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Do anti-epileptic drugs, regardless of the treatment indication, predict an increased risk in the incidence of falls and fractures?

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Do anti-epileptic drugs, regardless of the treatment indication, predict an increased risk in the incidence of falls and fractures?

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A dissertation submitted in partial fulfilment of the requirement for Masters in Healthcare Ethics and Law

Department of General Practice

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Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree, Masters Science in Healthcare Ethics and Law, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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List of abbreviations

AED	Anti-epileptic drug
AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted odds ratio
AR	Absolute risk
CI	Confidence interval
CNS	Central nervous system
DXA/DEXA	Dual Energy X-ray Absorptiometry
EPSE	Established Populations for Epidemiologic Studies of the Elderly
GABA	Gamma-aminobutyric acid
GMC	General Medical Council
GPRD	General Practice Research Database
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
ICD	International Classification of Diseases
ICU	Intensive care unit
ILAE	International League Against Epilepsy
LEI	Liver enzyme inducing
MeSH	Medical subject heading
MHA	Mental Health Act
MHRA	Medicines Healthcare and Regulatory Agency
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MPS	Medical Protection Society
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
PTH	Parathyroid hormone
RR	Relative risk
SIGN	Scottish Intercollegiate Guidelines Network

SUDEP	Sudden Death in Epilepsy
UCD	University College Dublin
USA	United States of America
WHO	World Health Organisation

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Abstract

Anti-epileptic medications (AEDs) are an important group of medications and their use is increasing for treatment of not alone epilepsy but for their indications for mental illness such as bipolar affective disorder and schizoaffective disorder. There has been concern since the 1960s that these medications impacted on bone health and this was initially studied in people with epilepsy. This study was carried out to examine the totality of evidence from primary studies about fracture risk and falls risk in people using AEDs, regardless of the indication for use. This study consists of a systematic review of prospective cohort studies examining fracture and falls in adults using AEDs, regardless of indication. Eleven studies were selected for inclusion, seven from the United States, two from the Netherlands and one each from Finland and the United Kingdom. The results of the included studies were analysed and assessed from the standpoint of methodological quality. The studies were compared across their main outcomes of interest; risk of fracture and risk of fall. It was found that there was an increased risk of fracture with AED use and three of the five studies looking at falls found the risk to be increased. Initial and repeat prescriptions for AED treatment (with its risks of side effects) require the same attention to the four principles of bioethics as all medical care should receive. This process should be structured, aided and, if necessary informed, by regulatory and legal percept which have been developed over years of interaction between the legal system and complex healthcare matters.

Chapter 1: Introduction

1.1 Context

I am a psychiatrist by profession, and treat illnesses including schizophrenia, bipolar affective disorder, schizoaffective disorder and recurrent depressive and anxiety disorders. I have also worked in the learning disability services where many of my patients had epilepsy and attended neurology clinics to try to achieve optimum seizure control. I also attended a joint clinic run by the neurology physician, in collaboration with the learning disability service physician and psychiatrist.

When I went to the neurology clinic I observed the doctors prescribing “bone protection” for the patients who were on long term anti-epileptic drug treatment, e.g. sodium valproate. I was surprised as patients could be treated with the same medication, sodium valproate, for mood stabilisation, and I had not seen this practice in mental health clinics I have attended. This piqued my interest in this area of study.

1.2 Purpose

I want to look at whether the use of anticonvulsant medication, which can be used for seizure control, mood stabilisation and headache, predicts fracture or falls. I want to look at this relationship regardless of the reason for using the medication. I will do this by carrying out a systematic review and meta-analysis of the available literature as this type of study design serves to examine the totality of evidence with respect to the impact of an exposure (medication use) on outcomes of interest (fracture or falls). I want to look specifically at cohort studies where the exposure is identified prior to identifying the outcome. For this reason, they are associated with less risk of bias than case-control and cross sectional studies. These types of study designs will be considered in greater detail in the methods section (Chapter 2) of the thesis. I will then synthesize the information available from suitable studies as this will allow me to answer the question:

“Do anti-epileptic drugs, regardless of the treatment indication, predict an increased risk in the incidence of falls and fractures?”

To ensure clarity of the research question, the population (P), exposure (E) and outcome (O) have been clearly defined as follows:

Population – adults over 18 years of age

Exposure – anti-epileptic medication

Outcome – Falls and/or fracture.

Secondly I want to look at the ethical issues around prescribing medications with potentially serious long term side effects, insidious as the progression of same may be. I want to examine this issue with reference to when such treatments are initially instituted when a patient is very unwell, and their judgement impaired.

Thirdly I want to look at the regulatory advice for doctors who find themselves in the role of “repeat prescriber” of these kinds of medications over many years, particularly given that this job very often falls to the junior medical staff.

Lastly I want to make a recommendation, following thorough study, regarding whether local or national policy/guidelines should be instituted in this regard.

1.3 Background

1.3.1. Epilepsy

1.3.1.1. What is epilepsy?

In simple terms, epilepsy is the tendency to have seizures. However, a more precise definition of epilepsy has been developed in recent years by experts in the field of neurology. The International League Against Epilepsy (ILAE) produced an official report in 2014 following recommendations of a task force (1). This changed the previous working definition that had been in use since 2005. This had regarded someone as having epilepsy if they had experienced two unprovoked seizures more than 24 hours

apart (1). The revised definition states that the patient should be diagnosed with epilepsy, a disease of the brain, if they meet any of the following conditions:

“(i) At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;

(ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;

(iii) diagnosis of an epilepsy syndrome (1).”

The ILAE, founded in 1909, has more than 100 national chapters, including one in Ireland. Each national chapter has elected officers and members who are doctors and other health care professionals interested in epilepsy (2). They have formal links with the World Health Organisation for the Global Campaign Against Epilepsy (2). Their stated aims are “to advance and disseminate knowledge about epilepsy, to promote research, education and training, and to improve services and care for patients, especially by prevention, diagnosis and treatment” (2). Whereas previously epilepsy was considered a “disorder” or a “condition”, the ILAE and the International Bureau for Epilepsy have agreed it should be considered a disease (1). It was felt this better reflected the serious nature of epilepsy.

A seizure occurs when a large number of the cells send out an electrical charge at the same time (3). This abnormal and intense wave of electricity overwhelms the brain and results in a seizure, which can cause muscle spasms, a loss of consciousness, strange behaviour, changes in emotions and changes in body functions, such as blood pressure and heart rate (4). Because the abnormal electrical activity can arise in any part of the brain a seizure can affect any of the functions we know the brain has. Seizures vary in frequency, with some people having less than one per year and others experiencing several per day (3). They also vary considerably in duration, from very brief absences to prolonged convulsions (3).

1.3.1.2 What causes epilepsy?

The cause of epilepsy is regarded as multifactorial, that is, a number of factors may be at play, interacting to increase the risk. It is thought that between 10 and 30% of cases of epilepsy are due to genetic illness (3). Furthermore, any illness or disease process that affects the grey matter in the brain can cause epilepsy (3). For example, between 5 and 10% of newly diagnosed epilepsy is caused by brain tumours. The most common acquired causes of epilepsy are vascular, post infection or post trauma (3). In around 30% of cases no cause is identified (3).

1.3.1.3 Prevalence of epilepsy

The prevalence of a disease is defined as the number of cases of a disease existing in a given population (5). According to the World Health Organisation approximately 50 million people currently live with epilepsy worldwide with an estimated prevalence of between 4 and 10 cases per 1000 population (6). This number is higher in lower income countries, at between 7 and 14 cases per 1000 people. In 2009 a study was commissioned by 'Brainwave The Irish Epilepsy Association' to examine the prevalence of epilepsy in Ireland. This was conducted by the University College Dublin Centre for Disability Studies and the study was published in *Epilepsia*, the official journal of the ILAE (7). This study used self-report data, ant-epileptic drug prescription data, primary care data, specialist care data and inpatient data in Ireland (7). The findings showed a national lifetime prevalence of self-reported epilepsy among adults of 10 per 1,000 population. They also found that there was a national prevalence of treated epilepsy in Ireland of 8.3 per 1,000 (2002) rising to 9 per 1,000 (2005) for those over the age of 5 years (7).

Incidence is the rate of new (or newly diagnosed) cases of the disease. It is generally reported as the number of new cases occurring within a period of time, usually reported per year (5). The Irish study quoted above did not report any data on incidence of epilepsy in Ireland (7). However, the World Health Organisation report that annually between 30 and 50 per 100 000 people in the general population are diagnosed with epilepsy (6).

1.3.1.4 Morbidity and mortality associated with epilepsy

Seizures cause physical and emotional distress, missed days at work and school and limitations on some activities, such as driving and swimming (3). Along with the morbidity associated with seizures, there is also a risk of sudden death (3). This is called Sudden Death in Epilepsy (SUDEP). It is defined as "sudden unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in an individual with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus where post-mortem examination does not reveal a cause for death" (8). There are approximately 130 epilepsy related deaths every year in Ireland with epilepsy being one of the top ten causes of death in young people (early or premature deaths) (9). There is a higher risk of SUDEP in poorly controlled epilepsy.

1.3.1.5 Prognosis with epilepsy

Around 60% of the people who are diagnosed with epilepsy stop having seizures within five of years of being diagnosed, following the introduction of anti-epilepsy treatment (3). In 20% of people diagnosed with epilepsy they have periods of remission and periods of relapse (3). For a further 20% of people diagnosed with epilepsy remission is never achieved (3). Risk factors for poorer prognosis include diagnosis of intellectual disability, multiple seizure types and having clusters of seizures (3).

1.3.1.6 Treatment for epilepsy

The mainstay of treatment is with anti-epileptic medication, or anti-epileptic drugs (commonly, and hereafter in this thesis, referred to as AEDs). A balance must be sought between the benefits and drawbacks of treatment. Approximately 70% of people stop having seizures at some point after introducing treatment (3). These types of antiepileptic medication do not stop a seizure once it has started and they are not viewed as cures for epilepsy, nor are they cures for the cause of epilepsy (3). The goal of treatment is to try to prevent a seizure occurring.

The medications used to treat epilepsy vary in the way they act on the brain and their side effect profiles. Examples of medications used include Acetazolamide, Carbamazepine, Clobazam, Clonazepam, Ethosuximide, Felbamate, Gabapentin, Lamotrigine, Levetiracetam, Lorazepam, Phenobarbital, Phenytoin, Pregabalin, Oxcarbazepine, Rufinamide, Tiagabine, Topiramate, Valproate, Vigabatrin, Zonisamide (3). Some of these medications are benzodiazepine medications, clobazam, lorazepam, clonazepam.

As stated above there are a number of mechanisms of action of the AEDs. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter; that is, it blocks transmission between nerve cells in the brain. Some of the AEDs work by increasing the activity of GABA including clonazepam, clobazam, phenobarbital, and tiagabine (3). Sodium valproate is thought to work by increasing the activity of GABA but also affects potassium and sodium conduction (3). Nerve cells are excitable cells and sodium channels play a role in transmission of action potentials. Some of the AEDs act on neuronal sodium channels: carbamazepine, lamotrigine, phenytoin (3). Other medications act on calcium channels, glutamate (an excitatory neurotransmitter) and enzyme activity (3). The exact mechanism of action of all of the AEDs is not fully understood (3).

The issue of when epilepsy is deemed inactive or to have resolved was also the subject of the ILAE report in 2014. The report identified that “Epilepsy is considered to be resolved for individuals who either had an age dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off anti-seizure medicines for at least the last 5 years” (1). “Resolved” is not necessarily identical to the conventional view of “remission or “cure” but it was hoped that formulating a view on this issue would reduce the burden and stigma of having epilepsy (1, 10).

In addition to treatment to try to prevent seizures some patients are prescribed ‘rescue medication’ which is designed to be used to try to stop a seizure that has already started. The National Institute for Health and Care Excellence (NICE) provides national guidance regarding health and social care in England. NICE is a non-departmental public body established under primary legislation and based in London

(10). Its summaries and guidance are often referenced by doctors in other countries, including Ireland. Regarding rescue treatment for epilepsy their guidance is as follows: “Only prescribe buccal midazolam or rectal diazepam for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures”(11).

If epilepsy is not responsive to medication after five years of treatment, during which time a number of medications are trialled, epilepsy surgery may be considered (3). This can take the form of lobectomy, or vagal nerve stimulator placement (3). These surgeries are designed to remove the part of the brain causing the seizures (e.g. in the case of lobectomy for tumour or hippocampal sclerosis) or palliation of severe intractable epilepsy (in the case of vagal nerve stimulator) (3).

1.3.2 Bipolar affective disorder and Schizoaffective Disorder

1.3.2.1 What is bipolar affective disorder?

The World Health Organisation’s Tenth Edition of the International Classification of Diseases (12) is one of two diagnostic manuals used in Ireland. It uses the following definition for bipolar affective disorder. “Bipolar affective disorder is a disorder characterized by two or more episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (hypomania or mania) and on others of a lowering of mood and decreased energy and activity (depression)” (12). Some manic episodes and some depressive episodes are accompanied by psychotic symptoms (12). However, people with bipolar affective disorder do not experience psychosis when their mood is stable (12).

Usually recovery is achieved between these episodes, the duration of which may vary (12). For example, an episode of mania may have an abrupt onset, with a median duration of four months (12). An episode of depression can last longer with a median length of six months (12). Bipolar affective disorder can present any time from

childhood to old age though the mean age of onset in community studies is at seventeen years of age (13).

1.3.2.2 Prevalence of bipolar affective disorder

The lifetime risk for bipolar affective disorder lies between 0.3 and 1.5% (13). The Irish mental health charity 'Aware' state on their website that "40,000 Irish people suffer with bipolar affective disorder" (14). However, they do not cite the origin of this statistic. A review looking at articles that examined prevalence data in Europe found that the majority of studies reported 12-month estimates of between 0.5-1.1%. The cumulative lifetime incidence was reviewed from two prospective-longitudinal studies was found to be between 1.5 and 2%. There was a higher lifetime incidence calculated from the studies when bipolar II disorder was included at 6% (15).

The incidence of bipolar affective disorder is reported much less often as compared to the prevalence rate due to the wide variation in data, with published studies reporting an incidence rate ranging from 2.6 to 20.0 per 100 000 per year (16).

1.3.2.3 Definition of schizoaffective disorder

As stated above, the World Health Organisation's Tenth Edition of the International Classification of Diseases (ICD 10) is one of two diagnostic manuals used in Ireland (12). Regarding schizoaffective disorder, the ICD 10 uses the following definition: "A disorder in which the individual suffers from both symptoms that qualify as schizophrenia and symptoms that qualify as a mood disorder (e.g.k depression or bipolar disorder) for a substantial portion (but not all) of the active period of the illness; for the remainder of the active period of the illness, the individual suffers from delusions or hallucinations in the absence of prominent mood symptoms" (12). When the ICD 10 refers to symptoms that qualify as schizophrenia it means symptoms of psychosis in this instance.

1.3.2.4 Prevalence of schizoaffective disorder

The prevalence of schizoaffective disorder was estimated by Perälä et al in 2007 at 0.32% of the population in Finland (17). A French review by Azorin et al estimated the prevalence at 0.5 to 0.8% (18). An earlier Irish study cites the lifetime prevalence at between 0.2 and 1.1% (19). There are limited data available regarding the incidence of schizoaffective disorder and this is likely to be due to issues regarding diagnostic stability. That is, patients may become unwell and receive a diagnosis, e.g. of depression, then later during the period of that illness develop psychosis and receive a diagnosis of schizoaffective disorder (14).

