis NOS
Kyu9000	[X]Other endometriosis
K590.11	Amenorrhoea
K590000	Primary amenorrhoea
K590100	Secondary amenorrhoea

K590111	Post-pill amenorrhoea
K590z00	Amenorrhoea NOS
Eu45y11	[X]Psychogenic dysmenorrhoea
K583.00	Dysmenorrhoea
K583.14	Spasmodic dysmenorrhoea
K583000	Primary dysmenorrhoea
K583100	Secondary dysmenorrhoea
K5E..00	Other abnormal uterine and vaginal bleeding
K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified
Kyu9D00	[X]Other specified abnormal uterine and vaginal bleeding
K5E2.00	Abnormal vaginal bleeding, unspecified
158..12	Vaginal bleeding

Nutrient and mineral comorbidities

Read code	**Description**
D00..00	Iron deficiency anaemias
D000.00	Iron deficiency anaemia due to chronic blood loss
D000.12	Iron deficiency anaemia due to blood loss
D001.00	Iron deficiency anaemia due to dietary causes
D00y.00	Other specified iron deficiency anaemia
D00yz00	Other specified iron deficiency anaemia NOS
D00z.00	Unspecified iron deficiency anaemia
D00zz00	Iron deficiency anaemia NOS
Dyu0000	[X]Other iron deficiency anaemias
L182500	Iron deficiency anaemia of pregnancy
D013000	Combined B12 and folate deficiency anaemia
Dyu0300	[X]Other folate deficiency anaemias
Dyu0.00	[X]Nutritional anaemias
1JM..00	Suspected hypothyroidism
1JM0.00	Suspected congenital hypothyroidism

44qV.00	Congenital hypothyroidism screening test
44qV000	Congenital hypothyroidism screening, borderline result
66BB.00	Hypothyroidism annual review
687H.00	Congenital hypothyroidism screening related finding
687H200	Congenital hypothyroidism screening, insufficient sample
687HC00	Con hypothyroidism screening, too premature for testing
8CR5.00	Hypothyroidism clinical management plan
8IEf.00	Congenital hypothyroidism screening declined
9Oj..00	Hypothyroidism monitoring administration
9Oj0.00	Hypothyroidism monitoring first letter
9Oj1.00	Hypothyroidism monitoring second letter
9Oj2.00	Hypothyroidism monitoring third letter
9Oj3.00	Hypothyroidism monitoring verbal invite
9Oj4.00	Hypothyroidism monitoring telephone invitation
C03..00	Congenital hypothyroidism
C03y.00	Other specified congenital hypothyroidism
C03y000	Congenital hypothyroidism with diffuse goitre
C03y100	Congenital hypothyroidism without goitre
C03z.00	Congenital hypothyroidism NOS
C04..00	Acquired hypothyroidism
C04..13	Hypothyroidism
C040.00	Postsurgical hypothyroidism
C040.11	Post ablative hypothyroidism
C041.00	Other postablative hypothyroidism
C041000	Irradiation hypothyroidism
C041z00	Postablative hypothyroidism NOS
C042.00	Iodine hypothyroidism
C043.00	Other iatrogenic hypothyroidism

C043000	Hypothyroidism resulting from para-aminosalicylic acid
C043100	Hypothyroidism resulting from phenylbutazone
C043200	Hypothyroidism resulting from resorcinol
C043z00	Iatrogenic hypothyroidism NOS
C044.00	Postinfectious hypothyroidism
C047.00	Subclinical hypothyroidism
C04y.00	Other acquired hypothyroidism
C04z.00	Hypothyroidism NOS
C04z000	Premature puberty due to hypothyroidism
C0A5.00	Subclinical iodine-deficiency hypothyroidism
Cyu1100	[X]Other specified hypothyroidism
F381400	Myasthenic syndrome due to hypothyroidism
Q433700	Neonatal jaundice with congenital hypothyroidism
212P.00	Hyperthyroidism resolved
C02..11	Hyperthyroidism
C025.00	Subclinical hyperthyroidism
C20zX00	Unspecified severe protein-energy malnutrition
C2A0.00	Sequelae of protein-energy malnutrition
Cyu5000	[X]Unspecified severe protein-energy malnutrition

Appendix 9

Drug list

Antidepressants

Drug code	Generic name
87251998	Citalopram 10mg tablets
91380997	Citalopram 10mg tablets
91395997	Citalopram 10mg tablets
93948990	Citalopram 10mg tablets
93994990	Citalopram 10mg tablets
94895990	Citalopram 10mg tablets
95271990	Citalopram 10mg tablets
95335990	Citalopram 10mg tablets
95421990	Citalopram 10mg tablets
95633990	Citalopram 10mg tablets
95668990	Citalopram 10mg tablets
95705990	Citalopram 10mg tablets
95995979	Citalopram 10mg tablets
91380998	Citalopram 20mg tablets
91395998	Citalopram 20mg tablets
93947990	Citalopram 20mg tablets
93996990	Citalopram 20mg tablets
94603990	Citalopram 20mg tablets
94894990	Citalopram 20mg tablets
94937990	Citalopram 20mg tablets
95270990	Citalopram 20mg tablets
95334990	Citalopram 20mg tablets
95420990	Citalopram 20mg tablets
95632990	Citalopram 20mg tablets
95667990	Citalopram 20mg tablets
95704990	Citalopram 20mg tablets
91380996	Citalopram 40mg tablets
91395996	Citalopram 40mg tablets
93946990	Citalopram 40mg tablets
94880990	Citalopram 40mg tablets
94893990	Citalopram 40mg tablets
94936990	Citalopram 40mg tablets
95269990	Citalopram 40mg tablets

95333990	Citalopram 40mg tablets
95418990	Citalopram 40mg tablets
95631990	Citalopram 40mg tablets
95666990	Citalopram 40mg tablets
95703990	Citalopram 40mg tablets
95979979	Citalopram 40mg tablets
95984979	Citalopram 40mg tablets
92172998	Citalopram 40mg/ml oral drops sugar free
92174998	Citalopram 40mg/ml oral drops sugar free
69605979	Citalopram 10mg/5ml oral suspension
69606979	Citalopram 10mg/5ml oral suspension
69604979	Citalopram 20mg/5ml oral suspension
88285998	Escitalopram 10mg tablets
89381979	Escitalopram 10mg tablets
89383979	Escitalopram 10mg tablets
91671998	Escitalopram 10mg tablets
85970998	Escitalopram 10mg/ml drops
85971998	Escitalopram 10mg/ml oral drops sugar free
98088998	Escitalopram 20mg tablets
98561998	Escitalopram 20mg tablets
82790998	Escitalopram 20mg/ml oral drops sugar free
82791998	Escitalopram 20mg/ml oral drops sugar free
87662998	Escitalopram 5mg tablets
87663998	Escitalopram 5mg tablets
90159998	Fluoxetine 20mg capsules
90814998	Fluoxetine 20mg capsules
93066990	Fluoxetine 20mg capsules
93905990	Fluoxetine 20mg capsules
94447998	Fluoxetine 20mg capsules
94490998	Fluoxetine 20mg capsules
95388990	Fluoxetine 20mg capsules
96161979	Fluoxetine 20mg capsules
96162979	Fluoxetine 20mg capsules
96168979	Fluoxetine 20mg capsules
96272990	Fluoxetine 20mg capsules

96281990	Fluoxetine 20mg capsules
96606990	Fluoxetine 20mg capsules
96643990	Fluoxetine 20mg capsules
96644990	Fluoxetine 20mg capsules
96647990	Fluoxetine 20mg capsules
96651990	Fluoxetine 20mg capsules
96654990	Fluoxetine 20mg capsules
96659990	Fluoxetine 20mg capsules
96674990	Fluoxetine 20mg capsules
96709990	Fluoxetine 20mg capsules
96729990	Fluoxetine 20mg capsules
99592998	Fluoxetine 20mg capsules
75904978	Fluoxetine 20mg dispersible tablets sugar free
75905978	Fluoxetine 20mg dispersible tablets sugar free
76398978	Fluoxetine 20mg dispersible tablets sugar free
84403998	Fluoxetine 20mg/5ml oral solution
90766998	Fluoxetine 20mg/5ml oral solution
91923990	Fluoxetine 20mg/5ml oral solution
91928990	Fluoxetine 20mg/5ml oral solution
94447997	Fluoxetine 20mg/5ml oral solution
94490997	Fluoxetine 20mg/5ml oral solution
95426990	Fluoxetine 20mg/5ml oral solution
95813990	Fluoxetine 20mg/5ml oral solution
95820990	Fluoxetine 20mg/5ml oral solution
96155979	Fluoxetine 20mg/5ml oral solution
84436998	Fluoxetine 20mg/5ml oral solution sugar free
94447996	Fluoxetine 60mg capsules
94490996	Fluoxetine 60mg capsules
95610990	Fluoxetine 60mg capsules
96143979	Fluoxetine 60mg capsules
30932978	Fluoxetine 10mg capsules
82367998	Fluoxetine 10mg tablets