1.3.2.5 Prognosis in bipolar affective disorder and schizoaffective disorder

Bipolar affective disorder and schizoaffective disorder is associated with high levels of morbidity due to episodes of illness, and also mortality. The rate of completed suicide in these groups is approximately 10% (20). Some patients do not respond to the initial treatment and require trials of alternative medication or to take a number of different medications together. There is evidence for poorer overall physical health in these patient groups, with higher mortality from physical health problems than in the general population (21). Hoang et al compared mortality ratios in a cohort with psychiatric illness and a cohort from the general population following general hospital admission. The study demonstrated that the mortality gap widened over time, and for bipolar disorder, the ratio was 1.9 (1.6 to 2.2) (21). Ratios were higher for unnatural than for natural causes but three quarters of all deaths were certified as natural. Increases in ratios for natural causes, especially circulatory disease and respiratory diseases, were the main components of the increase in all-cause mortality (21).

1.3.2.6 Treatments for bipolar affective disorder and schizoaffective disorder

The treatment for mental illness, including bipolar and schizoaffective disorder, takes the form of medication and psychotherapy and also social support. Psychotherapy is less studied in bipolar affective disorder than in depression that occurs alone (called

unipolar depression) but psychoeducation regarding relapse prevention has been shown to reduce the rate of relapse (13). Some psychotherapy options have been studied in psychosis also including cognitive behaviour therapy for persistent hallucinations or delusions and cognitive remediation (13).

The mainstay of treatment for bipolar affective disorder is pharmacological treatment with a mood stabiliser medication (13). The medications used for this are lithium, sodium valproate, carbamazepine and lamotrigine. Sometimes newer antipsychotic medications are also used with the purpose of stabilising mood (13). However there have been concerns around the long term safety of this approach due to fears regarding development of metabolic syndrome, resulting in higher risk of diabetes, obesity and elevated cholesterol (22). In schizoaffective disorder antipsychotic medications are often used to control the psychotic symptoms of the illness. Even when this is the case mood stabiliser medication is usually required to treat the mood disorder component (13). The mood stabilisers used are the same as the ones used in bipolar affective disorder.

Three of the mood stabiliser medications are also used as anticonvulsant medication. These are sodium valproate, carbamazepine and lamotrigine (13).

1.3.3 Prescribing of anti-epileptic medication:

The group of medications referred to in the epilepsy section are called anticonvulsant or antiepileptic medications. This is correct terminology. However, it is also correct to refer to the three medications mentioned in the above paragraph, used in mood disorders, as mood stabilisers. For the purpose of this thesis I will refer to the group of medications as antiepileptic medication. This term, and its abbreviation 'AED', was the most often used in the literature I reviewed. However, this is not intended to infer the indication for use. The uses, as outlined above, include epilepsy, bipolar affective disorder, and schizoaffective disorder. However, this group of medications is also used to treat chronic pain, nerve pain and headache (23).

In the report carried out by the UCD School of Disability Studies, anti-epilepsy drug data were used to help to calculate the prevalence of epilepsy (7). However, the figure was adjusted to reflect the possibility that the drug was being used for another indication. The original data were not included in the study (7). The prevalence data calculated from the figures they used was for treated epilepsy, therefore the prevalence data from this section of the study reflects the prevalence of prescribing of any one of 15 anti-epileptic medications, once adjustments were made. This showed a prevalence of prescribing, post adjustment, of 8.3 per 1,000 people in Ireland in 2002 to 9.0 per 1,000 people in 2005 (7).

1.3.3.1 Prevalence of prescribing of anticonvulsant/anti-epileptic medication

It is helpful then to get an idea of how many people are prescribed these medications, regardless of their indications. In 2014, De Groot et al published their review of AED prescribing calculated from national drug databases in Spain, Denmark, Germany, and two each from the Netherlands and the United Kingdom (24). The prevalence of prescribing of any AED varied from 88 per 10,000 persons (The Netherlands) to 144 per 10,000 in Spain and Denmark in 2001 (24). In all of the databases reviewed, prevalence of prescribing increased year on year during the period of assessment from 2001 to 2010. The increase seen was between 6% in Denmark and 15% in Spain (24). The authors felt that this increase over time was unlikely to reflect an increase in the diagnosis of epilepsy and more likely to reflect the increasing number of newer AEDs, many of whom have indications for use other than epilepsy. This was deemed to be the case as in a recent meta-analysis prevalence of long term epilepsy in developed countries was found to be 5.8 with a figure of 4.9 for active epilepsy (25).

1.3.4 Bone mineral density, osteoporosis and fractures

Bones make up the human skeleton and have been referred to as our scaffolding. Bone has a complex array of functions and sometimes problems can arise, such as osteopenia, osteoporosis and fractures.

1.3.4.1 Bone

Bone is made of crystals of mineral bound to protein (26). This gives the bone strength and resilience so that the skeleton can absorb impact without breaking (26). These minerals and collagen comprise two types of bone material; compact bone and spongy bone. Compact bone is the outer portion of each bone which looks like a solid mass; cancellous (spongy) bone refers to a network of columns called trabeculae whose aim is to reduce stress and pressure on the bone (26). The outer layer of cancellous bone is composed of compact bone. Bones without an interior mass of cancellous bone have a medullary cavity instead (26). The shaft of the long bones (such as the humerus of the arm or the femur of the thigh) are hollow (27). This space is filled with adipose tissue and/or red marrow, which forms blood cells (27). The medullary cavity is lined with endosteum, a thin layer of connective tissue. At birth, the marrow of all bones created blood cells. In adulthood, blood cells are only produced in the bones of the skull, thoracic cage, spinal column, pelvic and shoulder girdles, and heads of the humerus and femur (27). The hip joint is where the femur inserts into the pelvis in a ball and socket joint.

1.3.4.2 Our changing bones

The mineral part of the bone contains calcium and phosphorus and this is bound to collagen (26). Bone reaches its peak density in humans in our early twenties but remodelling continues throughout life. Bones are modelled and remodelled, or changed, in response to many stimuli. These include the physical stress on the bone, damage to the bone, or need for minerals stored in bone that arise elsewhere in the body (26).

One of the things bone architecture responds to is mechanical force, or lack thereof. Therefore, bones reduce in density when someone does not bear weight on them- an extreme example of this occurs in space when the astronauts are in a weightless environment for an extended period of time (26). The outer cortical bone of a person's dominant arm is seen to be denser in response to greater demand or stress placed upon it (26).

Phosphorous and calcium are necessary for other parts of the body to function and survive, including nerves and muscle, such as the heart (26). We need the right amount of calcium in our cells for them to work adequately (26). Bone must be responsive to changes in mechanical loading or weight bearing, both of which require strong bones that have ample supplies of calcium and phosphorus, as outlined above (26). Also, when calcium and phosphorus are scarce, regulating hormones take them out of the bone and divert them to where they are needed. If too much is removed from the bone, it can become weak and at risk of fracture (26). Osteoblasts are the cells that lay down new bone. Osteoclasts are the cells responsible for breaking down bone by dissolving it, which is called resorption (26).

The systems that govern this remodelling of bone are dependent on signalling. This signalling is largely conducted by a system of hormones that aims to keep the levels of calcium in our cells at an optimum level. The main hormones involved are calcium regulating hormones: parathyroid hormone, calcitriol (active vitamin D) and calcitonin; sex hormones: oestrogen and testosterone; and other systemic hormones: growth hormone (Insulin-Like Growth Factor), thyroid hormone and cortisol (sometimes referred to as the “stress hormone”) (26).

Parathyroid hormone (PTH) is produced by the four parathyroid glands, which are located near the thyroid gland, in a person’s neck. The PTH acts on both bone and kidney, telling these organs how much calcium they should hold on to. If the body’s level of calcium is low the parathyroid gland will generate more PTH (26). PTH also manages how much calcium a person absorbs from their gastrointestinal tract, by stimulation of the active hormone generated from vitamin D (calcitriol), which acts on the intestines. Too much PTH can result in bone loss (26). Calcitonin promotes the action of osteoblasts in generating bone and inhibits the action of osteoclasts in breaking down bone.

The sex hormones are also important in maintaining bone. Oestrogen acts on both osteoclasts and osteoblasts to stop bone breakdown throughout life. The marked decrease in oestrogen at menopause is associated with rapid bone loss (26). The high levels of sex hormones at puberty have a role in growth and strengthening of long bones (25). Testosterone stimulates muscle which promotes bone growth.

Testosterone is also converted to oestrogen and this has the same effects on bone in men as it does in women (26). This is one of the reasons why age and gender are important factors in risk of fractures and why many of the studies included later control for these. Sex hormones can get disrupted in severe weight loss, such as anorexia nervosa, and this can increase the risk of osteoporosis.

Growth hormone is produced by the pituitary gland and promotes skeletal bone growth. Thyroid hormones control the energy and activity level of cells in the body including those in bone (26). Cortisol is necessary for normal bone development, but in larger quantities it can inhibit bone growth (26). Synthetic forms of cortisol, called glucocorticoids, are used to treat many diseases such as asthma and arthritis. They can cause bone loss due both to decreased bone formation and to increased bone breakdown, both of which lead to a high risk of fracture (28). For this reason, these drugs are referred to in many of the studies referred to later in the thesis.

1.3.4.3 Problems for our bones: Focus on Osteoporosis

Deficiencies in calcium, vitamin D and phosphorus can result in reduced bone strength. Genetic disorders and hormonal disorders involving the hormones described above can also result in bone ill-health.

Osteoporosis is defined as “a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture” (29). Bone strength refers not just to the amount of bone present, also called density, but also to the quality thereof (29). Therefore, in osteoporosis, bones become gradually weaker. Sometimes young people have reduced bone strength due to genetic disorders or because of poor nutrition (e.g. low calcium and vitamin D levels) and lifestyle (e.g. little/no weight bearing activity). However, most fractures of bone in young people are due to significant force of the injury (26). Then, later in life, bone loss begins due to bone breakdown, which picks up speed after menopause in women (26). In general, bone formation decreases with age in men and women, and bone resorption continues. Therefore, an imbalance between bone resorption and bone formation results in loss of bone mass, leading to fragile bones (26). An osteoporotic fracture is “a fracture that

occurs with very little trauma or force and from a standing position, that is usually not great enough to cause broken bones, usually indicating that the bone is weak” (30).

Sometimes osteoporosis is only detected when someone suffers a fracture from a non-traumatic event. Osteopenia is the early stage of Osteoporosis and once someone has osteopenia they are at high risk of developing Osteoporosis (30). Osteoporosis and osteopenia are diagnosed using a bone density scan of the spine and hips called a Dual Energy X-ray Absorptiometry (DXA /DEXA) scan (30). It is used to measure the density (thickness) of bones which is used as a proxy to estimate the strength of the bone.

1.3.4.4 Prevalence of osteoporosis and osteoporotic fractures

Johnell and Kanis carried out a systematic review and meta-analysis of fractures which was published in Osteoporosis International in 2006 (31). They concluded that, in the year 2000, there were an estimated 9.0 million osteoporotic fractures of which 1.6 million were at the hip, 1.7 million at the forearm and 1.4 million were clinical vertebral fractures (31). They found that the greatest number of osteoporotic fractures occurred in Europe (34.8%) (31). They also found that, world-wide, osteoporotic fractures accounted for 0.83% of the global burden of non-communicable disease, and for 1.75% of the global burden of non-communicable disease in Europe (31). The National Institute of Health in the United State estimates that 10 million people there have osteoporosis (26). In Europe, it is estimated that 30% of people aged 65 years and over fall each year and that approximately 10% of these result in fractures and that 20% require medical care (32).

The rates of fracture for the total population of Ireland were assessed by a population based study published in 2009 in Osteoporosis International. The authors reported the rates of fracture, in those aged 50 years and over, were 407 and 140 per 100,000 for females and males, respectively (33). They also projected this would increase by 100% by the year 2026, assuming stable incidence rate (33).

1.4 What do we know about the link between medications for epilepsy and bipolar affective disorder and bone health?

For many decades, clinicians and researchers have been concerned about a link between AEDs and bone health (34, 35). Many of the early studies focussed only on people with severe epilepsy and very often these studies were carried out on people in institutions. This was without consideration of possible confounding factors such as lack of weight-bearing activity, poor nutritional intake or medical ill-health (36).

Epilepsy itself has been shown to deliver an increased risk of fracture, about double that of people without epilepsy (37). Therefore, methodologically sound, longitudinal studies were required to try to clarify the extent to which seizures and injuries therefrom, side effects from medication and other issues were contributing. There then ensued a number of studies showing individuals treated with liver enzyme inducing AEDs had lower bone mineral density than those treated with non-liver enzyme inducing AEDs, which were latterly synthesised into a meta-analysis published by Fraser et al in 2015 (38). This study looked only at people treated with AEDs due to epilepsy. The mechanism of action for this effect relates to increased metabolism of vitamin D in the liver as a result of the liver enzyme inducing medication which then has a knock-on effect on PTH (39).

In addition to studies about LEI versus non-LEI AEDs there followed a number of studies showing both types of AEDs were associated with increased risk, though many of these were retrospective studies or case-control studies (40, 41). Shen et al, 2014, published a systematic review of studies looking at individuals treated with all types of and demonstrated an increased risk of fracture associated with AEDs (42). While this paper examined the risk of fractures in detail it did not review the risk of falls associated with AEDs. Also the evidence included in this systematic review included retrospective studies and case control studies. Of note the Shen paper synthesised evidence relating to use of AEDs regardless of whether the participants had a diagnosis of seizure disorder.

1.5 Where is the gap?

There is no research I have identified which examines the totality of evidence with respect to the impact of an exposure (AED medication use) on the outcomes of interest (fracture or falls).

There are national guidelines in other countries (including the NHS in the UK) regarding the use of these medications in treatment of epilepsy (43). These give recommendations about advice for patients and prescription of bone protection. The National Institute for Clinical Excellence (NICE) clinical guideline for management of epilepsy recommends monitoring vitamin D levels and other measures of bone health and bone metabolism, including serum calcium and alkaline phosphatase every 2-5 years for all patients taking enzyme inducing drugs (43). The same set of guidelines for management of bipolar affective disorder do not mention the risk of bone loss or fracture, nor do they make any recommendations regarding prevention of same (44).

Therefore, this review of the totality of evidence available pertaining to all users of these medications is important. The results of the review have important ethical and legal implications which will be considered in the discussion section of the thesis.

1.6 Dissertation outline

Chapter 2 of the thesis will outline the methodology used for the systematic review of cohort studies included therein. The exact nature of both systematic review and a cohort study will be explained in detail. The standardised guidelines adhered to and the reasons for same will also be explained. The strategy used to identify all relevant studies will be outlined and the methods whereby relevant studies were selected will be explained. The MeSH terms used will be included in this chapter. Methods of assessment of methodological quality of the studies will also be made clear.

Chapter 3 will identify how the studies were selected initially, including a flow chart demonstrating same. There will be a description of each of the studies relating to AED use and fractures only. There will be a description of each of the studies relating to AED use and falls only and there will then follow a description of the studies that

looked AED use and both falls and fractures. A table will represent the main findings of each study. The impact on fracture risk, falls risk and the confounders included in the study will be discussed, as well as the population studied.

Chapter 4 will include a discussion of the findings of the studies included in the systematic review. The ethical issues relating to prescribing medications with potentially serious long term side effects will be reviewed. The discussion will be structured using the four principles of biomedical ethics: autonomy, beneficence, non-maleficence and justice.

The legal implications of the results for clinicians and patients will be discussed. The author will examine in particular the role of “repeat prescriber” of medications, noting that this job very often falls to junior medical staff. Here the focus will be on Duty of Care of Healthcare Professionals.

Chapter 5 will comprise a summary of the key components in the thesis. The potential policy implications of the results of the review will be outlined in the context of the ethical and legal implications outlined in the previous chapter. The strengths and weaknesses thereof will be highlighted and areas for further research suggested.

Chapter 2: Methodology

2.1 Introduction

The overall aim of this chapter is to detail the methods used for this systematic review of cohort studies. The rationale for completing a systematic review is discussed along with a justification for including studies with a cohort design only. The search strategy will detail the efforts made to identify all relevant studies that focus on exposure to anti-epileptic medication (AEDs) and on the occurrence of falls and fractures as the outcome. The inclusion and exclusion criteria for study selection and data extraction will be described followed by a description of the how the methodological quality of the studies was assessed. The purpose of this section is to enhance the transparency and reproducibility of the methods, in accordance with the relevant standardised reporting guidelines.

2.2 Study Design

The study consists of a systematic review of cohort studies. There may be many studies conducted all over the world looking at similar issues and a systematic review is a method of combining that knowledge and information in a thorough and appropriate way, making it more useful for clinicians. A review is a re-examination of findings but its remit is not clearly defined. A review is a systematic review when it uses a consistent approach to identify all potentially relevant studies that address a particular research question. The research question itself must be clearly formulated; i.e. it must relate to a specific population, the exposure must be clearly identified, and the outcome of interest must be clearly stated. The kind of study design best suited to the research question must be examined. In the case of this study the outcome of interest is fractures and falls. As this is an adverse outcome that can take some time to occur, large observational studies are the most suited to capture this event.

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE) (45). The reason for doing so is to ensure the research was conducted and reported in a standardised fashion.

Stroup et al proposed this system of reported systematic reviews and meta-analyses. A steering committee of 27 members studied practice at that time in systematic reviews and generated a checklist for future practice. Their work was funded by the Centre for Disease Control and Prevention in the United States. Their paper states: “use of the checklist should improve the usefulness of meta-analyses for authors, reviewers, editors, readers, and decision makers”. The over-arching goal is to allow informed timely clinical decisions be made using a synthesis of the research available This is possible due to improved transparency and reproducibility of reviews of cohort studies (45).

2.3 Cohort Study

A cohort study is one of a number of observational studies. This means that participants are exposed to something (e.g. medication or risk factor) and observed for an outcome (e.g. adverse event or disease) as they are followed up over time. An exposed population is usually compared to an unexposed population to allow calculation of the risk of the outcome occurring. The exposure is not assigned by the researcher, as in a randomised trial, but observed as having happened due to prescribed treatment in the case of AED use as the exposure. At the end of a period of time, the number of times the outcome occurred in each group is calculated. These figures are then compared with one another. Cohort studies have higher external validity than randomised controlled trials, and therefore the research is deemed to be more applicable to the general population.

Some the outcomes of interest in cohort studies can take a long time to develop, e.g. disease, and so the duration of follow up is often lengthy. This gives rise to risks of bias if a large number of the population have been lost to follow up. It is imperative to the quality of the study that the researchers are cognisant of the risk of bias, including the contribution of confounders. This is assessed for when looking at the quality of the studies included and will be further discussed in the quality assessment paragraph of this chapter. A confounder is an exposure that is not the exposure of interest. It is associated with the outcome of interest, and could potentially cause/prevent same.

Therefore, a false association could be assumed to arise from the exposure of interest if this exposure is not assessed managed within the study. With respect to the outcome of interest in this systematic review, the potential confounders are the known causes and risk factors in the development of osteoporosis and fractures. As there are many of these, some of the studies will have selected different confounders for which they will control. The summary table of the included studies will list the confounders used by each study.

The question to be addressed by this thesis is “Do anti-epileptic drugs, regardless of the treatment indication, predict an increased risk in the incidence of falls and fractures?” This is best answered by cohort studies as they are at reduced risk of bias as compared to case control and cross sectional studies. Only prospective cohort studies will be included. In a prospective cohort study the exposure is identified and measured and the population is then followed up, thereby further reducing the risk of bias.

2.4 Search Strategy

The systematic review aimed to identify all studies that examined the impact of using AEDs on incidence of falls and fractures. Screening of Pubmed, ISI Web of Science, the Cochrane Library, EMBASE and PSYCHInfo was completed for the period June 1967 to June 2016. This was carried out in March 2016. In June 2016 the saved searches were reviewed for emergence of any new relevant studies. No restrictions were applied with respect to age, gender, or language. The search terms were “anticonvulsants”, “carbamazepine”, valproic acid”, phenobarbitone”, “phenytoin”, “lamotrigine”, “topiramate”, “gabapentin”, “leviteracetam”, and “fracture”, “fall”, “bone density”, “osteoporosis” and “osteopenia”. To identify as many articles as possible the PSYCHInfo database was included to try to reflect psychiatric use of AEDs also. The list of search terms can be viewed in appendix 1. The search was supplemented by hand-searching references of retrieved articles and searching Google Scholar. The databases were searched using both free text and MeSH terms to reflect the most recent additions to their libraries. In EMBASE the ‘explosion’ feature was used to optimise the

results obtained. The search was reviewed by a research librarian in Royal College of Surgeons, Dublin.

2.5 Study Selection and Data Extraction

Studies were included if they were prospective cohort studies or randomised controlled trials that looked at the relationship between AED use and fractures and falls. They comprised original data from epidemiological studies. The exposure of interest was treatment with AEDs, regardless of the reason. There were two outcomes of interest; fractures and falls. Studies were included if risk estimates were provided with adjustments for potential confounders.

The author read the titles and/or abstracts of the identified references and eliminated irrelevant studies. Studies that were considered eligible for inclusion were read fully in duplicate and their suitability for inclusion was determined by the author. The supervisor acted as a second independent reviewer in cases where there was uncertainty around inclusion/exclusion of studies. Disagreements were managed by consensus.

The studies were examined and all essential information was extracted using a standardised form. The following data were collected from each study: author, year, country of research team, study design, population, sex, age, follow-up year, outcome and exposure definition, effect estimates with 95% confidence intervals and variables adjusted for. Appendix 2 contains a template of the data extraction form.

2.6 Quality Assessment

The quality of the studies was assessed by using the Newcastle-Ottawa Scale (NOS) criteria. The Newcastle-Ottawa scale was developed during collaboration between the Universities of Newcastle, Australia and Ottawa, Canada. It was developed to assess the quality of nonrandomised studies. A 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome

of interest for case-control or cohort studies respectively (46). For cohort studies the NOS criteria were: (i) representativeness of the exposed cohort; (ii) selection of the non-exposed cohort; (iii) ascertainment of exposure; (iv) demonstration that the outcome of interest was not present at the start of the study; (v) adjustments and matching; (vi) assessment of outcome; (vii) long term follow up and (viii) response rate. Each item was scored from 0 to 1 except (v) which has a maximum score of 2. The studies scoring higher than 7 were deemed to be high quality studies. Studies scoring between 4 and 6 on the scale were assessed as being of 'moderate quality', and 0-3 as being of 'poor quality'.

2.7 Narrative synthesis

In Chapter 3 the results of each included study will be summarised. The results will be described in terms of the outcome measures used in each study. Studies may describe the risk of the outcome of interest occurring using absolute risk, relative risk, odds ratio and hazard ratio.

Absolute risk (AR) is the rate of occurrence of an event in a group, e.g. 10% of the people who were exposed to the risk factor got the illness. Relative risk (RR) is the size of effect of an intervention of interest relative to the size of effect of a comparison intervention (which might be no intervention/exposure). If 10% of the unexposed cohort have the outcome and 5% of the exposed cohort have the outcome, then the RR is $10/5 = 2$.

Odds ratio (OR) expresses the odds of having an event compared with not having an event in two different groups (likely to be an exposed and unexposed group).

Therefore, in the example used above the risk in the exposed group is 10/90 and the risk in the unexposed group is 5/95. Then the OR is calculated as follows:

$(10/90)/(5/95) = 2.11$. The adjusted odds ratio (AOR) is the OR adjusted for confounders, as stated in each individual paper. An AOR >1 demonstrates increased risk of fracture or fall in those exposed to AEDs. An AOR of <1 would demonstrate that the exposure is protective with regard the outcome (47). This is a better estimate of the true effect of the exposure on the outcome in most instances.

The hazard ratio (HR) in a study is also called the weighted risk ratio and this looks at risk but takes into account survival to that point in the study, i.e. it takes account of time (3). It is an estimate of risk at any given time and is a ratio of the estimate of risk in one arm of the study as compared with the estimate in the other arm, at that time. Both odds ratios and risk ratios are cumulative risk ratios whereas hazard ratios are not (47).

As the outcome of interest in this research question is dichotomous – i.e. fall/no fall or fracture/no fracture, the relative risk or odds ratio can be pooled if there are sufficient good quality studies using these measures. Confidence intervals (CI) of 95% are used to estimate how precise the number shown in the risk ratio is. The studies, regardless of how large, are not reflecting absolutely everyone everywhere. Therefore, confidence intervals are used to tell us that there is a 95% chance that the true population value lies between the two numbers reported (47).

2.8 Summary

This chapter described the method used to identify and select relevant studies for the systematic review. The nature of the studies we will be encountering have been described and the statistical terms we will encounter in the results chapter of the thesis have also been explained. The next chapter will describe the results of this systematic review.

Chapter 3: Results

3.1 Introduction

This chapter will identify and describe the studies included in detail. A flow diagram will show how the results from the original search were refined to those included in the discussion below. The summary points regarding the populations studied will be outlined. A table will be used to show clearly the main points in each study. There will follow a narrative synthesis, reviewing the findings of each study. This will include a brief description of the study, the exposure and outcome definitions, the potential confounders included and the results. There will be an assessment of the quality of each study and a synthesis of the relevant findings.

3.2 Study identification

The original search string in Pubmed yielded 1750 results, and the search in the Cochrane Library yielded 179 results. There were 1059 results from the Web of Science search and 7925 results from the Embase search. PsychInfo database resulted in 104 results. This gave a total of 11019 results. When duplicates were removed there were 9720 results. These articles were screened by title and abstract and 127 full text articles were reviewed. Of the full text articles reviewed, a total of 11 were deemed eligible for inclusion. These were read fully by the author and by the supervisor and their suitability for inclusion confirmed. Of these, three were concerned only with falls, six only with fractures and two studies had both fractures and falls as two primary endpoints.

The most common reason for excluding articles was that they were not prospective cohort studies. Some of those excluded pertained to children. Some of the articles had falls and fractures as primary outcomes but only looked at benzodiazepine or Z hypnotic medication as exposures.

Figure 3.1 illustrates the flow of articles included in this systematic review.

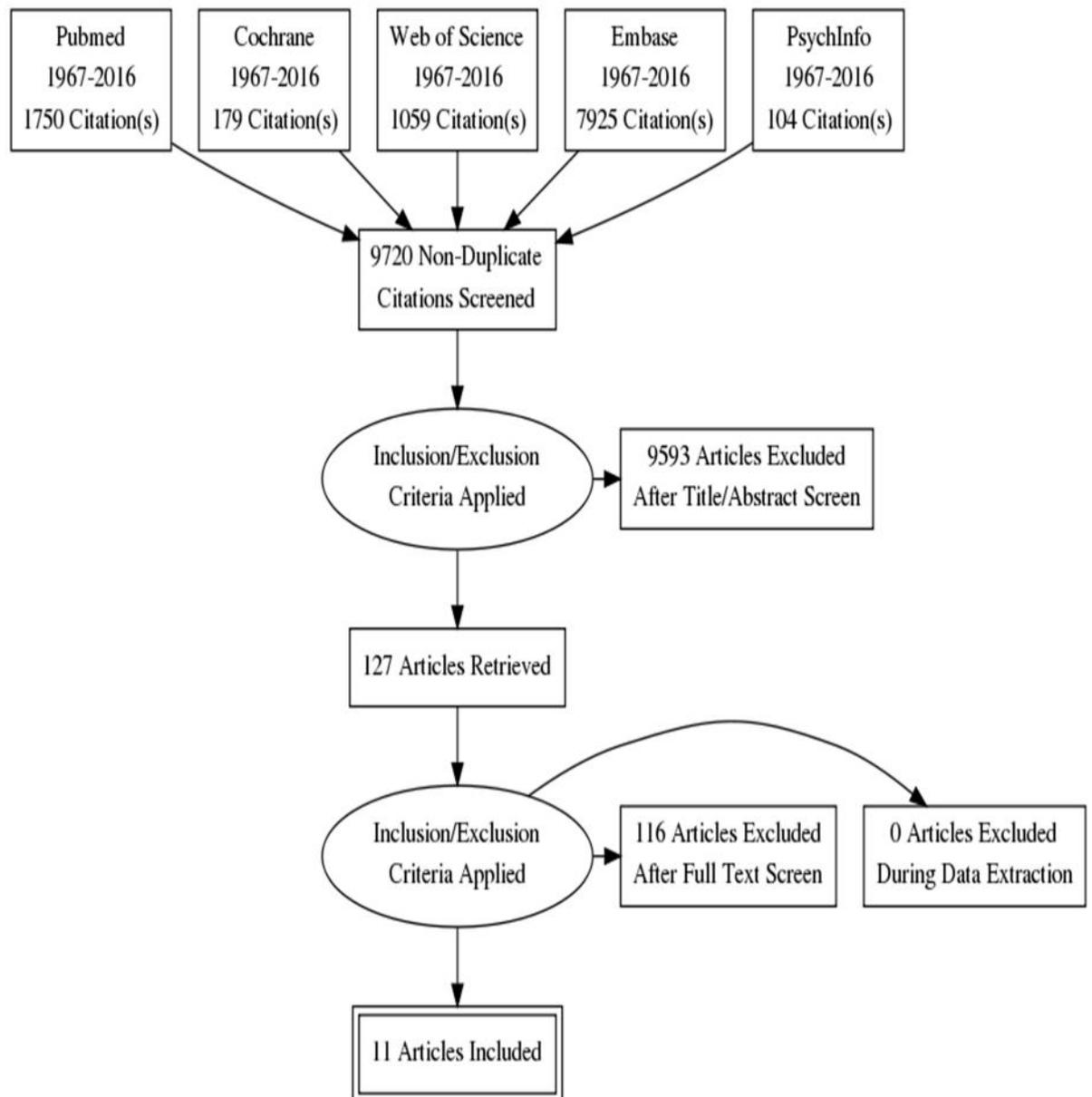


Figure 3.1- Flow Diagram of articles included in systematic review

3.3 Description of the Studies

Eleven prospective cohort studies appropriate to this systematic review were selected; Tromp et al, 1998 (48), Bohannon et al 1999 (49), Ensrud et al 2002 (50), Ensrud et al 2003 (51), Merrill et al 2005 (52), Carbone et al 2010 (53), Mezuk et al 2010 (54), Nicholas et al 2013 (55), Nurminen et al 2013 (56), Ham et al 2014 (57), Velez et al 2014 (58).

The studies selected included people from all over the world using AEDs for a variety of reasons. Of the studies with fracture as the primary outcome four studied populations in the United States of America (49, 51, 54, 58). There was one study each from the United Kingdom (55) and Finland (56). Two of the studies with falls as the primary outcome were from the United States (50, 52), with the third based on a population in the Netherlands (57). There were two studies with both falls and fractures as primary outcomes, one each from the United States (53) and the Netherlands (48). Sample sizes in the studies ranged from 51 (52) to 194,734 (58).

The included studies focused on diverse population groups. The recruitment for the studies on fractures only is set out first. Bohannon et al recruited 2590 women from the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) focussing on five counties in North Carolina, USA (49). Ensrud et al examined a cohort of 8127 women recruited for the Study of Osteoporotic Fractures, from population-based listings in Maryland, Minnesota, Oregon and Pennsylvania, USA (51). Mezuk et al recruited 67,387 (mainly male) patients receiving care through the Veteran's Health Administration, USA (54). Nicholas et al sourced a cohort of 63,259 men and women in their study from the General Practice Research Database in the UK (55). Nurminen et al used data 1283 men and women who participated in a longitudinal population based study carried out in Lieto, Finland (56). Velez et al studied 194734 people registered with a large administrative claims database PharMetrics Database, USA (58).