80064979	Fluoxetine 2.5mg/5ml oral solution
80062979	Fluoxetine 2.5mg/5ml oral suspension
30041978	Fluoxetine 30mg capsules
29604978	Fluoxetine 40mg capsules
30444978	Fluoxetine 40mg capsules
66539979	Paroxetine 10mg/5ml oral suspension
29586978	Paroxetine 40mg tablets
54494979	Paroxetine 10mg tablets
54495979	Paroxetine 10mg tablets
84807998	Paroxetine 10mg tablets
85382998	Paroxetine 10mg tablets
66541979	Paroxetine 10mg/5ml oral suspension sugar free
93489996	Paroxetine 10mg/5ml oral suspension sugar free
93490996	Paroxetine 10mg/5ml oral suspension sugar free
96068979	Paroxetine 10mg/5ml oral suspension sugar free
96070979	Paroxetine 10mg/5ml oral suspension sugar free
93489998	Paroxetine 20mg tablets
93490998	Paroxetine 20mg tablets
95051990	Paroxetine 20mg tablets
95332990	Paroxetine 20mg tablets
95350990	Paroxetine 20mg tablets
95578990	Paroxetine 20mg tablets
96087990	Paroxetine 20mg tablets
96098979	Paroxetine 20mg tablets
93487990	Paroxetine 30mg tablets
93489997	Paroxetine 30mg tablets
93490997	Paroxetine 30mg tablets
94852990	Paroxetine 30mg tablets
95007990	Paroxetine 30mg tablets
95028990	Paroxetine 30mg tablets

96082979	Paroxetine 30mg tablets
52706979	Sertraline 100mg tablets
60187979	Sertraline 100mg tablets
92729990	Sertraline 100mg tablets
93173997	Sertraline 100mg tablets
93174997	Sertraline 100mg tablets
93732990	Sertraline 100mg tablets
93752990	Sertraline 100mg tablets
93842990	Sertraline 100mg tablets
96114979	Sertraline 100mg tablets
96118979	Sertraline 100mg tablets
60188979	Sertraline 50mg tablets
92728990	Sertraline 50mg tablets
93173998	Sertraline 50mg tablets
93174998	Sertraline 50mg tablets
93694990	Sertraline 50mg tablets
93733990	Sertraline 50mg tablets
93749990	Sertraline 50mg tablets
93753990	Sertraline 50mg tablets
93843990	Sertraline 50mg tablets
96136979	Sertraline 50mg tablets
86159998	Sertraline 50mg/5ml oral suspension
79261979	Sertraline 100mg/5ml oral suspension
66189979	Sertraline 12.5mg/5ml oral suspension
66187979	Sertraline 150mg/5ml oral suspension
66185979	Sertraline 20mg/5ml oral suspension
66183979	Sertraline 25mg/5ml oral suspension
58747979	Mirtazapine 15mg orodispersible tablets
87685998	Mirtazapine 15mg orodispersible tablets
87687998	Mirtazapine 15mg orodispersible tablets
90119979	Mirtazapine 15mg orodispersible tablets
90125979	Mirtazapine 15mg orodispersible tablets
92454990	Mirtazapine 15mg orodispersible tablets
92906990	Mirtazapine 15mg orodispersible tablets
92981990	Mirtazapine 15mg orodispersible tablets

92988990	Mirtazapine 15mg orodispersible tablets
92994990	Mirtazapine 15mg orodispersible tablets
93180990	Mirtazapine 15mg orodispersible tablets
86982998	Mirtazapine 15mg tablets
92814990	Mirtazapine 15mg tablets
94037990	Mirtazapine 15mg tablets
94250990	Mirtazapine 15mg tablets
94401990	Mirtazapine 15mg tablets
87430998	Mirtazapine 15mg/ml oral solution sugar free
94870990	Mirtazapine 15mg/ml oral solution sugar free
87945998	Mirtazapine 30mg orodispersible tablets
87946998	Mirtazapine 30mg orodispersible tablets
90094979	Mirtazapine 30mg orodispersible tablets
90097979	Mirtazapine 30mg orodispersible tablets
90105979	Mirtazapine 30mg orodispersible tablets
92980990	Mirtazapine 30mg orodispersible tablets
88715998	Mirtazapine 30mg tablets
88717998	Mirtazapine 30mg tablets
94126990	Mirtazapine 30mg tablets
94611990	Mirtazapine 30mg tablets
94773990	Mirtazapine 30mg tablets
94797990	Mirtazapine 30mg tablets
94847990	Mirtazapine 30mg tablets
95949979	Mirtazapine 30mg tablets
87684998	Mirtazapine 45mg orodispersible tablets
58745979	Mirtazapine 45mg tablets
86981998	Mirtazapine 45mg tablets
87686998	Mirtazapine 45mg tablets
92813990	Mirtazapine 45mg tablets
92903990	Mirtazapine 45mg tablets
92979990	Mirtazapine 45mg tablets
92986990	Mirtazapine 45mg tablets
92992990	Mirtazapine 45mg tablets
93178990	Mirtazapine 45mg tablets
94035990	Mirtazapine 45mg tablets

94400990	Mirtazapine 45mg tablets

Antipsychotics

Drug code	Generic name
91077998	Amisulpride 100mg tablets
91083998	Amisulpride 100mg tablets
94545990	Amisulpride 100mg tablets
94845990	Amisulpride 100mg tablets
90209998	Amisulpride 100mg/ml oral solution sugar free
91425998	Amisulpride 100mg/ml oral solution sugar free
64991979	Amisulpride 12.5mg/5ml oral solution
64989979	Amisulpride 12.5mg/5ml oral suspension
88383997	Amisulpride 200mg tablets
88387997	Amisulpride 200mg tablets
94544990	Amisulpride 200mg tablets
94844990	Amisulpride 200mg tablets
96360979	Amisulpride 200mg tablets
96363979	Amisulpride 200mg tablets
81131998	Amisulpride 25mg/5ml oral solution
86433998	Amisulpride 25mg/5ml oral suspension
88383996	Amisulpride 400mg tablets
88387996	Amisulpride 400mg tablets
88383998	Amisulpride 50mg tablets
88387998	Amisulpride 50mg tablets
91785990	Amisulpride 50mg tablets
94546990	Amisulpride 50mg tablets
94846990	Amisulpride 50mg tablets
81029979	Amisulpride 50mg/5ml oral suspension
85834998	Aripiprazole 10mg orodispersible tablets sugar free
85837998	Aripiprazole 10mg orodispersible tablets sugar free

87450998	Aripiprazole 10mg tablets
87453998	Aripiprazole 10mg tablets
89524979	Aripiprazole 10mg tablets
85833998	Aripiprazole 15mg orodispersible tablets sugar free
85836998	Aripiprazole 15mg orodispersible tablets sugar free
55724978	Aripiprazole 15mg tablets
87449998	Aripiprazole 15mg tablets
87452998	Aripiprazole 15mg tablets
89520979	Aripiprazole 15mg tablets
85832998	Aripiprazole 1mg/ml oral solution
85835998	Aripiprazole 1mg/ml oral solution
39298978	Aripiprazole 30mg tablets
55056978	Aripiprazole 30mg tablets
87448998	Aripiprazole 30mg tablets
87451998	Aripiprazole 30mg tablets
39109978	Aripiprazole 400mg powder and solvent for suspension for injection vials
39110978	Aripiprazole 400mg powder and solvent for suspension for injection vials
78405978	Aripiprazole 400mg powder and solvent for suspension for injection vials
78406978	Aripiprazole 400mg powder and solvent for suspension for injection vials
39301978	Aripiprazole 5mg tablets
87089998	Aripiprazole 5mg tablets
87090998	Aripiprazole 5mg tablets
89532979	Aripiprazole 5mg tablets
83903998	Aripiprazole 9.75mg/1.3ml solution for injection vials
39109978	Aripiprazole 400mg powder and solvent for suspension for injection vials
39110978	Aripiprazole 400mg powder and solvent for suspension for injection vials

78405978	Aripiprazole 400mg powder and solvent for suspension for injection vials
78406978	Aripiprazole 400mg powder and solvent for suspension for injection vials
91618997	Olanzapine 10mg oral lyophilisates sugar free
96404979	Olanzapine 10mg oral lyophilisates sugar free
61165979	Olanzapine 10mg orodispersible tablets sugar free
61585979	Olanzapine 10mg orodispersible tablets sugar free
80976998	Olanzapine 10mg orodispersible tablets sugar free
80977998	Olanzapine 10mg orodispersible tablets sugar free
80978998	Olanzapine 10mg orodispersible tablets sugar free
81040998	Olanzapine 10mg orodispersible tablets sugar free
90659996	Olanzapine 10mg orodispersible tablets sugar free
91866990	Olanzapine 10mg orodispersible tablets sugar free
87647998	Olanzapine 10mg powder for solution for injection vials
89567996	Olanzapine 10mg tablets
89569996	Olanzapine 10mg tablets
91870990	Olanzapine 10mg tablets
60067979	Olanzapine 15mg oral lyophilisates sugar free
91364998	Olanzapine 15mg oral lyophilisates sugar free
61131979	Olanzapine 15mg orodispersible tablets sugar free
61583979	Olanzapine 15mg orodispersible tablets sugar free
61610979	Olanzapine 15mg orodispersible tablets sugar free

80972998	Olanzapine 15mg orodispersible tablets sugar free
80973998	Olanzapine 15mg orodispersible tablets sugar free
80974998	Olanzapine 15mg orodispersible tablets sugar free
91825990	Olanzapine 15mg orodispersible tablets sugar free
97995998	Olanzapine 15mg orodispersible tablets sugar free
81043998	Olanzapine 15mg tablets
91869990	Olanzapine 15mg tablets
97111998	Olanzapine 15mg tablets
97433998	Olanzapine 15mg tablets
90659998	Olanzapine 2.5mg tablets
90664998	Olanzapine 2.5mg tablets
96421979	Olanzapine 2.5mg tablets
64673979	Olanzapine 2.5mg/5ml oral suspension
85376998	Olanzapine 20mg oral lyophilisates sugar free
86324998	Olanzapine 20mg oral lyophilisates sugar free
61145979	Olanzapine 20mg orodispersible tablets
61581979	Olanzapine 20mg orodispersible tablets
80969998	Olanzapine 20mg orodispersible tablets
80970998	Olanzapine 20mg orodispersible tablets
80971998	Olanzapine 20mg orodispersible tablets
86325998	Olanzapine 20mg orodispersible tablets
91824990	Olanzapine 20mg orodispersible tablets
91864990	Olanzapine 20mg orodispersible tablets
85377998	Olanzapine 20mg tablets
90190979	Olanzapine 20mg tablets
91828990	Olanzapine 20mg tablets
91618998	Olanzapine 5mg oral lyophilisates sugar free
61166979	Olanzapine 5mg orodispersible tablets sugar free

61579979	Olanzapine 5mg orodispersible tablets sugar free
61602979	Olanzapine 5mg orodispersible tablets sugar free
80979998	Olanzapine 5mg orodispersible tablets sugar free
80980998	Olanzapine 5mg orodispersible tablets sugar free
80981998	Olanzapine 5mg orodispersible tablets sugar free
81041998	Olanzapine 5mg orodispersible tablets sugar free
90659997	Olanzapine 5mg orodispersible tablets sugar free
91827990	Olanzapine 5mg orodispersible tablets sugar free
91867990	Olanzapine 5mg orodispersible tablets sugar free
89567998	Olanzapine 5mg tablets
89569998	Olanzapine 5mg tablets
96450979	Olanzapine 5mg tablets
89567997	Olanzapine 7.5mg tablets
89569997	Olanzapine 7.5mg tablets
91871990	Olanzapine 7.5mg tablets
82202998	Olanzapine embonate 210mg powder and solvent for suspension for injection vials
82199998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82201998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82198998	Olanzapine embonate 405mg powder and solvent for suspension for injection vials
82202998	Olanzapine embonate 210mg powder and solvent for suspension for injection vials
82199998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials

82201998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82198998	Olanzapine embonate 405mg powder and solvent for suspension for injection vials
68663978	Quetiapine 100mg tablets
88734996	Quetiapine 100mg tablets
88737996	Quetiapine 100mg tablets
96395979	Quetiapine 100mg tablets
82773998	Quetiapine 100mg/5ml oral solution
82772998	Quetiapine 100mg/5ml oral suspension
81236998	Quetiapine 12.5mg/5ml oral solution
81113998	Quetiapine 12.5mg/5ml oral suspension
66395979	Quetiapine 125mg/5ml oral suspension
53079979	Quetiapine 150mg modified-release tablets
55253978	Quetiapine 150mg modified-release tablets
55254978	Quetiapine 150mg modified-release tablets
81923998	Quetiapine 150mg modified-release tablets
81924998	Quetiapine 150mg modified-release tablets
88733997	Quetiapine 150mg tablets
88736997	Quetiapine 150mg tablets
66391979	Quetiapine 150mg/5ml oral suspension
55544979	Quetiapine 200mg modified-release tablets
55703978	Quetiapine 200mg modified-release tablets
55704978	Quetiapine 200mg modified-release tablets
59369979	Quetiapine 200mg modified-release tablets
72639978	Quetiapine 200mg modified-release tablets
83492998	Quetiapine 200mg modified-release tablets
83995998	Quetiapine 200mg modified-release tablets
52736979	Quetiapine 200mg tablets
88733998	Quetiapine 200mg tablets
88736998	Quetiapine 200mg tablets
96387979	Quetiapine 200mg tablets
82888978	Quetiapine 200mg/5ml oral suspension
52738979	Quetiapine 25mg tablets
53211979	Quetiapine 25mg tablets

58638979	Quetiapine 25mg tablets
59467979	Quetiapine 25mg tablets
59468979	Quetiapine 25mg tablets
59469979	Quetiapine 25mg tablets
88734997	Quetiapine 25mg tablets
88737997	Quetiapine 25mg tablets
96402979	Quetiapine 25mg tablets
66389979	Quetiapine 25mg/5ml oral solution
81473998	Quetiapine 25mg/5ml oral suspension
88734998	Quetiapine 25mg+100mg+150mg tablets starter pack
55705978	Quetiapine 300mg modified-release tablets
55706978	Quetiapine 300mg modified-release tablets
59370979	Quetiapine 300mg modified-release tablets
72640978	Quetiapine 300mg modified-release tablets
83491998	Quetiapine 300mg modified-release tablets
83994998	Quetiapine 300mg modified-release tablets
88938979	Quetiapine 300mg modified-release tablets
58553979	Quetiapine 300mg tablets
87907998	Quetiapine 300mg tablets
87908998	Quetiapine 300mg tablets
55701978	Quetiapine 400mg modified-release tablets
55702978	Quetiapine 400mg modified-release tablets
59368979	Quetiapine 400mg modified-release tablets
68593978	Quetiapine 400mg modified-release tablets
72638978	Quetiapine 400mg modified-release tablets
83490998	Quetiapine 400mg modified-release tablets
83993998	Quetiapine 400mg modified-release tablets
88924979	Quetiapine 400mg modified-release tablets
51498978	Quetiapine 50mg modified-release tablets
55083979	Quetiapine 50mg modified-release tablets
55266978	Quetiapine 50mg modified-release tablets
55267978	Quetiapine 50mg modified-release tablets
58799979	Quetiapine 50mg modified-release tablets
64621979	Quetiapine 50mg modified-release tablets

64622979	Quetiapine 50mg modified-release tablets
64625979	Quetiapine 50mg modified-release tablets
70478978	Quetiapine 50mg modified-release tablets
83493998	Quetiapine 50mg modified-release tablets
83996998	Quetiapine 50mg modified-release tablets
63673979	Quetiapine 50mg/5ml oral solution
63671979	Quetiapine 50mg/5ml oral suspension
88737998	Quetiapine starter pack
90395998	Risperidone 1mg orodispersible tablets sugar free
91374998	Risperidone 1mg orodispersible tablets sugar free
92917990	Risperidone 1mg tablets
92956990	Risperidone 1mg tablets
96554979	Risperidone 1mg tablets
98585998	Risperidone 1mg tablets
99649998	Risperidone 1mg tablets
46610978	Risperidone 1mg/ml oral solution sugar free
92908990	Risperidone 1mg/ml oral solution sugar free
93240997	Risperidone 1mg/ml oral solution sugar free
99637997	Risperidone 1mg/ml oral solution sugar free
55523979	Risperidone 25mg powder and solvent for suspension for injection vials
88164998	Risperidone 25mg powder and solvent for suspension for injection vials
91676998	Risperidone 25mg powder and solvent for suspension for injection vials
90396998	Risperidone 2mg orodispersible tablets sugar free
92107998	Risperidone 2mg orodispersible tablets sugar free
52748979	Risperidone 2mg tablets
79816978	Risperidone 2mg tablets
92955990	Risperidone 2mg tablets
98585997	Risperidone 2mg tablets

99649997	Risperidone 2mg tablets
88163998	Risperidone 37.5mg powder and solvent for suspension for injection vials
92089998	Risperidone 37.5mg powder and solvent for suspension for injection vials
85039998	Risperidone 3mg orodispersible tablets sugar free
85042998	Risperidone 3mg orodispersible tablets sugar free
92954990	Risperidone 3mg tablets
96914992	Risperidone 3mg tablets
98585996	Risperidone 3mg tablets
99649996	Risperidone 3mg tablets
85038998	Risperidone 4mg orodispersible tablets sf
85040998	Risperidone 4mg orodispersible tablets sf
92953990	Risperidone 4mg tablets
93240998	Risperidone 4mg tablets
99637998	Risperidone 4mg tablets
86983998	Risperidone 500microgram orodispersible tablets sugar free
86984998	Risperidone 500microgram orodispersible tablets sugar free
92491990	Risperidone 500microgram orodispersible tablets sugar free
92625990	Risperidone 500microgram orodispersible tablets sugar free
91968998	Risperidone 500microgram tablets
92023998	Risperidone 500microgram tablets
92957990	Risperidone 500microgram tablets
89908998	Risperidone 50mg powder and solvent for suspension for injection vials
95519998	Risperidone 50mg powder and solvent for suspension for injection vials
93240996	Risperidone 6mg tablets
99637996	Risperidone 6mg tablets

Appendix 10

Code list

Extrapyramidal symptoms

Read code	Description
2942.00	O/E - muscle tone hypertonic
2944.00	O/E - muscle rigid - cogwheel
2944.11	O/E - cog wheel rigidity
2987.00	O/E -Parkinson flexion posture
2987.11	O/E - Parkinson posture
2994.00	O/E-festination-Parkinson gait
2994.11	O/E - Parkinson gait
1B22.00	Has a tremor
1B22.11	Tremor symptom
1B22.12	Shaking
1B23.00	Trembles
1B23.11	Trembles - symptom
294..11	O/E - rigid muscle
297A.00	O/E - Parkinsonian tremor
29M..00	Extrapyramidal movements
F121.00	Parkinsonism secondary to drugs
F121.11	Drug induced parkinsonism
F12W.00	Secondary parkinsonism due to other external agents
F12X.00	Secondary parkinsonism, unspecified
F13..00	Other extrapyramidal disease and abnormal movement disorders
F13..11	Extrapyramidal disease excluding Parkinson's disease
F131200	Drug-induced tremor
F13z.00	Other/unspecified extrapyramidal/abnormal movement disorders
F13z000	Unspecified extrapyramidal disease
F13zz00	Extrapyramidal disease and abnormal movement disorder NOS
Fyu2.00	[X]Extrapyramidal and movement disorders
Fyu2000	[X]Other drug-induced secondary parkinsonism