Ensrud et al studied 6,301 participants from the same cohort described in their fracture study above, recruited for the Study of Osteoporotic Fractures, from population-based listings in Maryland, Minnesota, Oregon and Pennsylvania, USA, for their study concerning falls and AEDs (50). Merrill et al examined a cohort of 51 inpatients in the Buffalo Psychiatric Inpatient Centre, New York, USA (52). Ham et al studied 2,407 participants from the B-PROOF study (B vitamins for the prevention of osteoporotic fractures) in which the participants were from three Dutch cities (57).

Tromp et al studied a cohort of 1449 men and women from the Longitudinal Aging Study in Amsterdam for their paper concerning predictors of falls and fractures (48). This studied people in three regions of the Netherlands over a period of 10 years.

Carbone et al, in looking at falls and fractures, examined 138,667 participants from the Women's Health Initiative, a long term national health study in the United States (53).

Regarding age and gender profile, there was also evidence of some diversity across the studies. Three of the six studies relating to fractures and AED were concerned with a cohort aged 65 and older (49, 51, 56). Two of these studies state explicitly that these were "community dwelling" (49, 51). The third study (56) states that one in 20 of the population included resided in institutions. The remaining studies pertaining to fractures included one population aged 50 and older (54) and two populations with a mean age of 47.6 years (58) and 42.2 years (55) respectively. Of these six studies two were concerned with women only (49, 51) and one with a population that was 97% male (54).

Of the studies looking at AED use and falls, two were concerned with a community dwelling cohort aged over 65 years (50, 57). The third was concerned with psychiatry inpatients with a mean age of 59 years (52). One of these studies (50) was based on an all-female population. Of the studies looking at both falls and fractures in AED users one looked at women only between the ages of 50 and 79 years (mean age 63 years) (53). The second examined a population described as "community dwelling" who were 65 and older (48). One of these two studied an all-female population (6). Table 3.1 displays the descriptive characteristics of the included studies.

3.4 Key findings of the Studies

3.4.1 Narrative Synthesis of the Included Studies

3.4.1.1 Studies concerned with risk of fracture only

Bohannon et al in the United States, 1999, set out to determine if sociodemographic, lifestyle, health and drug use factors were associated with a higher risk of incident non-vertebral fracture. 2,590 women were recruited through the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) focussing on five counties in North Carolina. This all female population included African American women are described as community dwelling, and they were followed up for six years. The

baseline assessment was an in person interview, conducted in participants' homes. It included information regarding demographics, physical functioning, presence of selected health conditions, current medication, use of health services and social support. This was in order to ascertain independent variables of interest known to be associated with increased fracture risk. Participants were also assessed for depression and cognitive impairment. There was a second in person interview after three years. Telephone interviews were conducted annually for the six years of follow up.

Regarding exposures of interest, medication use was recorded for the following: diuretics, phenytoin, prednisolone, thyroid supplements, calcium supplements and oestrogen. Of these, one is an anti-epileptic medication; phenytoin. This study included the medications above, regardless of indication for use. The primary outcome of interest was incident non-vertebral fracture. This outcome was defined as "a fracture involving the hip, arm wrist, or other site, excluding the back or spine". The mechanism of ascertaining whether the primary outcome had occurred was via self-report of a fracture during one of these interviews. Secondary outcomes were all incident non-hip, non-vertebral fractures; and subsequent fractures reported during follow up interviews (49). Potential confounders included in the Bohannon study were age, race, education, income, residence, lifestyle (including alcohol and smoking), medications (as outlined above) and condition of health.

In the results, regarding the exposure of interest, the authors did not report how many of the participants were taking phenytoin. Phenytoin was given a weighted mean value of 0.015 among the white participants and 0.006 among the black participants. The results showed that phenytoin use was associated with an increased risk of all fractures (odds ratio 3.06, CI 95% 1.11-8.48). When phenytoin use and non-hip, non-vertebral fractures were examined there was also an increased risk (OR 3.74, CI 1.42-9.84). Bohannon et al also found that phenytoin led to increased risk of a subsequent fracture (OR 3.09, CI 0.87-10.97) (49) but in the case of this finding there was a wide confidence interval which crossed the value of one. Therefore, this second finding regarding phenytoin is not significant.

Ensrud et al, 2003 also conducted their study in the United States. They set out to see if Central Nervous System (CNS) active medications increased the risk of fractures in

8,127 community dwelling older women. The authors noted that black women were excluded from the study due to their lower rate of fracture. This was a cohort recruited for the Study of Osteoporotic Fractures, from population-based listings in Maryland, Minnesota, Oregon and Pennsylvania, USA and they were followed up for an average of 4.8 years. The initial recruitment for the Study of Osteoporotic Fractures was in 1986-1988 (9,704 women) and baseline examination took place at this time. In 1992 the survivors from that original cohort were invited to have a fourth examination which included a questionnaire and 8,127 did so by 1994. These women were then contacted by postcard or telephone every four months to ask whether they had experienced any incident non-spine fractures until 1999.

The CNS active medication the participants were taking is the exposure in the study. This was ascertained in interview at a clinic visit. The participants had a clinic visit or a home visit (or a telephone interview if neither of the above were possible) to ascertain the medication they were taking. All containers of prescription and non-prescription medication were reviewed by the interviewer in the face to face interviews. The authors generated a list of four classes of CNS active medications: benzodiazepines, antidepressants, anticonvulsants and narcotics. The indication for prescription of the AED was not assessed.

The outcome of interest was "all non-spine fractures". This was defined as all non-traumatic, non-vertebral fractures and, as stated above, was reported during quarterly telephone or postal contact. All fractures were confirmed by radiographic reports; hip fractures were confirmed by reviewing pre-operative x rays. Fractures occurring because of major trauma were excluded.

Potential confounders included in the Ensrud study were age, self-reported health status, oestrogen use, lifestyle (including activity level and smoking), previous dizziness and falls, cognitive impairment, weight change, bone mineral density, speed when walking and ability to rise from a chair.

Of the 8127 participants, 123 (or 2%) were taking one AED, 65 were taking phenytoin, 34 were taking phenobarbital, 27 were taking carbamazepine and 12 were taking another AED which was not specified. The authors found that after the results were

adjusted for age, women taking AEDs were at increased risk for any fracture (HR 1.68, 95% CI 1.16-2.43). They were also found to be at increased risk for hip fracture specifically (HR 2.00, 95% CI 0.94-4.25). This hazard ratio was reduced when the statistics were also adjusted for bone mineral density (HR 1.38, 95% CI 0.88-2.18 for any non-spine fracture and HR 1.51, 95% CI 0.56 to 4.08). When the hazard ratios were adjusted for multiple potential confounders the HR was reduced further still (multivariate HR 1.25; 95% CI 0.79 – 1.98 for any non-spine fracture and multivariate HR 1.37; CI 0.51-3.73). It was noted by the authors that while the HRs were still greater than 1.0, the confidence intervals were wide.

The authors also obtained adjusted risk estimates for each fracture outcome. They state that they did this by adding covariates individually and simultaneously to models that included current use and age as predictors. The result using this method showed a higher risk of any non-spine fracture in someone using an AED (age adjusted RR 1.68; 95% CI 1.16-2.43, multivariate RR 1.25; 95% CI 0.79-1.98). The calculated relative risk of hip fracture (age adjusted) was RR 2.00; 95% CI 0.94-4.25). The calculated relative risk of hip fracture (multivariate) was RR 1.37; 95% CI 0.51-3.73). The authors state that excluding women with epilepsy did not alter these results (51).

Mezuk et al, United States 2010, sought to assess fracture risk in people aged 50 and older, with serious mental illness, treated with AEDs. People with bipolar affective disorder were identified from those receiving care through the Veteran's Health Administration, USA from the VA National Psychosis Registry. The cohort consisted of 67,387 people, of whom 97% were men. There were no racial exclusions. There was no information regarding accommodation. The cohort consisted of 29,029 people with bipolar affective disorder and 38,358 without a diagnosis of serious mental illness but in similar age demographic, also recruited from the Veterans Health Administration database. The participants were followed up for 4.5 years.

Exposure of interest was prescription of AED, which was identified from pharmacy records through the Veteran's Administration prescription benefits manager group. The authors included liver enzyme inducing medications phenytoin, fosphenytoin, mephenytoin, phenobarbital, carbamazepine, primidone, oxcarbazepine and topiramate. They also included non-enzyme inducers divalproex, lamotrigine,

gabapentin, tigabine, and levetiracetam. The exposure was recorded if any of the agents were used before the date of data. They included data regarding duration of AED use and when it was last used. The outcome of interest was “all fractures”. The authors stated they chose to include traumatic fractures also. The data regarding occurrence of a fracture was obtained from coding for diagnoses in both inpatient and outpatient administrative records. While all fractures were recorded, there was a separate analysis of hip fractures. Potential confounders included in the Mezuk study were age, gender, race, region, income, depression and alcohol or substance misuse.

The results showed that 65% of the sub-group with bipolar disorder used AEDs, compared with 2% of the group without bipolar disorder. Of the people prescribed AEDs, 45.7% were taking divalproex (sodium valproate in Europe), 25.9% were taking gabapentin, 9.5% were taking carbamazepine, 7.7% were taking lamotrigine and 5.2% were taking topiramate. Having ever used an AED resulted in an increased risk of all fractures over the study period for the whole study population (HR 2.42; 95% CI 2.23-2.63). There was also an increased risk for hip fractures specifically (HR 2.35; 95% CI 1.86-2.99). The study also noted that patients with bipolar disorder had an increased risk of fracture independent of AED use (HR 1.21, 95% CI 1.10-1.33, Wald $\chi^2 = 14.8$, $p = 0.0001$). The authors stated that the relationships between bipolar disorder and AED use and fracture were similar for men and women but they did not show this data. The authors also examined the relationship between enzyme inducing AEDs and any fracture and showed the risk to be higher than that with non-enzyme inducers (HR 2.19, 95% CI 1.97 – 2.43, and HR 1.66; 95% CI 1.54 – 1.79 respectively). The authors state that excluding people with epilepsy from the analysis did not alter the results (54).

Nicholas et al in the United Kingdom compared fracture risk in people using liver enzyme inducing medication with people using non liver enzyme inducing medication. The cohort was people with active epilepsy and was sourced from the General Practice Research Database in the United Kingdom. There were 63,259 participants and the median duration of follow up was 2.93 years. Individuals were included in the cohort if they had a received a diagnosis of epilepsy and received a prescription for an AED. 49%

of the cohort were women and the mean age of the participants was 42.2 years. The participants' type of residence was not recorded.

Exposure of interest in this study was AED treatment, and the information regarding this was also obtained from the General Practice Research Database (GPRD).

Participants were classified as being treated with (i) AED treatment including one or more liver enzyme inducer (LEI) or (ii) AED treatment including only non-liver enzyme inducing (non-LEI) AEDs. Everyone in this study had epilepsy, therefore the indication for use of AED must be deemed to be for epilepsy. The primary outcome of interest in this study was diagnosis of fracture recorded in the GPRD. The secondary outcome of interest was hip fracture. Possible confounding variables included were alcohol use, previous use of AEDs, previous seizures, falls or fractures, health condition and medication use.

The results showed that 9,754 men were prescribed non LEI AEDs and 16,508 were prescribed LEI AEDs. Of the women studied, 10,382 were in receipt of non-LEI AEDs while 15,222 were in receipt of LEI AEDs. The LEI AEDs were associated with an increased risk of fracture in people with epilepsy as compared to those with epilepsy treated with non-LEI AEDs. The increased risk for all fracture sites, in men, with LEI as compared with non-LEI was reflected by adjusted HR 1.09, 95% CI 0.98 – 1.2, $p = 0.123$ and was therefore not deemed to be significant. For women there was a slightly greater increase in the risk of fracture at any site (adjusted HR 1.22, 95% CI 1.12 – 1.34; $p < 0.0010$). When the sample was adjusted to include only those over 50 the author stated the results did not alter, but did not include same. Regarding hip fractures, there was a greater risk with LEI AEDs than non-LEI AEDs for men (adjusted HR 1.53; 95% CI 1.10 – 2.12, $p = 0.011$). There was also a greater risk with LEI AEDs than non-LEI AEDs for women (adjusted HR 1.49; 95% CI 1.15 – 1.94, $p = 0.002$). The authors state this suggested that hazard ratio for hip fracture was of a greater magnitude than that for fracture at all sites (55).

Nurminen et al in Finland, 2013, set out to assess the gender specific risk of fracture in a population over the age of 65 associated with opioid treatment, AED treatment and anticholinergic treatment. They also looked at fracture risk when these treatments were used in combination, or concomitantly with psychotropic medication. The cohort

consisted of 1,177 people over the age of 65. Of these, 482 were male, 695 were female, with a mean age of 73.2 years. It was noted by the authors that one in twenty of the participants resided in institutions and that the remainder lived in the community. This study formed part of a longitudinal population based study performed in Lieto in South-west Finland. For this study the participants were followed up for 6 years after baseline assessment.

The exposure of interest was medication treatment with opioids, AEDs, anticholinergics, benzodiazepines, antidepressants and antipsychotics. The AED exposures specifically were phenobarbital, primidone, phenytoin, ethosuximide, clonazepam, carbamazepine and valproic acid. The exposure information was recorded by a nurse during interview with the participants. The authors also state that prescription forms, medication containers and medical records were also checked. The outcome of interest in this study was fracture and information regarding fracture was obtained from medical records using “radiologic confirmation” (56). This appears to relate to fracture at any site as there is no specific reference to site made by the authors. The potential confounders taken into account for the female participants were age, poor handgrip strength, body mass index below 30kg/m², compression fracture in one or more upper lumbar or thoracic vertebrae. For the male participants the confounders included were old age, multiple depressive symptoms and compression fracture in one or more upper lumbar or thoracic vertebrae.

The results found that 11 men and 10 women used one AED and three men used two or more AEDs. No women in the study were found to use two or more AEDs. Three men and one woman used an AED and an antipsychotic medication. Six men and three women used an AED and a benzodiazepine. Three men and one woman used an AED and an antidepressant. The only reported result for men was the ‘two or more AEDs’ subgroup. At three year follow up one of the men had sustained a fracture, generating a RR 8.2, 95% CI 1.1 – 60.8, p = 0.04. When this was adjusted for age, the RR was 6.6, 95% CI 0.9 – 49.6, p = 0.07, and was therefore not significant. The results shown for women using one AED at 6 year follow up showed a RR of 3.5, 95% CI 1.3 – 9.7, p = 0.01. When this was adjusted for age, the RR was 3.0, 95% CI 1.1 – 8.2, p = 0.03. When multivariate analysis was carried out the RR was 2.7, 95% CI 0.8 – 9.2, p = 0.1.

Therefore, the association was not significant after adjustments were made for potential confounders (56).

Velez et al in the USA, 2014, sought to examine the risk of bone fracture among patients with epilepsy in the United States. The population in this cohort was sourced from the PharMetrics Database. This is a longitudinal population database with drug and diagnosis data, medical and pharmacy insurance claims and outpatient and inpatient information. It refers to people with Medicaid, Medicare or other commercial health insurance (59). The mean age of the patients was 47.6 years and the follow up period was for six years. The patients were 55% female. 97,362 patients were selected from the database with claims for epilepsy in the years preceding and immediately following the index date and a cohort of the same size, matched for demographics, without epilepsy, was also selected. The place of residence of the participants was not stated by the author.

Exposure to AED was assessed during follow up period from the same database. The names of the AEDs are not included by the author. Outcome of fracture was assessed from the database information. Site of fracture was not specified by the authors. Potential confounders assessed for in the study were age greater than 65, comorbid osteoporosis, imbalance disorder and Alzheimer's disease.