Fyu2100	[X]Other secondary parkinsonism
Fyu2700	[X]Other specified extrapyramidal and movement disorders
Fyu2800	[X]Extrapyramidal+movement disorders in diseases CE
Fyu2900	[X]Secondary parkinsonism, unspecified
Fyu2B00	[X]Secondary parkinsonism due to other external agents
R010300	[D]Tremor NOS
ZS42500	Extrapyramidal dysarthria
2974.00	O/E - spasm/tic
2974.11	O/E - spasm
2942000	Trismus
16A3.00	Wry neck/torticollis
16A3.11	Torticollis - symptom
1B25.00	Has "spasms"
1B25.11	Spasms - symptom
1B35.00	Attacks of rigidity
1B36.00	Trismus present
22B2.00	O/E - carpopedal spasm
7Q04000	Torsion dystonias other involuntary movements drugs band 1
F136.00	Idiopathic torsion dystonia
F136000	Idiopathic familial dystonia
F137.00	Symptomatic torsion dystonia
F137200	Drug-induced dystonia
F137y00	Other specified symptomatic torsion dystonia
F137z00	Symptomatic torsion dystonia NOS
F138.00	Fragments of torsion dystonia
F138000	Blepharospasm
F138200	Spasmodic torticollis
F13A.00	Paroxysmal dystonia
F13B.00	Myoclonic dystonia
F13X.00	Dystonia, unspecified
F4Jy911	Oculogyric crisis

Fyu2400	[X]Other dystonia
Fyu2A00	[X]Dystonia, unspecified
N135.00	Torticollis unspecified
N135000	Intermittent torticollis
N135z00	Torticollis NOS
R010200	[D]Spasms NOS
R010600	[D] Trismus
R017000	[D]Carpopedal spasm
1B1O.00	Restless
1P04.00	C/O - akathisia
F138111	Tardive dyskinesia
F138100	Orofacial dyskinesia
297..00	O/E - involuntary movements
297Z.00	O/E - involuntary movement NOS
1B2..00	Involuntary movement symptom
1B2Z.00	Involuntary movemt.symptom NOS
R010.00	[D]Abnormal involuntary movements
R010z00	[D]Abnormal involuntary movement NOS
Ryu3000	[X]Other and unspecified abnormal involuntary movements
1B2Z.00	Involuntary movemt.symptom NOS
1B2..00	Involuntary movement symptom

Cardiovascular symptoms

Read code	**Description**
G570000	paroxysmal atrial tachycardia
G570100	paroxysmal atrioventricular tachycardia
G570200	paroxysmal junctional tachycardia
G570300	paroxysmal nodal tachycardia
G570z00	paroxysmal supraventricular tachycardia nos
G571.00	paroxysmal ventricular tachycardia
G571.11	ventricular tachycardia
G572.00	paroxysmal tachycardia unspecified
G572000	essential paroxysmal tachycardia

G572z00	paroxysmal tachycardia nos
G57y900	supraventricular tachycardia nos
2426.00	O/E - pulse rate tachycardia
2426.11	O/E - tachycardia
3282.00	ECG: ventricular tachycardia
G570.00	Paroxysmal supraventricular tachycardia
G570000	Paroxysmal atrial tachycardia
G570100	Paroxysmal atrioventricular tachycardia
G570200	Paroxysmal junctional tachycardia
G570300	Paroxysmal nodal tachycardia
G570z00	Paroxysmal supraventricular tachycardia NOS
G571.00	Paroxysmal ventricular tachycardia
G571.11	Ventricular tachycardia
G572.00	Paroxysmal tachycardia unspecified
G572000	Essential paroxysmal tachycardia
G572z00	Paroxysmal tachycardia NOS
G57y700	Sinus tachycardia
G57y900	Supraventricular tachycardia NOS
R050.00	[D]Tachycardia, unspecified
14AN.00	h/o: atrial fibrillation
14AR.00	history of atrial flutter
212R.00	atrial fibrillation resolved
327..00	ecg: supraventricular arrhythmia
3272.00	ecg: atrial fibrillation
3273.00	ecg: atrial flutter
328..00	ecg: ventricular arrhythmia
3282.00	ecg: ventricular tachycardia
328Z.00	ecg: ventricular arrhythmia nos
662S.00	atrial fibrillation monitoring
6A9..00	atrial fibrillation annual review
7936A00	implant intravenous pacemaker for atrial fibrillation
8CMW200	atrial fibrillation care pathway
8HTy.00	referral to atrial fibrillation clinic

9hF..00	exception reporting: atrial fibrillation quality indicators
9hF1.00	excepted from atrial fibrillation qual indic: inform dissent
9Os..00	atrial fibrillation monitoring administration
9Os0.00	atrial fibrillation monitoring first letter
9Os1.00	atrial fibrillation monitoring second letter
9Os2.00	atrial fibrillation monitoring third letter
9Os3.00	atrial fibrillation monitoring verbal invite
9Os4.00	atrial fibrillation monitoring telephone invite
F256000	Hypsarrhythmia
G559.00	arrhythmogenic right ventricular cardiomyopathy
G55A.11	tachycardia-induced cardiomyopathy
G56..00	conduction disorders
G56..11	conduction disorders of heart
G567400	wolff-parkinson-white syndrome
G56y.00	other conduction disorders
G56y000	lown-ganong-levine syndrome
G56zz00	conduction disorders nos
G57..00	cardiac dysrhythmias
G57..11	cardiac arrhythmias
G573.00	atrial fibrillation and flutter
G573000	atrial fibrillation
G573100	atrial flutter
G573200	paroxysmal atrial fibrillation
G573300	non-rheumatic atrial fibrillation
G573400	permanent atrial fibrillation
G573500	persistent atrial fibrillation
G573600	paroxysmal atrial flutter
G573z00	atrial fibrillation and flutter nos
G574.00	ventricular fibrillation and flutter
G574100	ventricular flutter
G574z00	ventricular fibrillation and flutter nos
G576300	atrial premature depolarization

G576400	junctional premature depolarization
G576500	ventricular premature depolarization
G57y.00	other cardiac dysrhythmias
G57y600	nodal rhythm disorder
G57yA00	re-entry ventricular arrhythmia
G57yz00	other cardiac dysrhythmia nos
G57z.00	cardiac dysrhythmia nos
Gyu5a00	[x]other specified cardiac arrhythmias
Gyu5a00	[X]Other specified cardiac arrhythmias
F287.00	Idiopathic intracranial hypotension
F291000	Intracranial hypotension following ventricular shunting
G87..00	Hypotension
G870.00	Orthostatic hypotension
G870.11	Postural hypotension
G871.00	Chronic hypotension
G872.00	Idiopathic hypotension
G873.00	Hypotension due to drugs
G87z.00	Hypotension NOS
Gyu9000	[X]Other hypotension
8624.00	Hypothermia with hypotension

Sexual dysfunction symptoms

Read code	**Description**
E227311	Erectile dysfunction
Eu52212	[X]Male erectile disorder
1ABB.00	Cannot get an erection
1ABC.00	Cannot sustain an erection
1ABD.00	Painful erection
1ABE.00	Abnormal angle of erection
1D1B.00	C/O erectile dysfunction
7C25E00	Treatment of erectile dysfunction NEC
8HTj.00	Referral to erectile dysfunction clinic
K590.11	Amenorrhoea

K590.00	Absence of menstruation
K59..00	Menstruation disorders
K59..11	Period disorders
K590000	Primary amenorrhoea
K590100	Secondary amenorrhoea
K590z00	Amenorrhoea NOS
K591.11	Infrequent menstruation
K591000	Hypomenorrhoea
K594.00	Irregular menstrual cycle
K594000	Delayed period
K594011	Late period
K594012	Delayed menstruation
K594z00	Irregular menstrual cycle NOS
4435100	Prolactin level raised
4439.00	30 minute plasma prolactin level
443A.00	60 minute plasma prolactin level
443B.00	90 minute plasma prolactin level
443C.00	120 minute plasma prolactin level
443D.00	150 minute plasma prolactin level
443E.00	30 minute serum prolactin level
443F.00	60 minute serum prolactin level
443G.00	90 minute serum prolactin level
443g.00	Plasma prolactin level
443H.00	120 minute serum prolactin level
443I.00	150 minute serum prolactin level
443j.00	Serum prolactin level
443j000	Serum prolactin polyethylene glycol recovery level
443n.00	Monomeric prolactin level
443p.00	Macro prolactin level
BB5y400	[M]Prolactinoma
C131000	Hyperprolactinaemia
4435.00	Prolactin level

Appendix 11

Ethical approval for Chapter 8

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

13 September 2018

Dear Professor Wong

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Pharmacotherapy and weight change in adolescents with anorexia nervosa within child and adolescent eating disorder services**
IRAS project ID:	**228242**
Protocol number:	**17/0918**
REC reference:	**19/HRA/0360**
Sponsor	**University College London**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The attached document *"After HRA Approval – guidance for sponsors and investigators"* gives detailed guidance on reporting expectations for studies with HRA and HCRW Approval, including:

- Registration of Research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name:	Misha Ladva
Tel:	0203 447 5274
Email:	randd@uclh.nhs.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **228242**. Please quote this on all correspondence.