The results showed that 73% of the patients with epilepsy received an AED, compared with 30.7% of the patients without a diagnosis of epilepsy, according to the database. For those receiving the AED treatment, regardless of diagnosis of epilepsy, there was a higher risk of fracture with an adjusted OR 1.29, 95% CI 1.24-1.35. The p value was not reported. This study was presented as a poster and this may be the reason for the smaller amount of information supplied (58).

3.4.1.2 Studies concerned with risk of falls only

Ensrud et al in the USA, 2002, assessed whether Central Nervous System (CNS) active medications increased the risk of falls in 6,301 community dwelling older women. The authors noted that black women were excluded from the study due to their lower rate

of fracture. This was a cohort recruited for the Study of Osteoporotic Fractures, from population-based listings in the US states of Maryland, Minnesota, Oregon and Pennsylvania, USA. The cohort was followed up for an average of 4.8 years. The initial recruitment for the Study of Osteoporotic Fractures was in 1986-1988 (9,704 women) and baseline examination took place at this time. In 1992 the survivors from that original cohort were invited to have a fourth examination which included a questionnaire and 8,127 did so by 1994. These women were then contacted by postcard or telephone every four months, for a follow up period of one year, to ask whether they had experienced any incident falls. The average follow-up period was 356 days.

The CNS active medication that the participants were taking is the exposure in the study. This was ascertained in interview at a clinic visit. The participants had a clinic visit or a home visit (or a telephone interview if neither of the above were possible) to ascertain the medication they were taking. All containers of prescription and non-prescription medication were reviewed by the interviewer in the face to face interviews. The authors generated a list of four classes of CNS active medications: benzodiazepines, antidepressants, anticonvulsants and narcotics. The indication for prescription of the AED was not assessed. The outcome of interest was a fall, defined as "falling all the way to the floor or ground, or falling and hitting an object like a chair or stair". This was ascertained by the authors by contacting the participants every 4 months by postcard or telephone to ask about falls.

Potential confounders included in the Ensrud study were age, self-reported health status, oestrogen use, lifestyle (including activity level and smoking), previous dizziness and falls, cognitive impairment, weight change, bone mineral density, speed when walking and ability to rise from a chair.

Regarding AED use, 123 participants, or 2% of the cohort were active users of AEDs, almost all of whom (95%) were daily users. 65 were taking phenytoin, 34 were taking phenobarbital, 27 were taking carbamazepine and 12 were taking another AED which was not specified. The authors state that 50% of those using AEDs had a diagnosis of seizure disorder. Those using AEDs were found to be at a higher risk of falls with an age-adjusted RR 2.49, 95% CI 1.73 – 3.58. The multi-variate RR is 1.75, 95% CI 1.13 -

2.71. There was also at significantly increased risk of frequent falling when AEDs were used, with an age-adjusted RR 3.15, 95% CI 2.08 – 4.77. The multivariate adjusted RR was 2.56, 95% CI 1.49 – 4.41. The authors stated the results did not alter when seizure disorder was controlled for (50).

Merrill et al in the USA, 2005, carried out a prospective cohort study to investigate whether there was a link between use of the AED oxcarbazepine and falls. The cohort chosen was a group of psychiatric inpatients in Buffalo, New York. There were 23 men and 28 women included in the study and the mean age of participants was 59. It was noted by the authors that the oxcarbazepine, an AED, was used as an off licence treatment for mood disorder. The period of follow up was a total of two years. The comparison group were the patients themselves, when not on the medication, and the period of time on the treatment was 100 days. This was described by the author as a “rolling cohort study”.

The exposure of interest in this study was treatment with oxcarbazepine for duration greater than one day during the study period. Falls were the outcome of interest in this study, and the author states they were tracked using the hospital incident reporting system. The authors state they stratified their results by age in an attempt to control confounders.

The results showed that there were 0.69 falls per 100 patient days (95% CI 0.54 to 0.84) in those using the AED. There were 0.38 falls per 100 patient days in the participants when they were not using the AED (52).

Ham et al in the Netherlands, 2014, used data from the B-PROOF study (B vitamins for the prevention of osteoporotic fractures), in which the participants were from three Dutch cities, to investigate the association between medication usage and falls. There were 2,407 community dwelling Dutch people included in the study, and they were aged 65 years and older. The cohort comprised 49.1% women. The indication for the use of the medication was not assessed.

The exposure of interest in this study was use of medication. This was ascertained from pharmacy dispensing records obtained from the Dutch Foundation for Pharmaceutical Statistics. This holds data from 95% of the pharmacies in the

Netherlands. Cardiovascular, CNS, respiratory system and 'miscellaneous' medications were included. Among the CNS drugs was a section for AEDs but individual, named AEDs were not recorded. The outcome of interest was incidence of fall. A fall was defined as an unintentional change in position resulting in coming to rest at a lower level or on the ground (10). Fall incidents were recorded using a fall calendar, which was returned to the team every three months. If the details provided by the participant were unclear, the participant was contacted by a member of the team conducting the study, for more details. Potential confounders controlled for were age, gender, use of a walking aid, history of falls and fractures, health status variables which included smoking status, alcohol use, cardiovascular disease, diabetes and hypercholesterolemia.

Of the cohort, 42 (or 1.7%) were users of AEDs. The authors state there was no significance found in the risk of falls in users of AEDs versus non-users. The hazard ratio for the crude model showed HR 1.44; 95% CI 0.95 – 2.18. When this was adjusted for confounders the HR was 1.31; 95% CI 0.87 – 1.98. The p value was not reported. The wide confidence interval is notable here (57).

3.4.1.3 Studies concerned with risk of both falls and fractures

Tromp et al in the Netherlands, 1998, sought to identify easily measurable predictors for falls and fractures. They used data from the Longitudinal Aging Study in Amsterdam, which studied people in three regions of the Netherlands over a period of 10 years. The participants were 65 and older at the end date of the study, and the mean age of participants was 72.6 years. The authors noted that they excluded people living in institutions and described the participants as community dwelling. The cohort consisted of 764 men and 705 women (total 1405). The average follow-up period was 37.8 months.

There were a number of potential risk factors assessed in this study. The exposure of interest to this systematic review is treatment with medication, specifically AEDs. The information regarding medication usage was obtained from review of the participants' medication containers. The specific types of AEDs included were not recorded. The

indication for the medication was not specified. The outcome of interest was (i) the occurrence of falls in the year prior to the follow up examination and (ii) the occurrence of a fracture during a 38 month follow up period. A fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower surface level such as a chair or stair. Regarding the second outcome, recurrent falling was also captured. Both outcomes were captured via self-report. Confounders allowed for in this study were age and gender. The authors stated they initially calculated Odds Ratios without adjusting for these as they wanted to identify the sub groups with the highest risk and were not concerned with elucidating causality.

The results showed that 15 members of the cohort used AEDs. There was an increased risk of having one fall with an Odds Ratio of 6.2, 95% CI 2.0 – 19.7, $p < 0.05$. There was also an increased risk of recurrent falls, with an odds ratio of 7.1, 95% CI 2.5 – 19.8, $p < 0.05$. There was also shown to be an increased risk of fractures, OR 4.7, 95% CI 1.3 – 17.2, $p < 0.05$. Once the figures were adjusted for age and gender the use of AEDs continued to indicate an increased risk of recurrent falls with an OR of 4.7, 95% CI 1.4 – 15.9, $p < 0.05$. The authors acknowledged that only a small portion of the cohort used AEDs (1).

Carbone et al in the USA, 2009, looked at AED use, falls, fractures and bone mineral density in women aged 50 – 79 years. The cohort comprised 1385 AED users and 137, 282 non-users. The participants were from 40 clinical centres from the Women's Health Initiative, a long term national health study in the United States. The follow up period for assessment of falls and fractures was 7.7 years. Users of corticosteroids were excluded.

The exposure of interest was use of AEDs. This was assessed by having participants bring the containers from their medications in the preceding two weeks to the baseline and follow up assessments. The medication used by a participant was classified via category. The AEDs were divided into two groups; enzyme-inducing and non-enzyme inducing. The enzyme inducing category included carbamazepine, mephenytoin, phenytoin and primidone. The category of non-enzyme inducers included clonazepam, divalproex sodium (pharmacokinetically the same as sodium valproate, used in European countries), gabapentin, lamotrigine, methsuxime and

topiramate. The outcomes of interest were falls, fractures and bone mineral density. Here the focus will be on the falls and fractures. Hip fractures were confirmed by review of radiology reports. However, fractures at all sites were recorded. Information regarding falls was collected via questionnaires. Falls in the course of sporting activity were excluded.

Confounding variables included were age, ethnicity, BMI, smoking status, alcohol intake, calcium and vitamin D intake, prevalent fracture at age 55 and over, history of falls, medication use including hormonal treatment, diabetes, family history of hip fracture, medical history including of Multiple Sclerosis and Parkinson's Disease.

The results showed that of the 1385 AED users, 289 used carbamazepine, 470 used clonazepam, 110 used divalproex sodium, 81 used gabapentin, five used lamotrigine, three used mephenytoin, three used methsuximide, 370 used phenytoin, 67 used primidone, one used topiramate, and six used valproic acid. The indication for use was not recorded. When the data was adjusted for age and ethnicity and BMI, those using a single AED were at increased risk for fracture as compared to non-users, HR 1.60, 95% CI 1.42 – 1.79. Those using more than one AED were at a greater risk than non-users for fractures, HR 2.68, 95% CI 2.04 – 3.53. In fully adjusted models (adjusted for all potential confounders) those using a single AED were at increased risk for fracture as compared to non-users, HR 2.68; 95% CI 2.04 – 2.53. Those using more than one AED were at a greater risk than non-users for fractures, HR 2.12, 95% CI 1.61 – 2.80. When those using two or more AEDs were compared to those using just one AED (with the data adjusted for age and ethnicity and BMI), it was demonstrated that those using two or more AEDs were at greater risk of fracture; HR 1.68; 95% CI 1.25 – 2.26. In fully adjusted models (adjusted for all potential confounders, as listed above), those using two or more AEDs were compared to those using just one AED and were still found to be at increased risk of fracture; HR 1.55; 95% CI 1.15 – 2.09. Those using enzyme-inducing AEDs were found to be at increased risk of fracture compared to those using non-enzyme inducing AEDs. The hazard ratio for non-enzyme inducing AEDs was 1.44; 95% CI 1.22 – 1.71; while the hazard ratio for enzyme-inducing AED users was found to be 1.87; 95% CI 1.62 – 2.15 (with the data adjusted for age and ethnicity and BMI).

Participants using both types of AEDs had a fracture risk hazard ratio of 3.02; 95% CI 1.85 – 4.93 (with the data adjusted for age and ethnicity and BMI).

With regard to falls, those using AEDs for less than two years had an increased risk of falls as demonstrated by hazard ratio 2.15, 95% CI 2.00 – 2.31. Those using AEDs for between 2 and 5 years had an increased risk of fracture as demonstrated by hazard ratio 2.05; 95% CI 1.80 – 2.33. Those using AEDs for more than 5 years had an increased risk of falls also, with hazard ratio 2.16, 95% CI 1.92 – 2.44. The data here is adjusted for age and ethnicity and BMI. When the data is adjusted for all potential confounders included in the study, there was still an increased risk for users of AEDs with a hazard ratio of 1.62; 95% CI 1.50 – 1.74.

There follows a table summarising the key findings of the studies:

Table 3.1: Summary of key aspects of the studies chosen

Author, year, country	Cohort size	Gender, Age (mean)	Cohort diagnoses, indication for AED use	Population based sample	Exposure medications	Follow up period	Methods of ascertaining outcome	Confounders considered	Risk Ratio
<i>Fractures only</i>									
Bohannon et al, 1999, USA	2590	All female, 65 and older, (mean = 73.5)	Not specified	Yes	Phenytoin	6 years	Self-repost of any fracture at yearly interview; in person x 2, telephone x 4	Age, ethnicity, education, income, residence, lifestyle factors (including alcohol and smoking), medications, health conditions (including cognitive impairment and depression)	Odds ratio
Ensrud et al, 2003, USA	8127	All female, 65 and older, (mean = 78)	Not specified	Yes	Various AEDs, stated as phenytoin, phenobarbital, carbamazepine another AED which was not specified	4.8 years	Self-report of all non-traumatic non-spine or hip fracture when contacted by research team every four months by telephone or postcard	Age, self-reported health status, oestrogen use, lifestyle (including activity level and smoking), previous dizziness and falls, cognitive impairment, weight change, bone mineral density, speed when walking and ability to rise from a chair	Hazard ratio
Mezuk et al, 2010, USA	67,387	97% male, 50 and older	29,029 participants dx bipolar affective	Yes	Phenytoin, fosphenytoin, mephenytoin, phenobarbital,	4.5 years	Coding for diagnoses of any fracture, and hip fracture in both	Age, gender, race, region, income, depression and alcohol or substance misuse	Hazard ratio

			disorder, people with epilepsy excluded		carbamazepine, primidone, oxcarbazepine, topiramate, divalproex, lamotrigine, gabapentin, tigabine, levetiracetam		inpatient and outpatient administrative records. Traumatic fractures included.		
Nicholas et al, 2013, UK	63,259	49% female, mean age 42.2 years	People with active epilepsy	Yes	AED treatment including one or more liver enzyme inducer (LEI) or (ii) AED treatment including only non-liver enzyme inducing (non-LEI) AEDs.	2.9 years	Primary outcome of interest: diagnosis of fracture recorded in the GPRD. Secondary outcome of interest: hip fracture.	Alcohol use, previous use of AEDs, previous seizures, falls or fractures, health condition and medication use	Hazard ratio
Nurminen et al, 2013, Finland	1,283	59% female, 65 and older, Mean age 73.2 years	Not specified	Yes	Phenobarbital, primidone, phenytoin, ethosuximide, clonazepam, carbamazepine and valproic acid	6 years	Any fracture, data obtained from medical records using "radiologic confirmation"	Females: age, poor handgrip strength, body mass index below 30kg/m ² , Males: age, multiple depressive symptoms All: compression fracture in one or more upper lumbar or thoracic vertebrae	Risk ratio
Velez et al, 2014, USA	194734	55% female, mean	97,362 participants had epilepsy	Yes	Exposure to AED, names of which not specified	6	Fracture (no specifics re site mentioned) entered into	Age greater than 65, comorbid osteoporosis, imbalance disorder	Odds ratio

		age 47.6 years					PharMetrics database	and Alzheimer's disease	
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<i>Falls only</i>									
Author, year, country	Cohort size	Gender, Age (mean)	Cohort diagnoses, indication for AED use	Population based sample	Exposure medications	Follow up period	Methods of ascertaining outcome	Confounders considered	Risk Ratio
Ensrud et al, 2002, USA	6301	All female, 65 and older, mean age 77	Not stated	Yes	Various AEDs, stated as phenytoin, phenobarbital, carbamazepine another AED which was not specified	356 days	Fall = "falling all the way to the floor or ground, or falling and hitting an object like a chair or stair". Ascertained by the authors contacting the participants every 4 months by postcard or telephone	Age, self-reported health status, oestrogen use, lifestyle (including activity level and smoking), previous dizziness and falls, cognitive impairment, weight change, bone mineral density, speed when walking and ability to rise from a chair	Odds ratio
Merrill et al, 2005, USA	51	55% female, mean age = 59	Inpatients in a psychiatric hospital, treated for mood disorder	No	Oxcarbazepine	2 years-100 days on treatment	Falls, as reported to hospital incident reporting system	Age	Absolute risk

Ham et al, 2014, Netherlands	2407	49.1% female, 65 and older,	Not specified	Yes	Various AEDs, names not specified	3 years	Fall = unintentional change in position resulting in coming to rest at a lower level or the ground. Self-reported (fall calendar, returned every 3 months)	Age, gender, use of a walking aid, history of falls and fractures, health status including smoking and alcohol, cardiovascular disease, diabetes and hypercholesterolemia	Hazard ratio
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<i>Falls and fractures</i>									
Author, year, country	Cohort size	Gender, Age (mean)	Cohort diagnoses, indication for AED use	Population based sample	Exposure medications	Follow up period	Methods of ascertaining outcome	Confounders considered	Risk Ratio
Tromp et al, 1998, Netherlands	1469	52% female, 65 and older, mean age 72.6 years	Not specified	Yes	Various AEDs, names not specified	4 years	(i) Fall in the year prior to the follow up examination; (ii) Fracture during a 38 month follow up period. Fall was defined in same way as Ham et al, above. Both outcomes captured via self-report	Age and gender	Odds ratio
Carbone et al, 2009, USA	138,667	All female, ages 50 - 79		Yes	LEI AEDs carbamazepine, mephenytoin, phenytoin and primidone.	7.7 years	Hip fractures confirmed by review of radiology reports. Fractures at all sites were	Age, ethnicity, BMI, smoking and alcohol, calcium and vitamin D intake, prevalent fracture at age 55+,	Hazard ratio

				<p>Non LEI AEDs clonazepam, divalproex sodium, valproate, gabapentin, lamotrigine, methsuxime topiramate</p>		<p>recorded. Information regarding falls was collected via questionnaires. Falls in the course of sporting activity were excluded.</p>	<p>history of falls, medication, including hormonal treatment, diabetes, family history hip fracture, medical history including of Multiple Sclerosis and Parkinson's Disease</p>	
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3.4.2 Methodological quality of the selected studies

Overall the quality of the studies was good. The findings following evaluation of methodological quality are presented in table 3.2, which is followed by an explanatory table, listing the aspects of the Newcastle Ottawa Scale for Cohort Studies, table 3.3. Most of the studies have a large number of participants and are population based, allowing for greater generalisability of results. The risk of selection bias, related to both outcome and exposure, is greatly lessened by the prospective nature of the studies chosen.

In some of the studies it was not possible to ascertain if any of the original cohort had been lost to follow up and this raises the possibility of loss to follow up bias. The outcomes and exposures assessed were clearly stated. However, their method of assessment differed across the studies. While some of the outcomes were recorded from medical records and radiography (51-56, 58) others were not (48-51). When self-report measures are employed, it raises the risk of recall bias on the part of the participant.

While the studies generally had very large cohorts, the numbers of those using AEDs was much smaller in some of the studies. For example, Ensrud et al, 2003 (51) reported on their population where 123 of 8127 participants were taking AEDs. Ham et al (57) reported on 42 of their 1707 participants who were taking AEDs. Of the 1405 participants in Tromp et al's study of falls and fractures, only 15 were using AEDs (48). Regarding exposure to AEDs, this was not recorded in the same manner across the studies. Some of the studies reported "any use" of an AED before the index date (54). However, this does not totally reflect the duration of usage of AEDs for those with chronic illnesses. In addition, participants' prior exposure to other AEDs was not always reflected as a covariate and this may affect the participants' risk, in addition to their treatment at the time of the assessment.

There are many potential risk factors for osteoporosis, including age, sex, race, low bone mass, low body weight, oestrogen deficiency and previous fracture. Other risk factors include tendency to fall, disability and immobilisation, low physical activity, use of psychotropic/anxiolytic/hypnotic drugs, use of corticosteroid, low calcium intake in

the elderly, osteomalacia, thyrotoxicosis, cigarette smoking, chronic alcoholism, diabetes mellitus, and insufficient sunlight exposure (60). While many of the studies took some or most of these potential confounders into account, they did not all take the same confounders into account in each study.

As shown in the summary table 3.1, the studies included assessed risk using different parameters. Some of them used odds ratios (48-50, 58). A further five studies reported hazard ratios (51, 53-55, 57). One study reported its findings in terms of risk ratios (56) and another reported absolute risk (52). This results in difficulty in pooling the data.

Table 3.2: Newcastle Ottawa Scale results for studies included in the systematic review

Study (by Author)	Newcastle Ottawa Scale							
	Selection				Comp	Outcome		
	1	2	3	4	1	1	2	3
<i>Fractures only</i>								
Bohannon et al, 1999	★	★	★	★	★★	0	★	★
Ensrud et al 2003	★	★	★	★	★	★	★	★
Mezuk et al, 2010	★	★	★	★	★★	★	0	?
Nicholas et al,	★	★	★	0	0	★	0	?
Nurminen et al. 2013	★	★	★	0	★	★	★	★
Velez et al, 2014	★	★	★	0	★	★	★	?
<i>Falls only</i>								
Ensrud et al, 2002	★	★	★	0	★	0	★	★
Merrill et al, 2005	0	★	★	0	★	★	0	★
Ham et al, 2014	★	★	★	0	★	0	★	★
<i>Falls and fractures</i>								
Tromp et al, 1998	★	★	★	0	★	0	0	★
Carbone et al, 2009	★	★	★	0	★★	★	★	?

Legend: ★ = ★ awarded as per NOS Quality Scale, 0= no award, ? = insufficient data

As outlined in Chapter 2, studies scoring higher than 7 are deemed high quality studies using NOS scale. Studies scoring between 4 and 6 on the scale were assessed as being of 'moderate quality', and 0-3 as being of 'poor quality' (46). All of the studies included were of moderate or high quality, with scores shown above.

Table 3.3: Newcastle Ottawa Quality Scale for Cohort Studies, Ottawa University (46)

Selection	1. Representativeness of the exposed cohort
	Truly representative of the average person taking AEDs in the community ★ Somewhat representative of the average person taking AEDs in the community ★ Selected group of users e.g. nurses, volunteers No description of the derivation of the cohort
Selection	2. Selection of the non-exposed cohort
	Drawn from the same community as the exposed cohort ★ Drawn from a different source No description of the derivation of the non-exposed cohort
Selection	3. Ascertainment of exposure
	Secure record (e.g. surgical records) ★ Structured interview ★ Written self-report No description
Selection	4. Demonstration that outcome of interest was not present at start of study
	Yes ★ No
Comparability	1. Comparability of cohorts on the basis of the design or analysis
	Study controls for age ★ Study controls for any additional factors: gender, health, race ★
Outcome	1. Assessment of outcome
	Independent blind assessment or reference to secure records, e.g. medical record ★ Record linkage (e.g. identified through ICD codes on database records) ★ Self-report No description
Outcome	2. Was follow-up long enough for outcomes to occur
	Yes (5 years for fracture to occur; 1 year for falls to occur) (61) ★ No
Outcome	3. Adequacy of follow up of cohorts
	Complete follow up - all subjects accounted for ★ Subjects lost to follow up unlikely to introduce bias - small number lost - > 15 % follow up, or description provided of those lost ★ (61) Follow up rate < 85% and no description of those lost No statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (46).

3.5 Summary

This section of the results chapter will summarise the findings of the selected studies across the outcome of interest: fall and/or fracture.

From the studies reviewed where fracture was an outcome it is evident that there is an increased risk of fracture with AED treatment. Bohannon et al (49), Ensrud et al (51), Tromp et al (48) and Carbone et al (53) demonstrated an increased risk of fractures in those receiving AEDs, after adjustment for potential confounders. In each of these the study population was a general population cohort and the indication for the use of medication was not specified. Nicholas et al (55) demonstrated an increased fracture risk in those using liver enzyme inducing AEDs in a population with epilepsy. Velez et al (58) demonstrated an increased fracture risk in those using AEDs in a population where half of the participants had epilepsy. Mezuk et al (54) showed an increased fracture risk in those exposed to AEDs in a population, almost half of whom who were diagnosed with bipolar affective disorder. Nurminen et al (56) demonstrated an increased risk of fractures with AED usage but this increase was not significant after adjustment for confounders.

Of the five studies that assessed AED use and risk of falls, three showed a demonstrably increased risk, after adjustment for confounders. These were Ensrud et al (50), Carbone et al (53) and Tromp et al (48). All of the studies looked at general populations, and had not selected a particular patient group. Ham et al (57) did not find a significant link between AED use and risk of falls. Merrill et al (52) described finding an increased risk of falls in psychiatry inpatients treated with an AED oxcarbazepine. However, the risks in the exposed group and unexposed group were not compared using bio-statistical measurements in order to clarify whether the difference in risk was significant.

Chapter 4: Discussion

4.1 Introduction

The aim of this systematic review was to identify relevant and appropriate studies to answer the question “Do anti-epileptic drugs, regardless of the treatment indication, predict an increased risk in the incidence of falls and fractures?” Because this was a systematic review the overarching aim was to select studies and analyse and summarise their results in a consistent fashion, in line with the MOOSE guidelines, as referenced in Chapter 2.

The main findings, as laid out in Chapter 3, revealed that AED use is associated with an increased risk of fractures among the population of interest, those over the age of 18 years. This risk increase was greater for those treated with LEI AEDs than non-LEI AEDs. The risk remained increased when seizure disorder was controlled for, and the risk was higher in older adults. Several of the papers reviewed suggested that dietary and lifestyle advice should be offered to those treated with AEDs and that prescribing guidelines should be updated to reflect the results in that paper (54, 55). Some of the researchers recommended further randomised trials of AEDs looking specifically at fall and fractures with AEDs (53). Still others suggested clinicians familiarise themselves with the other risk factors for falls and fractures and use this information to assist in the choice of treatment in epilepsy (48).

There was an increased risk of falls with AED use in three of five papers reviewed.

There will follow a review of the results obtained, using an ethical and legal prism to fully explore the breadth of the implications of the study. In order to do so the current clinical guidelines, likely to be consulted by an Irish prescriber, will be summarised below.

4.2 Current guidelines: A Summary

Despite the totality of evidence as summarised above, there is still a dearth of standardised recommendations on AED prescribing for clinicians, particularly clinicians outside neurology. As outlined in Chapter 1, NICE guidelines exist for prescribers when using AEDs for epilepsy in the NHS in the UK. These state that tests of bone metabolism should be carried out every 2-5 years for adults taking LEI AEDs (62). There is no reference to bone health in the NICE bipolar affective disorder management guideline (63) though it recommends using a number of the same medications as the epilepsy guideline. There are no recommendations in the guidelines from NICE regarding bone health advice, monitoring, or indeed bone conservation or Vitamin D treatment for those treated for mood stabilisation purposes (6).

In 2009 the Medicines Healthcare and Regulatory Agency (MHRA), an executive agency of the Department of Health in the United Kingdom, highlighted the effects of AEDs on bone and advised all healthcare professionals that “long term treatment with phenytoin, carbamazepine, primidone and sodium valproate are associated with decreased bone mineral density, which may lead to osteopenia, osteoporosis and increased fractures, particularly in the following at risk patients; those who are immobilised for long periods, those who have inadequate sun exposure, those with inadequate dietary calcium intake” (64). The MHRA’s advice was to consider supplementing vitamin D at risk patients who receive long term treatment with primidone, phenytoin, carbamazepine, phenobarbital and sodium valproate (64).

The Scottish Intercollegiate Guidelines Network, in their Epilepsy Management Guideline, advise that “patients taking AEDs should receive dietary and other lifestyle advice to minimise the risk of osteoporosis” (65). SIGN have withdrawn their last guideline on bipolar affective disorder, therefore there are no recommendations regarding bone health and treatment with mood stabilisers.

Furthermore, in the United States, a review of epilepsy treatment recommended that for those 60 and over, LEI AEDs should not be started unless the patient has failed to respond to two non-LEI AEDs previously (66).

Following on from this studies have been done looking at the ways to improve the prescribing of bone protection, including using computer automated reminders when there is a patient with epilepsy is at the clinic, in order to encourage compliance with the NICE guidelines (67).

It is clear from the above summary that the guidelines available concentrate on this issue as it pertains to epilepsy and are not in agreement regarding action in any case. This systematic review demonstrated that AEDs predict an increased risk of fractures, regardless of whether the indication is epilepsy, bipolar affective disorder or another illness.

4.3 Ethical Issues

4.3.1 Prescribing and the risk of side effects from an ethical perspective

The decision by a doctor or healthcare professional to include a treatment in a patient's care plan will be made following a consideration of the clinical presentation and diagnosis, characteristics of the patient and wishes of the patient, characteristics of the treatment itself and the resources available. The clinician's clinical knowledge and expertise in weighing these up will also come into play. The decision to treat an unwell patient with a medication with side effects is inevitable as virtually all medications have side effects, from over the counter preparations such as paracetamol to prescription medications for heart disease and cancer. The incidence and severity of these vary however. The studies included in the review showed that AEDS predict an increased risk of fracture; and three of five showed an increased risk of falls. When assessing an unwell patient, the clinician has an ethical obligation to make the best decision they can with the resources at their disposal. Using a treatment that might bring about harm to the patient will be decided after careful weighing up of the known risks and potential benefits to the patient. It will be helpful to demonstrate how this ethical obligation is discharged using the framework of the four principles of biomedical ethics; autonomy, beneficence, non-maleficence and justice.

4.3.2 Autonomy, beneficence and paternalism

Autonomy and beneficence sometimes meet in the middle, and decisions are shared equally between the clinician and the patient (68). This is the “shared decision making” model with the expert patient that is encouraged by our public health policy (69). However, this is not always the case. Sometimes autonomy advances and beneficence recedes, and vice versa (68). I want to examine autonomy and paternalism as they relate to treatment with AEDs for physical and mental illness.

John Stuart Mill wrote “The only purpose for which power can be rightfully exercised over any member of a civilised community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant. He cannot rightfully be compelled to do or forbear because it will be better for him to do so, because it will make him happier, because, in the opinion of others to do so would be wise, or even right” (70). The principle of respect for autonomy from the ethics sphere is applied in day to day clinical care when informed consent is obtained for treatment given.

The principle of beneficence invokes “a statement of moral obligation to act for the benefit of others” (71). It is not sufficient to refrain from harmful acts but “agents must take positive steps to help others” (71). Doctors, using their up to date clinical knowledge applied to a particular individual, taking into account that individuals other medical comorbidities, risk factors and treatments, decide on a course of treatment, in this case an AED. The clinician is acting for the benefit of the patient in alleviating suffering. However, when the beneficent act opposes the patient’s wishes, the act is deemed paternalistic.

Autonomy, for Beauchamp and Childress, means that a person acts “in accordance with a self-chosen plan” and is “free from controlling interference by others and limitations that prevent meaningful choice” (71). This definition leads us to the requirements for autonomous choice which are information, decision making capacity, and freedom to choose (68). The concept of autonomy is not considered an all or nothing entity; nor must it be present in a fixed amount. It can vary with time, illness and the decision in question. Equally paternalism can be present or absent, weak or

strong. It may be a silent manipulator or a loud coercion (68). Applying this definition of autonomy to the issue of treatment with AEDs, the autonomous patient requires information about AEDs and their side effects, including fracture risk. S/he also needs to have decision making capacity and the freedom to make a choice about the medication.

To achieve the requirement for information, the clinician must have access to clear transparent evidence and guidelines regarding the issue and then impart this clearly to the patient, using language that is easy to understand. The relevance of the information to the patient is important, i.e. if all previous studies were on people with epilepsy then the clinician will struggle to extrapolate the evidence to someone who is not a member of that population. The recommendations made by expert groups are very helpful in drawing together evidence. However, as we can see from the summary above, a clinician must not stick solely to the guidelines relating to the illness they are treat, e.g. treatment of bipolar affective disorder.

The capacity to decide about a medication is sometimes present for a patient, but not always. It is not an all or nothing concept and capacity can sometimes be diminished by illness. Sometimes all of these criteria are met for an autonomous decision, and the discussion, with written information provided, takes place in a pleasant calm outpatient department, with a clinician with plenty of time to spend with his/her patients. But this is not always the case.

Example A: In neurology an unwell patient having sustained a head injury develops seizures. This patient is started on an AED in the Intensive Care Unit (ICU). At the time of treatment initiation the patient is unconscious and does not have the capacity to make that decision as their capacity has been eroded by their illness.