Yours sincerely

Andrea Bell
Assessor

Email: hra.approval@nhs.net

Appendix 12

Approved study protocol for Chapter 8

STUDY PROTOCOL

FULL PROTOCOL TITLE OF THE STUDY

Pharmacotherapy and weight change in adolescents with anorexia nervosa within child and adolescent eating disorder services

SHORT STUDY TITLE / ACCRONYM

Pharmacotherapy and weight change in adolescents with anorexia nervosa

Chief Investigator:

Professor Ian CK Wong, PhD

Professor of Pharmacy Practice and Head of the Research Department of Practice and Policy

Supported by:

N/A

Sponsored by:

University College London (UCL)

Protocol version number and date:

Version 3 19/09/2019

R&D / Sponsor Reference Number(s):

17/0918

Study Registration Number:

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	Version 1	16/05/2018	[full name & title]	[appendix no] NB: Appendix is to be attached to current version of the protocol
Current	Version 2	27/08/2019	Maedeh Yakhchi Beykloo	Extension of study end date to 31st October 2019
Current	Version 3	03/12/2019	Maedeh Yakhchi Beykloo	Substantial amendment to include sample size to 400 patient records and extend study end date to 31st January 2020

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator

Signature: **Date:** 16/05/2018

Print Name (in full): Professor Ian CK Wong

Position: Head of Department for Practice and Policy, School of Pharmacy, UCL

ABBREVIATIONS

AN	Anorexia Nervosa
BMI	Body Mass Index
UCL	University College London
BMA	British Medical Association
CI	Chief Investigator
SAE	Serious Adverse Event

STUDY SUMMARY

Identifiers	
IRAS Number	228242
REC Reference No	
Sponsor Reference No	17/0918
Other research reference number(s) (if applicable)	
Full (Scientific) title	Pharmacotherapy and weight change in adolescents with Anorexia Nervosa within an eating disorder clinic
Health condition(s) or problem(s) studied	Anorexia Nervosa
Study Type i.e. Cohort etc	Descriptive retrospective observational study
Target sample size	400 anonymised patient records
STUDY TIMELINES	
Study Duration/length	12 months
Expected Start Date	July 2018
End of Study definition and anticipated date	31st January 2020
Key Study milestones	June 2018 – IRAS submission September 2018 to October 2019 – Data collection at designated child and adolescent eating disorder services May to December 2019 – Statistical analysis and presentation of results including publications and presentations January 2020 – Publication and dissemination. Thesis write up.
FUNDING & Other	
Funding	N/A
Other support	N/A
STORAGE of SAMPLES (if applicable)	
Human tissue samples	N/A
Data collected / Storage	N/A
KEY STUDY CONTACTS	
Chief Investigator	Professor Ian CK Wong
PhD student researcher	Maedeh Yakhchi Beykloo

INTRODUCTION

Anorexia nervosa (AN) is a mental health condition that is characterised by the individuals' extreme fear of gaining weight, despite evidently being underweight. This results in restrictions in eating, bad food habits, purging and excessive exercise. Anorexia therapy is mainly with a combination of psychological and medication treatments (Moore et al., 2013b). However little research is carried out or evidence available to support the use of medications in adolescents with anorexia nervosa, despite clinicians often prescribing medications adjunct to psychological therapies or as a primary step of treatment. The benefit of this research will be that it will provide information on the treatment outcomes of antipsychotic and antidepressant medications in resulting to BMI differences in patients and the adverse events associated with these medications in providing a safety measure.

As a result of a lack in guideline on medication treatment, this study will be conducted in Child and Adolescent Eating Disorders Service in designated hospitals in England, on adolescents aged 13 to 18 years who have been initiated on AN medication treatment. The study will 1) describe the medications that are prescribed for AN adolescents and 2) evaluate treatment outcomes of AN adolescents with regards to weight change and adverse events.

The study will examine the treatment outcomes of adolescents initiated on AN medication treatment (antipsychotic and antidepressants) from 01/01/2012 to 31/12/2016, with a one year follow up duration (31/12/17). Anonymised electronic records from the designated children and adolescent eating disorder services will be used to identify adolescents with drug treatments. As per normal standard procedure at clinics, BMI measurements of AN patients are calculated on a weekly basis for the first 12 weeks after treatment initiation. The aim of this study will be to describe the difference in BMI before and after treatment initiation on antipsychotic and antidepressant medications as a measure of treatment effectiveness. Similarly, we will analyse the adverse event profile for the prescribed drugs as a measure of medication safety.

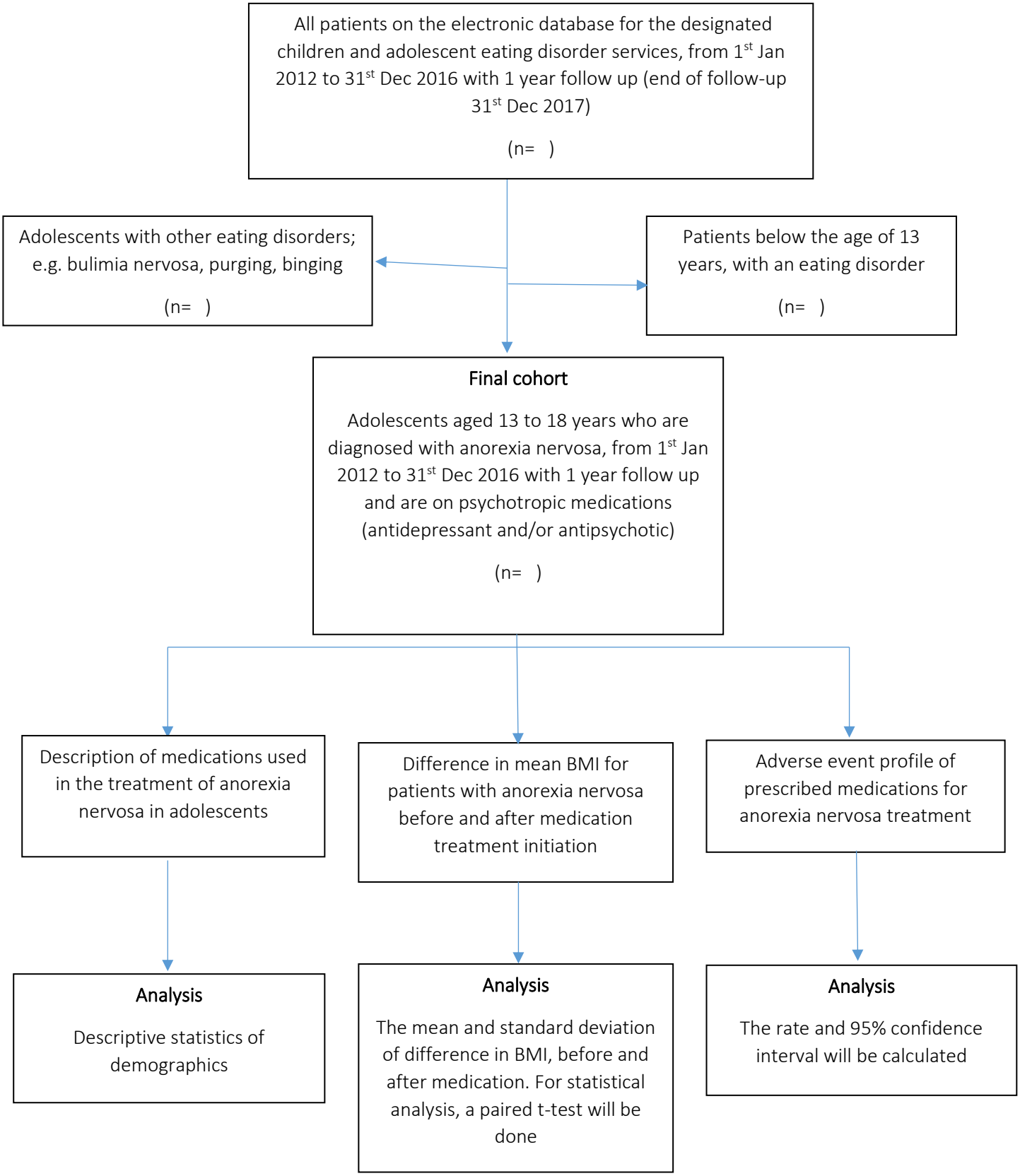


Figure 1: Flowchart of study

BACKGROUND AND RATIONALE

Eating disorders are serious mental health illnesses that affect over 1.6 million men and women of all ages in the UK (Qian et al., 2013). The National Collaborating Centre for Mental Health UK (2004) , has reported that in any year, 1.9% of women and 0.2% of men experience anorexia nervosa, with the condition usually lasting a duration of 6 years (National Collaborating Centre for Mental Health, 2004). Young people between the ages of 15 to 24 years who have been diagnosed with anorexia nervosa have 10 times the risk of dying in comparison to their peers who are the same age (Smink et al., 2012).

Comorbidities are common in anorexia nervosa, particularly those of psychiatric disorders (O'Brien and Vincent, 2003b), namely major depression (Herzog et al., 1992, O'Brien and Vincent, 2003b). Due to the nature of anorexia nervosa, nutritional disturbances cause a severe impact on drug response and result in cognitive function impairment.

Treatment of anorexia is mainly carried out through an integrative approach, with a combination of nutritional, social, medical and psychological care (Moore et al., 2013b). However the treatments often remain unsuccessful, with a 40% dropout rate (La Via et al., 2000). There is little research carried out or evidence available to support the use of medications in adolescents with anorexia nervosa (Couturier and Lock, 2007, McKnight and Park, 2010). Nevertheless, clinicians often prescribe medications to assist psychological therapies or as a primary step of treatment (Gowers et al., 2010a), despite no evidence for long-term improvement in patients with anorexia nervosa (Crow et al., 2009). Psychopharmacological therapies have been proposed, particularly with the use of atypical antipsychotics and antidepressants (Fazeli et al., 2012).

There are many potential reasons which play a role in medications not being selected as the primary mode of treatment in anorexia (Crow et al., 2009), with pharmacological adherence (compliance) accounting for the main one as patient drop-out rates are found to be between 35% and 75% (Halmi et al., 2005). Poor medication response as a result of starvation in anorexia and, adverse events resulting from prescribed medications such as metabolic disruptions, extrapyramidal symptoms and sexual/reproductive events must also be considered, particularly in patients with comorbid conditions (Jerrell et al., 2010). As a result of this lack of convincing evidence for drug efficacy for anorexia nervosa, no pharmacological treatment guidelines are currently in place within the England (NICE, 2018). Therefore, there is a need for evidence to guide pharmacotherapy procedures in patients with anorexia nervosa.

OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to describe the difference in BMI before and after initiating antipsychotic and antidepressant medication treatment in adolescents diagnosed with anorexia nervosa, through patient hospital records.

Secondary Objectives

The objectives of this study are as follows:

i. To describe the drugs that are prescribed by clinicians at the designated children and adolescent eating disorder services for patients with anorexia nervosa; including the dosage, strength, formulation and frequency in order to stratify them into the groups of medications used throughout treatment of anorexia nervosa

ii. To describe the adverse event profile associated with the main medications prescribed for AN in adolescents at the designated children and adolescent eating disorder services as found on their patient records and as experienced by patients.

STUDY DESIGN

The design of this study is that of a descriptive retrospective observational design that will be conducted at the designated children and adolescent eating disorder services. The study population consists of adolescents aged 13 to 18 years who are diagnosed with anorexia nervosa and initiated on medication therapy of either antipsychotics or antidepressants. Patient data will be identified from the 1st of Jan 2012 to 31st Dec 2016 with a one year follow-up; the end of follow-up is 31st Dec 2017.
The data for the identified patients will be used initially to describe the medications they were initiated on for anorexia treatment. The data will then be used to describe the difference in mean BMI before and after medication initiation.
The classical sample size calculation is not applicable as this is a descriptive study. However we estimate the available sample size based on the preliminary number of patients who fit the inclusion criteria as supplied by one eating disorder consultant at Maudsley hospital. The total number of anorexia patients in 2015 and 2016 was recorded as 115 and 121 respectively. From this total, 42 of the 115 were on medications (37%) in 2015 and 33 of the 121 patients were on medications (27%) in 2016. We can estimate that our sample size will be between 165 to 210 patients approximately for Maudsley hospital alone. As there are new sites that have been added to the study through non-substantial amendments, we anticipate our sample size will be significantly increasing due to the potential of these multi-sites. Thus, a further 200 more anonymised patient records must be accounted for, increasing the total UK sample size for this study to 400 to ensure data saturation.

STUDY SCHEDULE

This study will only use pseudonymised patient records that are stored on the electronic database at the designated children and adolescent eating disorder services. The pseudonymised data will be anonymised by the clinical care team at the designated children and adolescent eating disorder services, therefore no patients will be contacted for the purpose of the study. There will be no patient enrolment process, follow up and withdrawal criteria, as only retrospective data will be used.
The end of the follow up of each patient will be marked if any of the following are met:

d) The patient is deceased during the study or follow up time
e) The patient discontinues treatment at the designated children and adolescent eating disorder services or discharge from the clinics
f) The end date of the study which is the 31st December 2017 (end of follow up date)

CONSENT

Consent is not required as there are no participants involved in this study. Only automated, retrospectively, anonymised patient data will be accessed.

ELIGIBILITY CRITERIA

1.1 Inclusion Criteria

The inclusion criteria for this study will be:

- Patient records from adolescents aged 13 to 18 years with anorexia nervosa under the care of the designated children and adolescent eating disorder services
- Patients must be on prescribed antipsychotic and/or antidepressant medication(s) by the eating disorder clinicians for anorexia treatment
- Patients diagnosed with anorexia nervosa between 1st January 2012 until 31st December 2016, with a 1 year follow up

Exclusion Criteria

As this is a retrospective descriptive study, there will be no exclusion criteria for the study.

RECRUITMENT

This study is retrospective, so there will be no active recruitments of patients. The patients for the study will be identified by the clinical care team at the designated children and adolescent eating disorder services based on the listed inclusion criteria mentioned. As the electronic records are already pseudonymised, a list of patients for the study will be formed by the clinical care teams at each site, who will then anonymise the identified patient records for the research team. The student researcher will access the identified anonymised patient data and record the data required for the study.

STATISTICAL METHODS

The patient records will be used by the clinical care team at the designated children and adolescent eating disorder services to identify eligible patients. The classical sample size calculation is not applicable as this is a descriptive study.
The statistical analysis for the objectives:

i. Descriptive statistics will be presented of the observations made. These will include the frequency and percentages of the demographic information such as the gender and comorbidities etc. of the patients. Information on the age of patients will be presented as median and interquartile ranges.
ii. The mean and standard deviation of the BMI before and after medication initiation for AN patients will be calculated. The difference between the before and after BMI means will be calculated with 95% confidence intervals. If the differences in BMI measurements are normally distributed, the statistical analysis we will use is a paired t-test (McCluskey and Lalkhen, 2007). If the difference is skewed, a Wilcoxon sign rank test will be used.
iii. The rate and 95% confidence interval of the adverse events will be calculated with regards to the treatment medications. The rate will be calculated by determining the proportion of subjects who experienced the adverse event from the total population during the study time.

PATIENT AND PUBLIC INVOLVEMENT (PPI)

PPI is not applicable as we will not be using any patient and public involvement for this study.

FUNDING AND SUPPLY OF EQUIPMENT

This study is part of a PhD project and involves no external funding.
The student researcher will access the electronic database via a computer at the designated children and adolescent eating disorder services in order to extract the required anonymised patient data for the study

from each site. The review and analysis of the data will be conducted on a computer at the department of practice and policy at University College London in the British Medical Association House.

DATA HANDLING AND MANAGEMENT

The data source of this study will be previously recorded patient medical data on the electronic database at the designated children and adolescent eating disorder services. The initial dataset is pseudonymised. In the final dataset which will be used for the study by the research student, all identifiers will be removed and the data extracted will be in a completely anonymised format. The research student and research team will not have access to the initial dataset or any patient identifying factors, thus patient identification will not be possible. Once the patients have been identified, the research student will personally access and retrieve the data electronically under the supervision of the PhD supervisors (research team) from each designated site. The required information will be stored on a secure folder on a hard drive by the research student. The hard drive will then be stored in the UCL Research Department of Practice and Policy at the British Medical Association (BMA) house where it will be kept in a locked cabinet in the CI's office. The analysis of the data will be done at BMA house by the UCL research student.

MATERIAL/SAMPLE STORAGE

Biologically material or sample is not applicable to this study. This study only involves retrospective anonymised patient data.

PEER AND REGULATORY REVIEW

The study has been peer reviewed as part of an educational programme in accordance with the requirements outlined by UCL.

The peer review has been carried out by senior academic at the UCL School of Pharmacy including two supervisors and an independent academic staff at professorial level.

ASSESMENT AND MANAGEMENT OF RISK

Due to the retrospective nature of this study, no direct contact will be made with patients. Therefore, there will be no potential physical, psychological or social risks to participants.

RECORDING AND REPORTING OF EVENTS AND INCIDENTS

The study will be monitoring adverse events on patient medical records the designated children and adolescent eating disorder services. These adverse events are not all primarily drug related. We will be assessing patients who experience neurological, metabolic and cardiac adverse events. These include extra pyramidal symptoms, cardiovascular symptoms such as QT prolongation, arrhythmias and tachycardia, weight gain, elevated prolactin and sexual dysfunction. From the listed adverse events, we will identify those reported as serious. We will then assess the likelihood of the adverse events being drug induced (section 16.2.2) and evaluate whether it is expected of the drug to cause the events, based on the SPC and BNF. Once the serious adverse events have been identified, they will be recorded on a serious adverse event form, following the steps presented in the flowchart below. Serious adverse events that are considered to be unexpected will then be reported by the JRO to the Health Research Authority.

16.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

1.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

16.2.1 Severity

For this study, only serious adverse events (SAE) will be considered and its level will be categorised as severe. This category refers to the adverse event resulting in alteration, discomfort or disability which is clearly damaging to the patients' health.

16.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the patient record form. It is of particular importance in this study to capture events related to anorexia nervosa treatment. The assessment of relationship of an adverse event to these additional safety issues will also be carried out as part of the study.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However,

	the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

16.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the procedure listed in the SPC, manual of Operation and BNF.
Unexpected	An adverse event which is not consistent with the information about the procedure listed in the manual of operation.

Recording adverse events

It is anticipated that all adverse events experienced by patients were recorded in their medical records in the first instance. In certain instances where this was not the case, it is expected that all serious adverse reactions were collected and recorded by the clinicians.

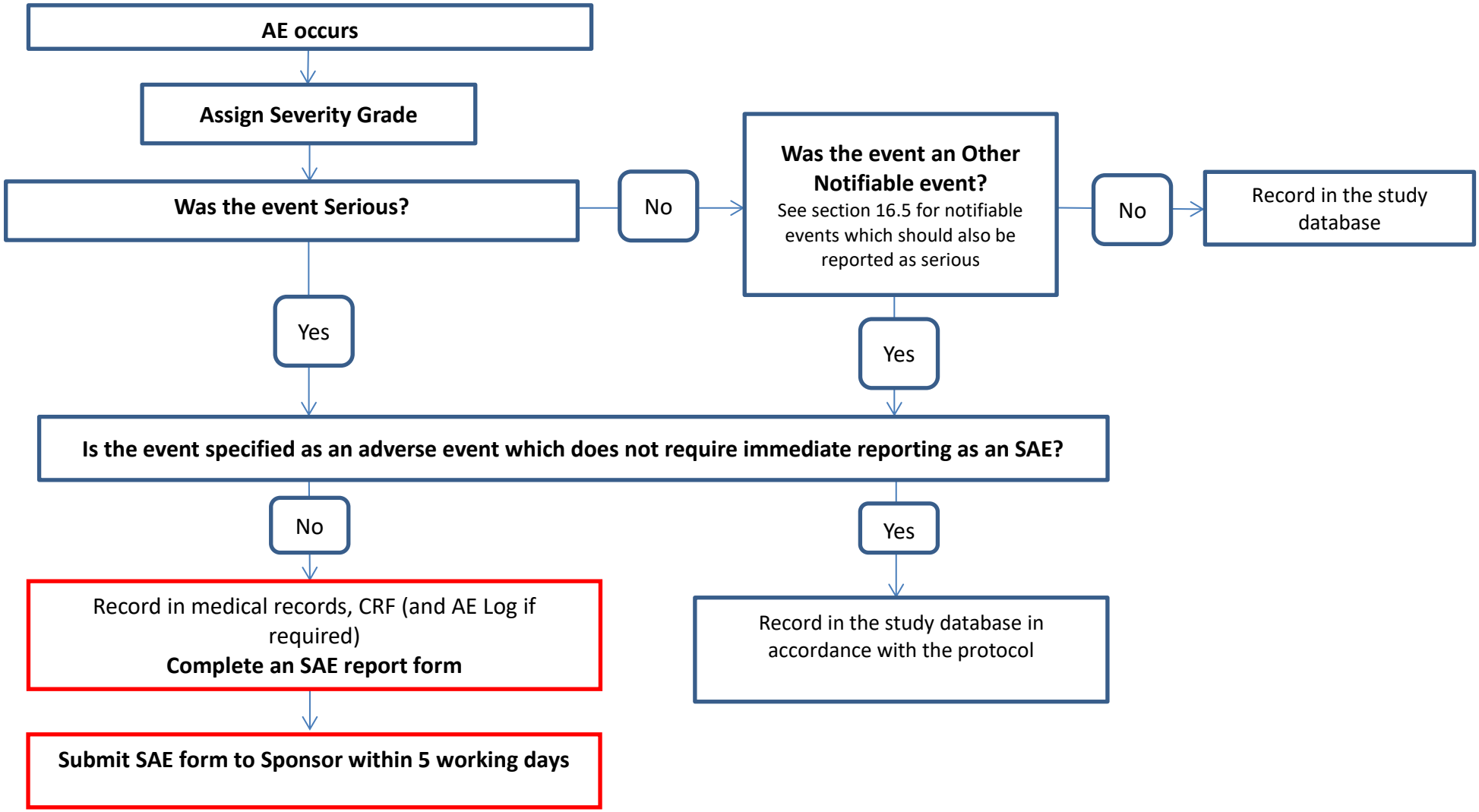
Procedures for recording and reporting Serious Adverse Events

As this is a retrospective study, all serious adverse events have already been recorded in the medical records. As the data will be collated on a database throughout the study, a list of all the SAEs can be extracted for review.

All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) will be recorded on a serious adverse event (SAE) form. The CI will complete an SAE form and the form will be emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Completed forms for unexpected SAES must be sent within 5 working days of becoming aware of the event to the Sponsor
Email forms to: Research-incidents@ucl.ac.uk

Flow Chart for SAE reporting



16.5 Serious Adverse Events that do not require reporting

Some particular SAEs may not be reported to the sponsor, for example if they are expected to occur on a regular basis and offer no further new information to the safety profile or are related to the disease area of the participants. Nevertheless, if the frequency and severity of these events appear to be unusual, they will be reported. The recording of these events has already been made in the medical records and study database, however it will be stated, with reasoning, that a SAE form will not be completed for it.

16.6 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the participants of the study; or
b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. As this is retrospective study, occurrence of protocol violations is highly unlikely.

16.7 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to UCL through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

17 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the research student. This will include adherence to the protocol and ensure adequate data quality.

An audit of the extracted medical data conducted by the student researcher will be conducted by the clinical research team at the designated children and adolescent eating disorder services. They will look at 10% of the records and evaluate the quality of the data extracted.

TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. This study is to be completed as part of a PhD at University College London, School of Pharmacy. An honorary contract has been obtained for the student researcher, allowing access to the facilities at the designated children and adolescent eating disorder services. A renewal of this contract can be requested if its validation date is exceeded. All necessary training for the completion of this study will be undertaken and records kept, by the student researcher, including data protection. In addition, training will be provided by the CI on Good Pharmacoepidemiology Practice (Ispe, 2008), which is equivalent to the Good Clinical Practice in clinical trial.

INTELLECTUAL PROPERTY

There will be no intellectual property arising from this study therefore this section is not applicable to this study.

INDEMNITY ARRANGEMENTS

There is no active involvement of patients in this study, therefore indemnity arrangement is not applicable to this study.

ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at the BMA house for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for [insert duration] and in line with all relevant legal and statutory requirements.

PUBLICATION AND DISSEMINATION POLICY

The results of this study will be disseminated in peer reviewed scientific journals or other academic publications like a PhD thesis.

Appendix 13

Stata outputs of results for Chapter 8

xtmixed BMI medication##time_point || patid:, residuals(ar 1, t(time_point)) reml

```
Mixed-effects REML regression                   Number of obs     =      1,147
Group variable: patid                           Number of groups  =        314

                                                Obs per group:
                                                              min =          1
                                                              avg =        3.7
                                                              max =          5

                                                Wald chi2(14)     =     355.57
Log restricted-likelihood = -1747.5242          Prob > chi2       =     0.0000
```

BMI	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medication						
1	-2.012176	.3614475	-5.57	0.000	-2.720601	-1.303752
2	.3962845	.2581255	1.54	0.125	-.1096321	.9022011
time_point						
1	.6798485	.0708766	9.59	0.000	.5409329	.8187641
2	1.127215	.0992927	11.35	0.000	.9326047	1.321825
3	1.533884	.1255529	12.22	0.000	1.287805	1.779963
4	1.900129	.1509323	12.59	0.000	1.604307	2.195951
medication#time_point						
1 1	.0080976	.1631393	0.05	0.960	-.3116496	.3278447
1 2	.227642	.2282134	1.00	0.319	-.2196482	.6749321
1 3	.5244786	.2783474	1.88	0.060	-.0210722	1.070029
1 4	.6291293	.3238772	1.94	0.052	-.0056584	1.263917
2 1	-.3333327	.1199456	-2.78	0.005	-.5684217	-.0982437
2 2	-.5590427	.1653996	-3.38	0.001	-.88322	-.2348654
2 3	-.7844324	.2026932	-3.87	0.000	-1.181704	-.3871611
2 4	-.6328519	.2407876	-2.63	0.009	-1.104787	-.1609168
_cons	17.22983	.1566338	110.00	0.000	16.92283	17.53683

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	1.01e-07	.0001691	0	.
Residual: AR(1)				
rho	.9120842	.0075467	.8960473	.9257441
sd(e)	2.060195	.0744449	1.919333	2.211396

LR test vs. linear model: chi2(2) = 1270.86 Prob > chi2 = 0.0000

xtmixed BMI b0.medication##b0.time_point || patid:, residuals(ar 1, t(time_point)) reml

```
Mixed-effects REML regression                   Number of obs     =      1,147
Group variable: patid                           Number of groups  =        314

                                                Obs per group:
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3	1.533884	.1255529	12.22	0.000	1.287805	1.779963
4	1.900129	.1509323	12.59	0.000	1.604307	2.195951
medication#time_point						
1 1	.0080976	.1631393	0.05	0.960	-.3116496	.3278447
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1 4	.6291293	.3238772	1.94	0.052	-.0056584	1.263917
2 1	-.3333327	.1199456	-2.78	0.005	-.5684217	-.0982437
2 2	-.5590427	.1653996	-3.38	0.001	-.88322	-.2348654
2 3	-.7844324	.2026932	-3.87	0.000	-1.181704	-.3871611
2 4	-.6328519	.2407876	-2.63	0.009	-1.104787	-.1609168
_cons	17.22983	.1566338	110.00	0.000	16.92283	17.53683

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	1.01e-07	.0001691	0	.
Residual: AR(1)				
rho	.9120842	.0075467	.8960473	.9257441
sd(e)	2.060195	.0744449	1.919333	2.211396

LR test vs. linear model: chi2(2) = 1270.86 Prob > chi2 = 0.0000

xtmixed BMI b1.medication##b0.time_point || patid:, residuals(ar 1, t(time_point)) reml

```
Mixed-effects REML regression                   Number of obs     =      1,147
Group variable: patid                           Number of groups  =        314

                                                Obs per group:
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                                                              avg =        3.7
                                                              max =          5

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medication						
0	2.012176	.3614475	5.57	0.000	1.303752	2.720601
2	2.408461	.3849737	6.26	0.000	1.653926	3.162996
time_point						
1	.6879461	.1469386	4.68	0.000	.3999518	.9759404
2	1.354857	.2054807	6.59	0.000	.9521219	1.757592
3	2.058362	.2484225	8.29	0.000	1.571463	2.545261
4	2.529258	.2865587	8.83	0.000	1.967613	3.090903
medication#time_point						
0 1	-.0080976	.1631393	-0.05	0.960	-.3278447	.3116496
0 2	-.227642	.2282134	-1.00	0.319	-.6749321	.2196481
0 3	-.5244786	.2783474	-1.88	0.060	-1.070029	.0210722
0 4	-.6291293	.3238772	-1.94	0.052	-1.263917	.0056584
2 1	-.3414303	.1759386	-1.94	0.052	-.6862636	.003403
2 2	-.7866847	.2443774	-3.22	0.001	-1.265656	-.3077137
2 3	-1.308911	.2950165	-4.44	0.000	-1.887133	-.7306893
2 4	-1.261981	.3425113	-3.68	0.000	-1.933291	-.5906713
_cons	15.21765	.3257455	46.72	0.000	14.5792	15.8561