Example B: A patient admitted for treatment of a manic episode with psychotic symptoms will often lack insight into the fact that they are unwell and need treatment and may require treatment, against their will, under mental health legislation. In Ireland the mechanism for same is the Mental Health Act, 2001 (72).

The patients in these, admittedly simplified, examples have had their capacity to make a decision about treatment eroded by physical and mental illness and will require treatment with medication (likely an AED) for the benefit of their health by a beneficent clinician. In very many cases this capacity is regained following a period of treatment. In both of these scenarios the requirement for medication continues once the initial symptoms have resolved. This is in order to prevent further seizures as in the first example, or relapse of mood disorder and psychosis, in the second example. Some people lack capacity to make healthcare decisions due to lack of cognitive ability for example in learning disability and dementia and these people do not typically regain capacity.

In the situation where the patient regains capacity, and the medication is still required, the benefits and side effects will be explained and the patient can then make a choice about continuing on the medication. The freedom to make this choice is the final component in the autonomous decision. The patients in examples A and B may be completely free to choose, or they may feel they are not. Remaining on the treatment that got them well is likely to be the advice of their clinician in both cases and a change to the treatment plan may lead to a delay in discharge and increased risk of relapse. Therefore, neither patient may feel they are completely free to choose.

In the case of the patient in example B, having been a detained patient under the Mental Health Act, s/he will be aware of a more overtly strongly paternalistic environment. The patient, now accepting voluntary treatment, may be concerned about future detention. This patient may feel this concern impacts his/her freedom to make choices regarding medication. The Mental Act states in Section 23 that a voluntary patient may be detained for a period of 24 hours. Within that time, they must be reviewed by a consultant psychiatrist who may proceed to an admission order under section 24 of the Act. In order to meet the criteria of an admission order the patient must have a mental illness in the context of the act: "A state of mind of a person which affects the person's thinking, perceiving, emotion or judgment and which seriously impairs the mental function of the person to the extent that he or she

requires care or medical treatment in his or her own interest or in the interest of other persons (68, 72).

Given that any and all of these possible variables may be in play around the time a treatment is initiated, the careful balance between autonomy and paternalism can be difficult to achieve. In a hospital setting there will inevitably be pressure for beds, along with patients' desires to return to their family and home and work. The repeat prescriber then has a significant responsibility in assisting the patient to make, or to continue making autonomous choices. In psychiatry in particular, with a reputation as strong paternalists, particular care must be taken. The obligation on the repeat prescriber will be examined in greater detail later in the discussion.

4.3.3 Non-maleficence

The principle of beneficence as outlined above is often tied closely with the principle of non-maleficence, which itself confers an obligation to abstain from doing harm to others (71). Since the review results detailed in chapter 3 reveal that harm (fracture and fall) is statistically more likely to arise when treated with the AED, then surely the clinician has caused the harm? This principle not only obligates the clinician not to cause harm but also not to impose risks of harm on the patient. But since, as outlined earlier, virtually all treatment has some side effect, then how can treatment go ahead? There are a number of reasons why treatment proceeds, even in the face of serious and not so serious side effects. Firstly, the four principles do not operate alone. WD Ross in *The Right and the Good* wrote about the four principles being viewed as prima facie obligations and not as absolute obligations. A prima facie obligation is one which is to be fulfilled unless it conflicts with an equal or stronger obligation (73). Therefore, the doctor faced with a patient with epilepsy, mood disorder or pain can prescribe a treatment with an associated risk or risks in order to perform his/her beneficent duty to treat. The beneficent nature of the act of prescribing an AED to treat mental and physical illness must be borne in mind when one considers the clinician's obligation vis a vis non-maleficence. That is to say, the obligation not to harm is sometimes more stringent than the obligation to help others, an extreme example of which is the

obligation not to kill or disable others (71). However, in cases where the harm inflicted is minor and a major benefit is received then the benefit is seen to outweigh the harm. The example given to illustrate this by Beauchamp and Childress is some swelling around an injection site (harm) when the injection brought about the lifesaving intervention required.

A helpful specification of the principle of non-maleficence is Negligence and the Standard of Due Care. The obligation not to impose harm also includes the obligation not to impose risks of harm, and this specification demands that the goals pursued justify the risks that must be imposed (71). There are two types of negligence viewed as part of this specification (i) intentionally imposing unreasonable risk and (ii) unintentionally but carelessly imposing risks of harm. In the case of treatment with AEDs and risk of adverse effects, the event is serious, i.e. fracture. However, the illness being treated is serious and can be fatal, so some risk can be accepted as part of the treatment. Here the standard of due care invokes a responsibility to be aware of the risk and ways to minimise that risk. The clinician whose patient develops a fracture while using an AED was not negligent if the medication was necessary, the lowest effective dose was used, the risks were explained and monitored for, and precautions taken regarding other modifiable risk factors. The same clinician would be negligent if he or she did not fulfil these obligations in exposing the patient to the smallest amount of risk in order to receive the treatment. Remaining up to date with medical developments and research regarding medications prescribed is an important practical day to day component of discharging the obligation of non-maleficence.

4.3.4 Justice in healthcare and clinical research

The principle of justice in healthcare refers to fair, equitable and appropriate treatment for people (71). The formal theory of justice, attributed by theorists to Aristotle, is common to all theories of justice (71). This states that equals must be treated equally and unequals treated unequally. It does not provide criteria for establishing equality of individuals and material principles of justice are required for same. The principles vary somewhat and come together to form a layered approach to

the concept of justice; these are Utilitarian theories, Libertarian theories, Communitarian theories, Egalitarian theories, Capabilities theories and Well-being theories. The concept of a “lottery” was used by Beauchamp and Childress (71) to explain the difficulties with reaching an understanding about justice as it pertains to health care. Indeed, it is easy to see injustice regarding the distribution of many social determinants. This is not equal and the individuals in society have no control over such attributes as their gender, race or disability status. Yet all of these factors impact access to healthcare, survival rates, and likelihood of inclusion in research (74, 75).

Healthcare resources are finite and difficult decisions must be made about distribution of these. The theories named above are a guide for how the principle of justice might be applied to healthcare when resources are scarce. But the principle of justice must also apply to research and research participation and application of the fruits of research. Regulation in healthcare research has evolved over time, from the earliest medical code in Prussia in 1900 which required the consent of the patient before involvement in research. This did not stop the widespread doctor’s experimentation that occurred in Nazi Germany during the 1940s (76) . This led to the development of the Nuremburg code in 1947 which again aimed to ensure openness and consent procedures (76). Regarding justice, the Nuremburg Code required that “the experiment should yield fruitful results, for the good of society, unprocurable by other methods” (76) perhaps reflecting a somewhat Utilitarian approach to the principle of justice, the greatest good for the greatest number. However, the problem of unethical research persisted and in the United States in 1974 the National Research Act was passed. This allowed for the setting up of a commission into research on humans and they published a report in 1979, the Belmont Report (77). Whilst there is ample discussion about beneficence and the respect for persons, the principle of justice as applied to research was discussed explicitly. The authors expressed concerns about the over-representation of minority groups in research studies due to their “easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied” (77). They also stated that benefits, knowledge, treatment or devices developed following research supported by public funds should “not provide advantages only to those who can afford them and

that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research” (77).

There was a change in how justice as it pertains to research was viewed in the 1990s with concerns that those in need might not be able to access clinical trials and the potential benefits of same. The backdrop to this was the emerging Human Immunodeficiency Virus (HIV) and Acquired Immuno-Deficiency Syndrome (AIDS). The focus, after Nuremburg and the Belmont Report had been to protect people from the risks from research whereas in the 1990s ensuring equitable access to research and the results of research became as important (71).

With an eye to the systematic review completed in this thesis it is clear that much research regarding the risks associated with AEDs has been completed. The vast majority of the earlier research was based solely on those with epilepsy, and published in neurology literature (78-84). Notwithstanding this, there have been some studies on population groups and those with mental illness (85, 86) published in psychiatry and general medical journals, broadening the awareness of the issue. As it stands, the benefit of the detected increased risk of fractures with AEDs appears to be diverted towards the population attending the neurology clinics with clinicians there availing of a broad literature base, prescribing guidelines (62, 67), and now developing strategies to better adhere to these guidelines (67).

4.4 Legal issues

4.4.1 Practising medicine and prescribing from a legal perspective

Doctors have an ethical obligation to manage his/her ongoing education and remain aware of up to date research in order to discharge the duty of beneficence and non-maleficence with regard to knowledge of important risk factors. The doctor also has an ethical obligation to share the information regarding illness and treatment appropriately and be aware of patient factors such as capacity and coercion or perceived coercion. These are in order to discharge his/her ethical obligation regarding patient autonomy with respect to the patient’s decision to proceed with treatment.

The doctor must be aware of research, sometimes from outside his/her own field, in order that their patients using AEDs have equitable access to the information available, pending inclusion of the information in all clinical guidelines. The legal considerations that will be examined, arising from this systematic review, in many ways reflect ways of protecting the ethical principles espoused in the previous section.

There is a hierarchical framework that governs legal issues as they arise in medicine. Irish Law comes from a number of sources; Bunreacht na hÉireann (the Irish Constitution), European Law, previous legislation and previous case law. Case law comes from decisions made by judges in the past which created precedents which are followed in court when a similar issue arises. Arising from these structures are additional mechanisms through which individual medico-legal concerns can be aired. These are via the European Court of Human Rights and the medical practitioner's regulatory body, the Irish Medical Council. Under Bunreacht na hÉireann there are express rights relevant to healthcare including the right to life, right to religious freedom and right to liberty (87). There are also implied rights to bodily integrity, privacy, dignity, autonomy and assisted decision making (87).

Sometimes patients develop complications from treatment. In the event that the individual believes their doctor was at fault, there are a number of options for recourse they may seek: a complaint to the doctor's regulatory body, or a civil action in a court of law. These are described below.

The Medical Council has power to regulate the performance of the medical profession under the Medical Practitioner's Act 2007 (88). Other professions have their own regulatory bodies and corresponding legislation, e.g. Nurses and Midwives Act 2011, Pharmacy Act 2007. An individual may make a complaint to the Medical Council regarding a doctor. If the initial complaint is upheld, a fitness to practice hearing will be held. The Medical Council has the power to revoke the doctor's licence to practice, or impose other sanctions, if the doctor was found to be at fault. There is no civil finding, i.e. there is no compensation, and there is no criminal finding. The Medical Council will examine the conduct of the doctor and whether he/she met the standards of ethical

conduct and behaviour, as laid out in their Guide to Professional Conduct and Ethics for Registered Medical Practitioners (89).

Under tort law, which is informed by common law and legislation (Medical Practitioner's Act), an individual may make a complaint of medical negligence about their doctor. Tort law attempts to balance the interests of the plaintiff's safety/right to bodily integrity vs. the defendant's freedom of action (90). This will be judged following the rules and precedent created by previous case law. The court will be interested in aspects of the clinical interaction including diagnosis, treatment and consent to treatment (90).

In Ireland there is no specific criminal law covering the act of medical negligence. This became topical when the case of Dr Michael Neary was in the public domain. Dr Neary was an obstetrician who was found to have carried out unnecessary hysterectomies on a large number of women and was struck off by the Medical Council in 2003. The Health Service arranged for a redress scheme to allow for compensation for the victims. Some of the women made complaints to the Gardaí but the Director of Public Prosecutions made the decision that there was insufficient evidence with which to proceed (91).

4.4.2 Duty of care by the prescriber

The prescriber of an AED, as with any medication, must comply with Medical Council regulations. These include guidelines relating to consent in order that patient autonomy in decision making be maintained. These enumerate the respect for patient choice, describe capacity to consent and explain provision of information for patients about the decision. The timing of, and responsibility for, the consent process is laid out clearly (89). The origins, in legal terms, of these regulatory guidelines will be traced in the next section.

Maintaining competence throughout a professional career is one of the requirements of the Medical Council. It means an onus on the doctor to update their knowledge and skill and to recognise the limitation of the knowledge and skill that they have. This

pertains to the prescription of medications found to have side effects, amongst other areas of practice. Perhaps the Scottish court put it most succinctly in its decision in the case of *Hunter v Hanley*, stating that it was indefensible for a doctor to say “that is what I learnt at university and I shall go on doing it” (90).

The Medical Council lay out specific guidance regarding prescription of medication which includes the need to “keep up to date with developments in medication safety”, and states that doctors should “seek independent evidence-based sources of information on the benefits and risks associated with the medication” (89).

4.4.3 Informed consent for treatment

As stated above, the requirement for informed consent for treatment is the legal mirroring of the right to autonomy. Doctors have a duty under common law to obtain informed consent. While this might seem obvious the precedent for same is set by previous cases. A classic judgement from a case, now over 100 years old, from New York reads “Every human being of adult years and sound mind has a right to determine what should be done with his body; and a surgeon who performs an operation without his patient’s consent commits an assault for which he is liable in damages” (92). The concept of consent was reviewed and examined in further court hearings over the last 100 years. These decisions and recommendations gave rise to the development of principles that guide doctors when they are communicating with a patient about a treatment or intervention (89). The patient must understand and appreciate the ramifications of a consent. If all necessary facts have not been made known in simple terms, with assistant pamphlets or information aids, then the consent is not an informed one.

An aspect of the informed consent process very pertinent to the systematic review conducted in this thesis is the information, the necessary facts, given to the patient about the risks associated with a particular treatment. The Medical Council states: “You must give patients enough information, in a way that they can understand, to enable them to exercise their right to make informed decisions about their care.

Consent is not valid if the patient has not been given enough information to make a decision” (89). The guideline goes on to recommend how to do this but acknowledges that the amount of information required will vary from patient to patient, depending on the nature of the condition, the type of treatment or intervention, the risks attendant on treatment and non-treatment and the patient’s wishes (89). The guideline notes that a patient’s beliefs, occupation and culture will also impact on their requirement for information and recommends checking to see if the information provided was understood (89). This is a summary of the recommendations regarding information to be given. These most up to date guidelines, published in 2016, and distributed in hard copy to every registered medical practitioner in Ireland, emphasize the importance of information sharing regarding treatment and intervention. This underscores previous rulings by the courts regarding medical negligence claims that hinged on the information sharing facet of the consent process.

In court rulings there have been three approaches to the disclosure of information: the first is the professional standards approach and the second is known as “the reasonable patient” approach, and lastly a middle ground between the two (90). The professional standards approach means that a doctor must give the patient the information that another doctor, also a specialist in their field, would give to a patient. The reasonable patient standard refers to giving all information, risks, and alternative options that a reasonable person in the patient's situation would consider important, in deciding to have, or not have, the proposed treatment. In the case of *Walsh v The Family Planning Services*, 1984, the members of the court disagreed as to which of the rules to apply. The members of the court felt the fact that adverse effects in the case were serious and had arisen from an elective, as opposed to a medically vital, procedure was important (90). In this case the professionals called said they would not have told the patient about the very tiny risk of the adverse effect (orchidalgia) either and the Chief Justice was happy with this (90). While the case did not hinge on this matter the disagreement left things somewhat unclear, but there did come a recognition of the different threshold required for disclosure of risks in elective versus medically essential treatment.

The case of *Geoghegan v Harris* (2001) raised this issue, again with an elective procedure. While judgments in the intervening period had come down on both side of the argument, in this case the court ruled that in the patient had the right to know all material risks (90).

While there is no criminal charge of medical negligence, an examination or intervention where informed consent is not given it could be viewed as an assault, which is a criminal charge. In summary, a doctor who does not obtained informed consent in the appropriate manner laid out in the regulatory guidelines could face civil proceedings under tort law, criminal proceedings if an assault charge is brought, and regulation by the Medical Council for breach of its code of ethics and conduct.