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	9.27e-07	1.46e-06	4.21e-08	.0000204
Residual: AR(1)				
rho	.9120843	.0096359	.8911402	.9291498
sd(e)	2.060196	.0886241	1.893617	2.241428

```
LR test vs. linear model: chi2(2) = 1270.86                   Prob > chi2 = 0.0000
```

xtmixed BMI b2.medication##b0.time_point || patid:, residuals(ar 1, t(time_point)) reml

```
Mixed-effects REML regression                   Number of obs     =      1,147
Group variable: patid                           Number of groups  =        314

                                                Obs per group:
                                                              min =          1
                                                              avg =        3.7
                                                              max =          5

                                                Wald chi2(14)     =     355.57
Log restricted-likelihood = -1747.5242          Prob > chi2       =     0.0000
```

BMI	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medication						
0	-.3962845	.2581264	-1.54	0.125	-.9022029	.1096339
1	-2.408461	.3849751	-6.26	0.000	-3.162998	-1.653924
time_point						
1	.3465156	.0967648	3.58	0.000	.1568602	.5361711
2	.5681719	.1322798	4.30	0.000	.3089083	.8274356
3	.7494509	.1591256	4.71	0.000	.4375705	1.061331
4	1.267277	.1876115	6.75	0.000	.899565	1.634988
medication#time_point						
0 1	.3333329	.1199454	2.78	0.005	.0982443	.5684216
0 2	.5590431	.1653994	3.38	0.001	.2348662	.8832199
0 3	.7844333	.2026929	3.87	0.000	.3871624	1.181704
0 4	.632853	.2407874	2.63	0.009	.1609183	1.104788
1 1	.3414305	.1759383	1.94	0.052	-.0034022	.6862633
1 2	.7866849	.2443771	3.22	0.001	.3077146	1.265655
1 3	1.308911	.2950162	4.44	0.000	.7306903	1.887132
1 4	1.261981	.342511	3.68	0.000	.5906719	1.93329
_cons	17.62612	.2051704	85.91	0.000	17.22399	18.02824

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	.0000367	.0213425	0	.
Residual: AR(1)				
rho	.9120852	.0075468	.8960481	.925745
sd(e)	2.060203	.0744467	1.919337	2.211407

LR test vs. linear model: chi2(2) = 1270.86 Prob > chi2 = 0.0000

xtmixed BMIdiff b0.medication##b1.time_point2 || patid:, residuals(ar 1, t(time_point2)) reml

```
Mixed-effects REML regression                   Number of obs     =        833
Group variable: patid                           Number of groups  =        280

                                                Obs per group:
                                                              min =          1
                                                              avg =        3.0
                                                              max =          4

                                                Wald chi2(11)     =     235.40
Log restricted-likelihood = -1139.4516          Prob > chi2       =     0.0000
```

BMIdiff	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medication						
1	.0477355	.2736947	0.17	0.862	-.4886963	.5841673
2	-.3305357	.1992342	-1.66	0.097	-.7210276	.0599562
time_point2						
2	.4665176	.0681929	6.84	0.000	.332862	.6001732
3	.8954213	.0975577	9.18	0.000	.7042117	1.086631
4	1.289839	.1218061	10.59	0.000	1.051104	1.528575
medication#time_point2						
1 2	.1807972	.1521143	1.19	0.235	-.1173414	.4789357
1 3	.4326568	.2120708	2.04	0.041	.0170056	.848308
1 4	.5181205	.2601223	1.99	0.046	.00829	1.027951
2 2	-.2432865	.1144811	-2.13	0.034	-.4676653	-.0189076
2 3	-.5125749	.1593033	-3.22	0.001	-.8248035	-.2003462
2 4	-.3948557	.1975342	-2.00	0.046	-.7820157	-.0076958
_cons	.6760028	.1184271	5.71	0.000	.4438899	.9081157

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	5.51e-08	.	.	.
Residual: AR(1)				
rho	.8618083	.0127379	.834657	.884781
sd(e)	1.455293	.0542529	1.352751	1.565608

LR test vs. linear model: chi2(2) = 662.38 Prob > chi2 = 0.0000

xtmixed BMIdiff b1.medication##b1.time_point2 || patid:, residuals(ar 1, t(time_point2)) reml

```
Mixed-effects REML regression                   Number of obs     =        833
Group variable: patid                           Number of groups  =        280

                                                Obs per group:
                                                              min =          1
                                                              avg =        3.0
                                                              max =          4

                                                Wald chi2(11)     =     235.40
Log restricted-likelihood = -1139.4516          Prob > chi2       =     0.0000
```

BMIdiff	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medication						
0	-.0477355	.2736947	-0.17	0.862	-.5841673	.4886963
2	-.3782712	.2941991	-1.29	0.199	-.9548909	.1983485
time_point2						
2	.6473148	.1359724	4.76	0.000	.3808138	.9138157
3	1.328078	.188299	7.05	0.000	.9590187	1.697137
4	1.80796	.2298411	7.87	0.000	1.357479	2.25844
medication#time_point2						
0 2	-.1807972	.1521143	-1.19	0.235	-.4789357	.1173414
0 3	-.4326568	.2120708	-2.04	0.041	-.848308	-.0170056
0 4	-.5181204	.2601223	-1.99	0.046	-1.027951	-.00829
2 2	-.4240836	.1641467	-2.58	0.010	-.7458053	-.102362
2 3	-.9452317	.2265316	-4.17	0.000	-1.389225	-.5012379
2 4	-.9129762	.2775067	-3.29	0.001	-1.456879	-.3690731
_cons	.7237383	.2467465	2.93	0.003	.2401241	1.207353

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	7.79e-08	1.25e-07	3.39e-09	1.79e-06
Residual: AR(1)				
rho	.8618083	.0139828	.8317573	.8868233
sd(e)	1.455293	.0572859	1.347237	1.572016

LR test vs. linear model: chi2(2) = 662.38 Prob > chi2 = 0.0000

xtmixed BMIdiff b0.medication##b4.time_point2 || patid:, residuals(ar 1, t(time_point2)) reml

```
Mixed-effects REML regression                   Number of obs     =        833
Group variable: patid                           Number of groups  =        280

                                                Obs per group:
                                                              min =          1
                                                              avg =        3.0
                                                              max =          4

                                                Wald chi2(11)     =     235.40
Log restricted-likelihood = -1139.4516          Prob > chi2       =     0.0000
```

BMIdiff	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medication						
1	.5658559	.2913791	1.94	0.052	-.0052365	1.136948
2	-.7253914	.2161966	-3.36	0.001	-1.149129	-.3016538
time_point2						
1	-1.289839	.1218061	-10.59	0.000	-1.528575	-1.051104
2	-.8233215	.1100775	-7.48	0.000	-1.039069	-.6075736
3	-.3944178	.0921098	-4.28	0.000	-.5749498	-.2138859
medication#time_point2						
1 1	-.5181205	.2601224	-1.99	0.046	-1.027951	-.00829
1 2	-.3373233	.2288281	-1.47	0.140	-.785818	.1111715
1 3	-.0854637	.1825908	-0.47	0.640	-.443335	.2724077
2 1	.3948557	.1975342	2.00	0.046	.0076958	.7820157
2 2	.1515693	.1749336	0.87	0.386	-.1912943	.4944329
2 3	-.1177191	.1416445	-0.83	0.406	-.3953371	.1598989
_cons	1.965842	.1350456	14.56	0.000	1.701157	2.230526

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	6.65e-09	1.46e-08	8.97e-11	4.93e-07
Residual: AR(1)				
rho	.8618083	.0187926	.8201161	.894398
sd(e)	1.455293	.0699104	1.324524	1.598973

```
LR test vs. linear model: chi2(2) = 662.38                Prob > chi2 = 0.0000
```

xtmixed BMIdiff b2.medication##b4.time_point2 || patid:, residuals(ar 1, t(time_point2)) reml

```
Mixed-effects REML regression                   Number of obs     =        833
Group variable: patid                           Number of groups  =        280

                                                Obs per group:
                                                              min =          1
                                                              avg =        3.0
                                                              max =          4

                                                Wald chi2(11)     =     235.40
Log restricted-likelihood = -1139.4516          Prob > chi2       =     0.0000
```

BMIdiff	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medication						
0	.7253914	.2161966	3.36	0.001	.3016538	1.149129
1	1.291247	.3084933	4.19	0.000	.6866116	1.895883
time_point2						
1	-.8949834	.155509	-5.76	0.000	-1.199775	-.5901913
2	-.6717522	.1359585	-4.94	0.000	-.9382261	-.4052784
3	-.512137	.1076054	-4.76	0.000	-.7230397	-.3012342
medication#time_point2						
0 1	-.3948557	.1975342	-2.00	0.046	-.7820157	-.0076958
0 2	-.1515693	.1749336	-0.87	0.386	-.4944329	.1912944
0 3	.1177191	.1416445	0.83	0.406	-.1598989	.3953372
1 1	-.9129762	.2775067	-3.29	0.001	-1.456879	-.3690731
1 2	-.4888926	.2423426	-2.02	0.044	-.9638754	-.0139097
1 3	.0322555	.1908772	0.17	0.866	-.341857	.4063679
_cons	1.24045	.1688303	7.35	0.000	.9095492	1.571352

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Identity				
sd(_cons)	4.93e-08	6.39e-08	3.88e-09	6.26e-07
Residual: AR(1)				
rho	.8618083	.0131428	.833719	.8854489
sd(e)	1.455293	.0552325	1.350968	1.567675

```
LR test vs. linear model: chi2(2) = 662.38                    Prob > chi2 = 0.0000
```