4.4.5 Regulatory guidelines for repeat prescribers

Much of the emphasis around ethical and legal duties regarding treatment so far has been focussed on what ought to happen prior to and at the time treatment is initiated. However as alluded to in the Medical Council guidelines, doctors need to keep up to date with developments regarding medication on an ongoing basis (89). While this is relevant to choosing a preparation it should also be read as pertaining to new developments with regard to medications that have already been started. When a medication is started in a specialist clinic, such as a psychiatry or neurology clinic, there is usually, if not always, senior medical team involvement. The follow up care may involve a return to the clinic where the patient may see any member of the team. Or they may be followed up by their general practitioner. For example, it has been shown that approximately 60% of medications for psychiatric illness are prescribed by general practitioners (93).

The General Medical Council is the Regulatory body for doctors in the UK. As with the Irish Medical Council, they give advice regarding professional conduct and ethics for doctors. In addition to general prescribing advice they also give specific recommendations regarding repeat prescriptions and the repeat prescriber, stating “You are responsible for any prescription you sign, including repeat prescriptions for

medicines initiated by colleagues, so you must make sure that any repeat prescription you sign is safe and appropriate. You should consider the benefits of prescribing with repeats to reduce the need for repeat prescribing” (94). Furthermore, there is the following recommendation: “When you issue repeat prescriptions or prescribe with repeats, you should make sure that procedures are in place to monitor whether the medicine is still safe and necessary for the patient” (94).

This facet regarding whether the medication is ‘still safe’ is relevant to the emergence of new research about side effects or the patient’s changing condition, e.g. developing other risk factors for developing a condition. The Medical Protection Society (MPS) are the medicolegal organisation through which healthcare professionals in Ireland and elsewhere obtain professional indemnity cover. Their advice sheet regarding prescribing makes this very clear; stating “responsibility is the same whether it is a first or repeat prescription. It is important to be aware that the person who signs the prescription will be held accountable should something go wrong” (95).

4.5 Strengths and weaknesses of the systematic review

This systematic review benefitted from its summarising the totality of evidence from a wide range of countries and populations. The cohort sizes were large and all but one of the studies was population based. A population based study benefits from greater generalisability of the results to the population at large. The populations studied included both men and women. Another strength of this systematic review was that the findings were consistent across the studies included in the review. This can be seen from the summary of the results of the included studies in chapter 3. Robust methods were used to screen the initial search results, and then identify and select titles. The methodological appraisal employed to assess methodological quality used validated criteria, the background to which was explained in Chapter 2. There were strengths evident in the assessment of outcomes of interest. The assessment of the outcome of fracture was by coding for diagnoses in hospital medical records. There were some studies where fractures were verified by radiographs. Both of these methods were found to be of high methodological quality by the Newcastle Ottawa Scale. Regarding

falls, Ensrud et al (50) contacted participants by postcard or telephone every four months, for a follow up period of one year, to ask whether they had experienced any incident falls. The average follow-up period was 356 days. This is keeping with best practice for assessment of falls in research, as assessed by the PROFANE group following systematic review (44).

There were a number of limitations experienced in conducting this study. The studies included were conducted in a number of countries; there were seven in the United States, two in the Netherlands, and one each in the UK and Finland. There were no high quality studies from countries with lower incomes. This is of concern as the WHO reports that 2.4 million people are diagnosed with epilepsy each year, but the burden of epilepsy is greater in poorer countries (6). "In high-income countries, annual new cases are between 30 and 50 per 100 000 people in the general population. In low- and middle-income countries, this figure can be up to two times higher" (6). Possible reasons for same include increased risk of endemic conditions such as malaria; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, availability of preventative health programmes and accessible care (6). The WHO estimate that close to 80% of people with epilepsy live in low- and middle-income countries (6).

Some of the population based cohort studies were based on primary data, that is, data collected for this specific study, such as the studies by Bohannon and et al and Ensrud et al (49, 51). Others, used secondary data from administrative databases to calculate the incidence of exposure and outcomes reported, an example of which was the Velez et al study (58) using the PharMetrics Database. When the study uses primary data there is greater ability to manage confounding variables and obtain greater detail about outcomes and exposures. However, many studies of longer duration (of follow up) use secondary data, such as that from databases, due to greater ease and lower cost of data collection.

Another limitation in this review was the heterogeneity evident with regards to how the exposure and outcome measures were determined. The exposure of interest in this study was the use of AEDs and the methods to ascertain same differed. Some of

the studies used in person interviews where the containers of medications used in the preceding two weeks were assessed by a trained interviewer. Others relied on the evidence from an administrative database that the medication was prescribed. Studies have shown that there is a compliance rate of approximately 50% with medication treatment for long-term illness (96). Therefore, accepting the exposure assessment from a prescription or General Practice database may not give a fully accurate account of the actual rates of AED use. While the use of in-person interviews to assess an exposure rate more highly than database findings there remains the likelihood that not all of the exposures were true exposures for the full period of follow up. That is to say, it brings the assessor to the point of dispensing of the medication with certainty but does not provide the same certainty with regard to regular ingestion. Serum levels of medication, while likely to give a very accurate reading of exposure, are not appropriate to these kinds of studies for ethical and cost reasons. Therefore, the most accurate, while still remaining pragmatic, approach to assessing this kind of exposure is an in-person interview. Regarding outcomes of interest there was also evidence of heterogeneity in the assessment of same. Some of the methods of assessment were of high quality as outlined above, however this was not consistent across all of the studies. For example, some of the studies reporting on fractures used self-report data and some of the studies on falls used hospital incident report data.

4.6 Areas for further research

Arising from the information found in this systematic review and ethical and legal discussion there are a number of areas where future research is indicated. Carbone et al in 2010 recommended randomised trials of AEDs looking particularly at falls and fractures (53). This is particularly relevant given the different findings for LEI AEDs versus non-LEI AEDs in the studies in the systematic review. Looking at the issue from a psychiatry standpoint, randomised trials of the AEDs used in bipolar affective disorder specifically with comparisons to atypical antipsychotic treatments from the perspective of physical health side effects may provide a more definitive answer for psychiatrists.

Randomised trials of bone protecting medicines in those using AEDs for both physical and mental illness would be the best way to assess whether making a recommendation for treatment with same is the best way to proceed. The increased risk of fracture is present in all groups using the medications and the recommendations around managing this risk should, if possible, be based on high quality evidence based on studies in all groups.

Another possibility for study is a trial of assessment of specific markers, such as vitamin D levels or bone density in those with mental illness and use of AEDs. This would be useful given the fact that some of the patients may have many more other risk factors for development of osteoporosis and osteoporotic fractures. Assessment of a particular marker may allow for selected treatment.

Mezuk et al and Nicholas et al advocated for the provision of dietary and lifestyle advice to those taking AEDs (54, 55). Observation of the impact of same on the outcome of fractures would best inform clinicians and allow for generation of a business case for service providers regarding provision of appropriate resources and personnel.

The above types of studies would allow for generation of more precise recommendations and definitions of terms used in the existing MHRA recommendations such as “long-term” and “high-risk” as they pertain to people using AEDs with comorbid mental illness.

The absence of poorer countries from the studies included was a reflection of the greater data generated by the initial search string (Appendix 1 and Flow Chart 3.1). Therefore, assessment of this important clinical issue as it pertains to those outside the United States and Western Europe is necessary so the management and treatment advice used by clinicians everywhere is appropriate to the population being treated.

4.7 Summary

Viewing the prescription of AED treatment (with risks of side effects) through an ethical and legal prism shows that constant attention to the four principles of bioethics is required, long after the initial treatment decision is made and initial prescription written. This process is structured and aided by regulatory and legal percept which have been developed over years of interaction between the legal system and complex healthcare matters. This is essential so that people are aware of the risks attendant on their treatment. Patients can then best make a decision that suits their needs and wishes.

Chapter 5 - Conclusion

5.1 Implications for policy makers

There have been no local policies in use in mental health care settings in Ireland, of which I am aware, regarding AED use and the management of risks of falls and fractures. Texts such as the Maudsley Prescribing Guidelines do not at present contain advice regarding management of bone health when prescribing mood stabilising AEDs (97). Given that this is a source often consulted by psychiatrists prior to beginning a treatment or indeed writing a repeat prescription, it would be highly beneficial to see the most up to date evidence there reflected. The policies used by the NHS have been discussed in the previous chapter. There is an urgent need to update the mental health arm of guidelines such as the NICE guidelines to reflect the risk as it pertains to all users of AEDs. The recommendations for future research, as discussed in the previous chapter, will help to inform policy makers about appropriate guidelines for monitoring and treatment of adverse effects encountered in relation to AEDs.

5.2 Other recommendations

Given that people with mental illness have poorer physical health than those without (as discussed in chapter 1) the importance of liaison between specialist mental health services and primary care services is vital. The shared management of a complex issue, like the one examined here, is best managed by close follow up with both general practitioner and psychiatry/neurology, as appropriate. Sharing of patient information is one of the best ways to do this. However other information must also be shared among medical colleagues regarding up to date information from conferences, lectures, research and Continued Professional Development activities.

5.3 Systematic review

This systematic review with its comprehensive and transparent search strategy allowed the author to identify the appropriate studies to be included. Standardised reporting guidelines were followed. As outlined in Chapter 4 further study is needed to more fully elucidate the problem, and reveal possible solutions.

5.4 Final comments

The importance of ongoing, appropriately shared research is evident from the study presented here. In order that medical practice and medical research continue to progress and develop the safeguards on research and practice in the form of regulation must be maintained, while simultaneously encouraging future research.

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Appendix 1- Search String

Search Strategy for NCBI (PubMed) from 1967 to June 2016

- #1 "Anticonvulsants" [MeSH]
- #2 "Carbamazepine" [MeSH]
- #3 "Phenobarbital" [MeSH]
- #4 "Lamotrigine" [MeSH]
- #5 "Gabapentin" [MeSH]
- #6 "Topiramate" [MeSH]
- #7 "Valproic acid" [MeSH]
- #8 "Etiracetam" [MeSH]
- #9 (OR #1-8)
- #10 (anticonvulsant* OR anticonvulsive agent* OR antiepileptic drug* OR Carbamazepine* OR Phenobarbital* OR Lamotrigine* OR Gabapentine* OR Topiramate* OR Valproic acid* OR Etiracetam*)
- #11 (#9 OR #10)
- #12 "Fractures, Bone" [Mesh]
- #13 (fracture* OR bone* broken)
- #14 (#12 OR #13)
- #15 "Osteoporosis" [Mesh]
- #16 (osteoporosis OR osteopenia)
- #17 (#15 OR #16)
- #18 "Bone Density" [Mesh]
- #19 (bone density OR bone loss OR bone mass)
- #20 (#18 OR #19)
- #21 (fall*)
- #22 (#11 AND #14)
- #23 (#11 AND #17)
- #24 (#11 AND #20)
- #25(#11 AND #21)
- #26 (#22 OR #23 OR #24 OR #25)
- #27 Humans/lim

Search Strategy for EMBASE from 1967 to June 2016

- #1 Anticonvulsants/exp
- #2 Carbamazepine/ exp
- #3 Phenobarbital/ exp
- #4 Lamotrigine/ exp
- #5 Gabapentine/ exp
- #6 Topiramate/ exp
- #7 Valproic acid/ exp
- #8 Etiracetam/ exp
- #9 (OR #1-8)
- #10 (anticonvulsant* OR anticonvulsive agent* OR antiepileptic drug* OR

Carbamazepine* OR Phenobarbital* OR Lamotrigine* OR Gabapentine* OR Topiramate*
 OR Valproic acid* OR Etiracetam*)
 #11 (#9 OR #10)
 #12 Fractures/exp
 #13 (fracture* OR bone* broken)
 #14 (#12 OR #13)
 #15 Osteoporosis/exp
 #16 (osteoporosis OR osteopenia)
 #17 (#15 OR #16)
 #18 Bone Density/
 #19 (bone density OR bone loss OR bone mass)
 #20 (#18 OR #19)
 #21 (fall).tw
 #22 (#11 AND #14)
 #23 (#11 AND #17)
 #24 (#11 AND #20)
 #25(#11 AND #21)
 #26 (#22 OR #23 OR #24 OR #25)
 #27 humans/lim

Search Strategy for ISI Web of Science from 1967 to June 2016

#1 (anticonvulsant* OR anticonvulsive agent* OR antiepileptic drug* OR
 Carbamazepine* OR Phenobarbital* OR Lamotrigine* OR Gabapentine* OR Topiramate*
 OR Valproic acid* OR Etiracetam*)/
 #2 (fracture* OR bone fracture* OR bone* broken)/
 #3 (osteoporosis OR osteopenia)/
 #4 (bone density OR bone loss OR bone mass)/
 #5 (fall*)/
 #6 (#1 AND #2)
 #7 (#1 AND #3)
 #8 (#1 AND #4)
 #9 (#1 AND #5)
 #10 (#6 OR #7 OR #8 OR #9)

Search Strategy for Cochrane Library from 1967 to June 2016

#1 "Anticonvulsants" [MeSH]
 #2 "Carbamazepine" [MeSH]
 #3 "Phenobarbital" [MeSH]
 #4 "Lamotrigine" [MeSH]
 #5 "Gabapentine" [MeSH]
 #6 "Topiramate" [MeSH]
 #7 "Valproic acid" [MeSH]
 #8 "Etiracetam" [MeSH]

#9 (OR #1-8)
 #10 (anticonvulsant* OR anticonvulsive agent* OR antiepileptic drug* OR Carbamazepine* OR Phenobarbital* OR Lamotrigine* OR Gabapentine* OR Topiramate* OR Valproic acid* OR Etiracetam*)
 #11 (#9 OR #10)
 #12 "Fractures, Bone" [Mesh]
 #13 (fracture* OR bone* broken)
 #14 (#12 OR #13)
 #15 "Osteoporosis" [Mesh]
 #16 (osteoporosis OR osteopenia)
 #17 (#15 OR #16)
 #18 "Bone Density" [Mesh]
 #19 (bone density OR bone loss OR bone mass)
 #20 (#18 OR #19)
 #21 (fall*)
 #22 (#11 AND #14)
 #23 (#11 AND #17)
 #24 (#11 AND #20)
 #25(#11 AND #21)
 #26 (#22 OR #23 OR #24 OR #25)

Search Strategy for PsychInfo from 1967 to June 2016

#1 "Anticonvulsants" [MeSH]
 #2 "Carbamazepine" [MeSH]
 #3 "Phenobarbital" [MeSH]
 #4 "Lamotrigine" [MeSH]
 #5 "Gabapentine" [MeSH]
 #6 "Topiramate" [MeSH]
 #7 "Valproic acid" [MeSH]
 #8 "Etiracetam" [MeSH]
 #9 (OR #1-8)
 #10 (anticonvulsant* OR anticonvulsive agent* OR antiepileptic drug* OR Carbamazepine* OR Phenobarbital* OR Lamotrigine* OR Gabapentine* OR Topiramate* OR Valproic acid* OR Etiracetam*)
 #11 (#9 OR #10)
 #12 "Fractures, Bone" [Mesh]
 #13 (fracture* OR bone* broken)
 #14 (#12 OR #13)
 #15 "Osteoporosis" [Mesh]
 #16 (osteoporosis OR osteopenia)
 #17 (#15 OR #16)
 #18 "Bone Density" [Mesh]
 #19 (bone density OR bone loss OR bone mass)
 #20 (#18 OR #19)
 #21 (fall*)

#22 (#11 AND #14)
#23 (#11 AND #17)
#24 (#11 AND #20)
#25(#11 AND #21)
#26 (#22 OR #23 OR #24 OR #25)

Data Extraction tool

Title:

Author:

Year:

Country of research team:

Study design:

Population:

Age:

Gender ratio:

Race/ethnicity:

Follow up year:

Outcome definition:

Exposure definition:

Effect estimates with 95% Cis and variables adjusted for: