ANTIEPILEPTIC DRUGS IN PREGNANCY

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SHUK-LI COLLINGS

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Declaration

‘I, Shuk-Li Collings, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.’

Signed _____

Dedication

‘I dedicate this thesis to my husband, Steven Collings, who has shown selfless support throughout this journey.’

Abstract

Background

Antiepileptic drugs are prescribed for chronic conditions such as epilepsy and bipolar disorder. Without adequate management, such conditions can have detrimental effects in pregnancy. However, first trimester use of some antiepileptic drugs is associated with a two-threefold increase in the risk of major congenital malformations. When women and their health care professionals consider treatment regimens, quantified relative risks can help decide which drug, if any, would be taken during pregnancy.

Methods

Three studies were performed using UK primary care data from The Health Improvement Network (THIN). Prescribing patterns of antiepileptic drugs in pregnancy were examined. A validation study for recording of major congenital malformations and perinatal death was performed. Lastly, a cohort study of pregnant women prescribed antiepileptic drugs prior to pregnancy was conducted to examine the risk of major congenital malformations or perinatal death in different first trimester antiepileptic drugs regimens.

Results

One in 200 women were prescribed antiepileptic drugs in pregnancy. Carbamazepine, sodium valproate and lamotrigine were the most commonly used antiepileptic drugs in pregnancy between 1994 and 2012.

In this period, 353,171 pregnancies were identified in THIN. The incidence of major congenital malformations was 1.9% and perinatal death was 0.4%.

Amongst 1,633 pregnant women regularly prescribed antiepileptic drugs before pregnancy, there were 54 cases of major congenital malformations and perinatal deaths (3.3%, 95% CI 2.5-4.3%). The risk amongst women prescribed sodium valproate polytherapy was 12% (95% CI 5.9-21.0%) - significantly greater than those prescribed carbamazepine monotherapy (IRR 2.72, 95% CI 1.23-5.99),

sodium valproate monotherapy (IRR 3.42, 95% CI 1.35-8.66) and lamotrigine monotherapy (IRR 5.03, 95% CI 1.99-12.74).

Conclusions

Women taking sodium valproate polytherapy face a greater risk of major congenital malformations or perinatal death compared to other common monotherapy regimens. Further research is needed to corroborate these findings, however women and their physicians should aim to avoid sodium valproate polytherapy if possible.

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Chapter 1

Background and Literature Review

1.1. Aim of the chapter

The aim of this chapter is to provide a rationale for the main study presented in this thesis. In this chapter I give the background to antiepileptic drugs, their uses and why there are concerns over the safety of their use in pregnancy. Further to this I review of the current literature up to the point when I started my PhD (October 2010) on antiepileptic drugs in pregnancy and risk of major congenital malformations.

1.2. Introduction

In 1957, the pharmaceutical company Chemie-Grunenthal launched an over-the-counter drug to the German market. The drug was a 'wonder' drug which claimed to alleviate a number of problems including morning sickness in pregnant women and, remarkably, this drug appeared safe and tolerable for pregnant women to take. Its rapid success led to worldwide distribution. But over the next five years one of the greatest medical tragedies was unfolded. Early estimates suggested that 40% of babies whose mothers had taken this drug whilst they were pregnant did not survive birth.[1] Of around 10,000 survivors, many were born with major congenital malformations - notably severe deformities of the limbs - and only 3,000 remain alive today. The drug which caused this was thalidomide.

Lessons were learned from the thalidomide scandal, however nearly 60 years later, we are still unable to know for certain whether or not a drug is harmful in pregnancy before it is marketed. Instead, it is increased testing, post-marketing surveillance and reporting of adverse drug reactions, which has led to around 30 drugs being identified as teratogenic – that is, the drug (known as the teratogen) is known to cause congenital malformations when taken in pregnancy.[2]

In the United Kingdom (UK), the background risk (the average risk in any pregnancy) of major congenital malformations (also known as birth defects,

congenital abnormalities or anomalies) in the general population is between 1 and 3%, of which only 2-5% is estimated to be caused by drugs.[3] Thalidomide increased the risk of major congenital malformations to a startling 20-30%; most other drug teratogens increase the risk by much less.[2] Certain older antiepileptic drugs are associated with two- to three-fold increase in the risk of major congenital malformations.[4;5] One older antiepileptic drug in particular, sodium valproate, is strongly linked with major congenital malformations and reduced childhood development.[6] Newer, or second generation, antiepileptic drugs have emerged in the last 20 years, but with the exception of one popular antiepileptic drug, lamotrigine, little research on their teratogenic effects has been conducted.

1.3. Prescribing drugs in pregnancy

Many women are prescribed drugs in pregnancy. Studies have found at least 45%, and as many as 95% of pregnant women receive one or more prescriptions during pregnancy, and on average a woman will receive three prescriptions over the course of pregnancy.[7;8] However, the decision to prescribe a drug to a pregnant woman can be a difficult one for both the woman and health care professionals. Most pregnant women understand the background risk of malformations is below 5% but many overestimate the teratogenic risk of taking drugs in pregnancy and have chosen not to take a drug because of this reason.[9] A small study of 36 women taking antidepressants or benzodiazepines found over 90% stopped when they realised they were pregnant, and 78% had been advised to stop by their general practitioner. Moreover, 70% reported physical and psychological effects in pregnancy, which potentially may have been prevented by drugs leaving one questioning whether or discontinuation itself caused more harm than good.[10]

Health care professionals are thus required to keep abreast of guidelines and research on the safe use of drugs in pregnancy, understanding not just the risk but also the benefits of maintaining therapy and thus the woman's health in pregnancy. This is especially relevant for managing women taking antiepileptic drugs. A particular antiepileptic drug mentioned earlier, sodium valproate, has been frequently linked to increased risks of major congenital malformations - evidence of teratogenicity has also been observed for some other antiepileptic

drugs, albeit to a lesser extent than sodium valproate.[6;11-20] However, antiepileptic drugs are usually taken regularly and for the long term to treat epilepsy, and more recently to treat the severe mental illness, bipolar disorder. Ceasing antiepileptic drug treatment due to concerns over the teratogenic risk must be considered alongside the benefits of managing the underlying condition. Poorly controlled epilepsy can result in seizures which themselves may harm the foetus, or the foetus may be at risk indirectly through falling from a seizure. Detrimental risks are also associated inadequately managed bipolar disorder.[21;22] Whilst alternative medication exist for bipolar disorder in terms of antipsychotics and antidepressants, none exists for epilepsy.

1.3.1. Antiepileptic drug prescribing in pregnancy

Advice on how to treat pregnant women with epilepsy and bipolar disorder can be found in the clinical guidelines from the National Institute for Health and Clinical Excellence (NICE). They advise pre-pregnancy planning involving individual assessment of the woman, her illness, treatment regimen, and lifestyle options.[23;24] Women must be made aware of the risks associated with antiepileptic drugs in pregnancy, as well as the benefits. For women with epilepsy, there is little advice on drug specific risks – the exception being sodium valproate where they specifically state that doses higher than 800mg/day or prescribed in polytherapy, further increases the risk of major congenital malformations. Furthermore, the guidelines note that there are limited data in relation to newer antiepileptic drugs and that seizure freedom should be aimed for but balanced with the teratogenic risks. In contrast, the guidance for managing bipolar disorder specifically advises against the use of sodium valproate, carbamazepine and lamotrigine in pregnancy for risk of harm to the foetus.[24] The British National Formulary (BNF), a reference for prescribing and pharmacology for health care professionals in the UK, goes further to specifically state phenytoin, primidone, phenobarbital, lamotrigine, carbamazepine and topiramate are associated with increased teratogenicity.[25] The BNF acknowledges that some women may be able to stop treatment before falling pregnant, but only if their condition allows. However, for unplanned pregnancies, they do not recommend stopping or changing treatment as the risk of harm to the mother and foetus from convulsive seizures outweighs the risk of continued therapy. These guidelines

from NICE and the BNF are exactly that – only guidance – each woman must be treated as an individual due to the heterogeneous nature of the underlying condition, particularly so with the epilepsies and bipolar disorder.

Many women are prescribed drugs in pregnancy, but both women and their health care providers have stated a need for more consistent information on the risks and benefits of their use during pregnancy.[9;26] There is even greater need for this information for antiepileptic drugs because some older drugs are teratogenic, newer drugs have been introduced but not thoroughly examined for teratogenicity, and because stopping treatment altogether is not an option for the large majority of women.

1.4. Background

1.4.1. Pregnancy and foetal development

From conception, a full term pregnancy lasts on average 38 weeks. The first 17 days post conception are the pre-embryonic phase where if the embryo is exposed to harm, it will result in either early pregnancy loss or powerful regulatory properties of the developing embryo will protect it. Major congenital malformations do not result from exposure to harmful agents during this period. However, week three to eight are the most vulnerable period for the developing embryo, which at this stage is in the embryonic phase. In this time, many of the organs are being defined and are highly sensitive to insult – once cells are damaged, they are unlikely to be replaced, resulting in major congenital malformations. This period of organ formation is called organogenesis. Each organ system has a specific critical period of development, for example, the heart forms between weeks three and eight, the most sensitive time being week three to six, whereas the central nervous system is developed over the entire pregnancy, but is most sensitive between weeks three and seven.[27] This understanding of the critical timeline of foetal development allows us to identify a time period in which a drug may cause specific deficits. For example, research conducted after the effects of thalidomide had unfolded found that it was only a risk for major congenital malformations if the drug was taken between the 20th and 36th day post conception and the commonly observed limb defects were a result of the exposure between the 24th and 31st day.[28;29]

The period of organogenesis falls across the first trimester (the first three months of pregnancy), hence much advice surrounding the prescribing of drugs to pregnant women is to avoid first trimester exposures if possible and safe. The foetal phase begins from week nine onwards as the organs are growing and maturing. Although major congenital malformations are less likely to occur in this time since the organs have now formed, the foetus is still vulnerable to teratogens which may affect the functioning of the organs, or cause minor malformations.[27]

1.4.2. Antiepileptic drugs

There are over 20 antiepileptic drugs available on the market in the UK and they are generally classified into two groups – older and newer. Phenytoin and phenobarbital were some of the earliest antiepileptic drugs and have been popular choices of treatment in the past but carry unfavourable side effects. Later, sodium valproate and carbamazepine were introduced and remain drugs of choice for particular kinds of seizures in epilepsy (focal and generalised seizures, respectively),[30] - they were later also found to be effective in treating bipolar disorder. Phenytoin, phenobarbital, sodium valproate and carbamazepine are thus considered as older antiepileptic drugs. Few drugs were introduced in the 20 years that followed until 1991 which marked the release of lamotrigine, a drug popular for treating focal seizures in epilepsy.[23;30] A further influx of another 10 antiepileptic drugs has included levetiracetam, gabapentin, pregabalin and topiramate. These 11 antiepileptic drugs are commonly referred to as the "newer" antiepileptic drugs.

The vast majority of people taking antiepileptic drugs in the UK will be for the treatment of epilepsy which is the primary indication for these drugs. Bipolar disorder, acute depression, acute mania, and other conditions including insomnia and pain, can also be treated with antiepileptic drugs. These are discussed in more detail later in this chapter.

The exact choice of treatment depends not only on symptoms of the underlying condition, but also takes into account the individual's lifestyle and preferences (such as how often is practical for individuals to take their medicines), co-

medication, co-morbidity, and tolerance of side effects. Side effects in particular can vary greatly between drugs and from one person to the next – Table 1 describes some of the common ones associated with each antiepileptic drug. These can range from mild effects on nausea to serious problems in mood and weight control which can affect ones daily life, however newer antiepileptic drugs are considered to be more tolerable than older antiepileptic drugs. This can be further complicated if polytherapy is needed – this is where more than one drug is used to treat the condition. A drug prescribed on its own (monotherapy) is preferable to prescribing polytherapy which can lead to toxicity and drug interactions. [31]

Table 1 Antiepileptic drugs in the UK, indications and potential side effects[30]

Generic name	Brand names	Conditions other than epilepsy	Side effects
Acetazolamide	Diamox		Nausea, vomiting, pins and needles/tingling when used in high doses
Carbamazepine	Tegretol	Bipolar disorder, trigeminal neuralgia	Nausea, vomiting, dizziness, drowsiness, headache, unsteadiness, confusion, blurred or double vision, rash, low white blood cell count
Clobazam	Frisium		Drowsiness, confusion, unsteadiness
Clonazepam	Rivotril		Drowsiness, confusion, unsteadiness
Eslicarbazepine acetate*	Zebinix		Gastro-intestinal disturbances, dizziness, drowsiness, headache, impaired coordination, tremor, visual disturbances, fatigue, rash
Ethosuximide	Emeside, Zarontin		Nausea, vomiting, headache, diarrhoea, abdominal pain, reduced appetite
Gabapentin*	Neurontin	Neuropathic pain, trigeminal neuralgia	Drowsiness, lethargy, nausea, weight gain
Lacosamide*	Vimpat		Nausea, vomiting, constipation, flatulence, dizziness, headache, impaired coordination, cognitive disorder, drowsiness, tremor, depression, fatigue, abnormal gait, blurred vision, nystagmus, pruritus
Lamotrigine*	Lamictal	Trigeminal neuralgia	Rash and other allergic reactions, liver dysfunctions, nausea, vomiting, headache, fatigue, dizziness, sleep disturbances, tremor, agitation, confusion
Levetiracetam*	Keppra		Nausea, vomiting, indigestion weight changes, drowsiness, unsteadiness and dizziness, emotional liability, insomnia, anxiety, aggression and irritability

Generic name	Brand names	Conditions other than epilepsy	Side effects
Oxcarbazepine*	Trileptal	Trigeminal neuralgia	Nausea, vomiting, constipation, diarrhoea, abdominal pain, dizziness, headache, drowsiness, agitation, unsteadiness, confusion, impaired concentration, rash, double or blurred vision
Phenobarbital	N/A		Liver dysfunction, jaundice, behavioural disturbances, irritability, drowsiness, lethargy, depression, unsteadiness, impaired memory, rash
Phenytoin	Epanutin	Trigeminal neuralgia	Nausea, vomiting, constipation, insomnia, dizziness, headache, gum swelling, rash, acne, facial hair, coarsening of facial features
Pregabalin*	Lyrica	Neuropathic pain	Dry mouth, constipation, nausea, vomiting, dizziness, drowsiness, irritability, reduced memory and concentration, fatigue, weight gain
Primidone	Mysoline	Benign essential tremors	Liver dysfunction, jaundice, behavioural disturbances, irritability, drowsiness, lethargy, depression, unsteadiness, impaired memory, rash
Rufinamide*	Inovelon		Drowsiness, dizziness, headache
Sodium valproate	Epilim Epilim Chrono Epilim Chronosphere Episenta	Migraine, bipolar disorder (valproic acid)	Nausea, gastric irritation, diarrhoea, weight gain, hyperammonaemia, thrombocytopenia, transient hair loss
Tiagabine*	Gabitril		Diarrhoea, dizziness, tiredness, nervousness, tremor, impaired concentration, emotional liability, speech impairment
Topiramate*	Topamax	Migraine	Nausea, abdominal pain, weight loss, headache, fatigue, dizziness, speech difficulty, reduced concentration and memory, anxiety, depression
Vigabatrin	Sabril		Increased appetite, irritability, visual field constriction(possibly irreversible)

Generic name	Brand names	Conditions other than epilepsy	Side effects
Zonisamide*	Zonegran		Nausea, diarrhoea, abdominal pain, reduced appetite, weight loss, drowsiness, dizziness, confusion, agitation, irritability, depression, unsteadiness, impaired memory and attention, double vision and rash

**Newer antiepileptic drugs*

Antiepileptic drugs also have several drug interactions that need to be considered when choosing a treatment regimen:

- carbamazepine, phenytoin, phenobarbital, topiramate and rufinamide interfere with the oral contraceptive pill
- the combined oral contraceptive pill interferes with lamotrigine
- sodium valproate taken with aspirin can lead to excessive bleeding after a cut
- theophylline, a drug taken for asthma, interferes with carbamazepine
- some antibiotics interact with some antiepileptic drugs.[30]

A person who is well-established on treatment and has successfully managed their underlying condition may, in the future, consider withdrawing from medication. Withdrawal from antiepileptic drugs is, like the introduction of a new drug, a gradual process and evidence on whether or not there is an improved quality of life is conflicting.[32;33]

Antiepileptic drugs are essential for many people with epilepsy, bipolar disorder and pain related conditions. The process by which drugs are chosen is not straightforward and varies greatly between individuals to meet the demands on their practical circumstances and their tolerance to side effects. It is a fine balance of effectiveness and management for the individual which highlights the need of a health care professional to advise, monitor and review the treatment regimen as and when is needed.

1.4.3. Indications for antiepileptic drugs

A number of conditions can be treated with antiepileptic drugs, mostly neurological including epilepsy, migraine and neuropathic pain, and some mental health disorders namely bipolar disorder, but also depression and anxiety. Described here are epilepsy – the main indication for antiepileptic drugs – and bipolar disorder, a severe mental illness where antiepileptic drugs have been increasingly prescribed.[34]

Epilepsy

Epilepsy is the most common neurological condition affecting 3-4% of the population by the age of 75.[30] It is characterised by frequent, often unprovoked, seizures caused by abnormal, sudden excess electrical discharges of nerve cells in the brain. These discharges vary in their origin in the brain and the way they spread, resulting in differences in the way they are externally observed. These variations form epilepsy syndromes, or epilepsies, which differ in the antiepileptic drugs used to treat them. These epilepsies are commonly unified and referred to as epilepsy.

The majority of people diagnosed with epilepsy use antiepileptic drugs to manage their seizures, which is successful at stopping seizures for approximately 60% of users.[30] Other interventions include surgery and a ketogenic diet, however, there is no cure. The long term prognosis is a higher risk of death, estimated to be threefold that of an age-matched general population.[35-37] Most deaths are, however, from causes unrelated to epilepsy.[37] There is a risk of sudden death from epilepsy but this is rare affecting less than one percent of those with epilepsy.[38]

In pregnancy, the great majority of women with epilepsy have healthy, normal births.[23;30] There are however some elevated risks - the risk of maternal death is approximately ten times than that of the general population and the risk of complications in pregnancy and labour are also higher.[5;21;23] Women with epilepsy also need closer monitoring throughout pregnancy due to altered clearance of antiepileptic drugs in the blood, thus doses may need to be increased to ensure seizure freedom is maintained. Certain seizures, if they do occur in pregnancy (generalised tonic-clonic seizures) carry a risk of harm to the unborn foetus during the seizure, but the absolute risk is still low.[23]

Bipolar disorder

Bipolar disorder is a mood disorder characterised by extreme changes in mood from intense mania to deep depression, and sometimes a “mixed” state of mania and depression. It is a chronic and lifelong condition which can have a devastating impact on one’s personal, work and social life and is associated with a greater risk of

suicide.[39] In the UK, it is estimated to affect around 1-2% of adults in their lifetime.[40] Its cause is still unknown. In some cases it is triggered by a major event in one's life such as childbirth, a major birthday or the wedding of a close friend or relative, and in others there are familial links.[41] The diagnosis of bipolar disorder is set out in the Diagnostic and Statistical Manual (DSM-IV),[42] which defines four types of bipolar disorder - bipolar I, bipolar II, cyclothymia and bipolar not otherwise specified. Each type has a pattern of episodes of major depression, mania, hypomania or mixed states.

Drug treatment is used to reduce the severity of symptoms, stabilise the mood and prevent a relapse. Lithium (not an antiepileptic drug) is the only drug licensed for the prophylaxis of bipolar disorder, however antiepileptic drugs (sodium valproate, lamotrigine and carbamazepine) have also been used. Some antipsychotics and valproic acid (a form of sodium valproate) are licensed for treating acute manic episodes and antidepressants are used for treating depressive episodes.[24] Psychotherapy is also available as a non-pharmacological intervention. This includes cognitive behavioural therapy and family focussed treatment. However, it is unclear as to the effectiveness of these types of treatment alone as opposed to in conjunction with medication.[43-45] Management of the illness can therefore be tricky and effective pharmacological intervention can highly depend on current mood episode.

Treatment and management provide control of mood but the prognosis is poor – 50% of episodes last on average for three months, full recovery is rare and the risk of death and in particular, suicide, are high as are other co-morbid conditions including alcohol and drug abuse and other psychiatric disorders, namely anxiety disorders, schizophrenia and personality disorders.[24;39;46;46-50]

Pregnant women with bipolar disorder face a similar dilemma to pregnant women with epilepsy – the decision over whether or not to continue antiepileptic drug use in pregnancy requires weighing up the risks of the drugs to the foetus and benefits of being stable. As mentioned earlier, bipolar disorder can be treated with other

antidepressants and antipsychotics, which have a more favourable safety profile in pregnancy, but whether or not these alternative adequately manage one's bipolar disorder comes down to the individual. The need for women with bipolar disorder to remain stable in pregnancy is compounded by the general increased risk of relapse of a mood episode during pregnancy,[51] and the increased risk of postpartum psychosis after birth – an acute, sudden psychotic episode usually in the first few weeks after birth which can lead to high mania, depression, confusion, delusions and hallucinations.[22;52;53]

There are clear clinical differences between epilepsy and bipolar disorder, however they are similar in that:

- drugs are the main stay treatment;
- they are lifelong conditions;
- there are elevated risks associated with pregnancy;
- there can be detrimental maternal and foetal outcomes associated with poor management of the condition in pregnancy.

Thus, the research in this thesis is aimed at these women who rely on antiepileptic drugs to maintain their health and who have to consider how pregnancy affects the management of their condition.

Having described some of the background to the exposure of interest in this thesis – antiepileptic drugs during pregnancy - the next section gives an overview of the primary outcome of interest – major congenital malformations.

1.4.4. Major congenital malformations

Major congenital malformations are structural abnormalities, present at birth, which lead to severe physical disability or functional impairment resulting in medical treatment, care, surgery or death.[27] They are also commonly referred to as major congenital abnormalities, anomalies, or birth defects. The latter term can be misleading – major congenital malformations are a result of structural changes which have occurred *during* pregnancy, and are *present* at birth – they are not defects of birth, which is how "birth defects" is sometimes interpreted. The majority of major

congenital malformations will be obvious at birth though it is possible for some to be unnoticed until later in life. An example of a major congenital malformation is *spina bifida* which is the abnormal development of the neural tube (the tube which eventually becomes the spine and spinal cord). Usually, spina bifida requires surgery and long term therapy to improve the quality of life.

It is important to distinguish major and minor congenital malformations – minor malformations are also structural abnormalities but, as the name suggests, they are minor and are less likely to affect one's life and furthermore, may not need any correction. Such examples include birthmarks and slight curvature of fingers or toes (clinodactyly).

The prevalence of major congenital malformations amongst all births in the general population is low – between 1 and 3%. However, they are a leading cause of infant mortality contributing to 20% of deaths in infancy.[54] There are thousands of different types, many with multiple causes and over 50% with unknown causes.[3] Several factors can contribute to causing congenital malformations – but it is estimated that only 2-5% are caused by medication, such as antiepileptic drugs.[3] Other factors include genetic mutations, infections, maternal diet and other teratogenic agents such as alcohol and certain chemicals.

In the UK, pregnant women are screened for congenital abnormalities at around 20 weeks gestation. At this point, many major structural abnormalities, which developed in the first trimester, should be detected by ultrasound scan. Further imaging and possibly other techniques such as sampling the amniotic fluid can help to diagnose a major congenital malformation prenatally. This provides women and their partners valuable information on the implications of the diagnosis in the future care of the child, in some cases whether or not to continue the pregnancy.

Antiepileptic drug exposure in pregnancy and major congenital malformations have long been researched. In the 60s, the first questions were raised about antiepileptic drugs and major congenital malformations following case reports of cleft lip and

palate in children born to women with epilepsy.[55] Then, in 1967, it was recognised that antiepileptic drugs could pass across the placenta after phenobarbital was found in human umbilical cord serum at 95% concentration of that in maternal serum.[56] Much research followed on investigating the link with epilepsy and the link with the antiepileptic drugs themselves. It soon became clear that there were key antiepileptic drugs which were associated with structural abnormalities observed at birth, prompting syndromes of common features to be defined. An example is the foetal hydantoin syndrome which is found in babies exposed to the antiepileptic drug phenytoin *in utero*. The features of the syndrome include growth deficiencies such as being small at birth, abnormalities of the skull or facial features – notably flat nasal bridge, eyes slanted downwards, spaced widely apart and crossed – and as well as the structural abnormalities, mild developmental delays.[57;58]

Sodium valproate is an antiepileptic drug which was licensed for use in 1978. It is commonly prescribed for different epilepsies either on its own or with other antiepileptic drugs. Concerns over its use in pregnancy emerged soon after it was licensed in around 1980 and since then several outcomes have been associated with prenatal exposure including the foetal valproate syndrome which describes a pattern of mainly facial malformations, delays in childhood development and notably a specific malformation, neural tube defects – abnormalities of the neural tube which includes the aforementioned *spina bifida*.[59] Compared to other antiepileptic drugs, the research in this area has been consistent and evident enough for recommendations against it use in pregnancy to be made in clinical practice.[31]

For other antiepileptic drugs, the effects, if any, are less understood – evidence is lacking, sparse or inconsistent. Some common malformations have been identified including heart defects, cleft lip and palate and midline facial deformities.

Exactly how antiepileptic drugs cause congenital malformations is not known for certain. Animal studies have been performed and several theories have been postulated which centre on interference with critical development of the foetus. For example, Bittigau *et al* found antiepileptic drugs used on foetal rats caused apoptotic

neurodegeneration – cell death – of the developing brain.[60] More recently Hernandez-Diaz *et al* suggested that the mechanism, by which antiepileptic drugs attain seizure control in epilepsy, can interfere with controlled regulatory mechanisms vital for cued processes to occur in foetal development.[61] Similar theories related to an interference of foetal development also exist.[62]

Major congenital malformations are rare; however, they can have a heavy burden on the parents of a child with a malformation at a time in life which is already challenging. Technology allows some diagnoses to be made before the child is born, somewhat preparing the parents, however identifying causes and preventing malformations occurring can protect parents from making such difficult decisions on their child's future. One potential cause is antiepileptic drugs, and although the elevated risks of one particular antiepileptic drug have been established, there is little guidance on the use of other antiepileptic drugs leaving women in a dilemma over how to weigh up the risks and benefits of continuing antiepileptic medication throughout pregnancy.

1.5. Literature review

1.5.1. Aim

In the next section a systematic review of the literature is presented which aims to collate the current research findings (up to October 2010) on the effect of antiepileptic drugs on the risk of major congenital malformations and to highlight areas where research is lacking and thus inform my research for this PhD.

1.5.2. Hypotheses

1) The use of antiepileptic drugs in the first trimester of pregnancy significantly increases the risk of major congenital malformations.
2) These risks differ between antiepileptic drugs with sodium valproate bearing the highest risk.

1.5.3. Methods

In 2009, the American Academy of Neurology and American Epilepsy Society published a systematic review of the teratogenicity of antiepileptic drugs in order to inform a practice parameter guideline advising health care professionals on the treatment of pregnant women.[63] To avoid duplication of research, I performed a literature review covering the period since this published review. Thus, the published review examines literature published prior to January 2007 and my updated literature review examines articles from January 2007 to October 2010. The method used for the updated literature search is described next.

Updated literature search

Searches of published articles were carried out using electronic journal databases PubMed, EMBASE and Web of Science - the latter database also providing conference abstracts. The search consisted of synonyms and combinations of words used to describe the following: mother, baby, antiepileptic drugs, and congenital malformations. The time period for this search was January 2007 to October 2010. Literature was restricted to human studies and those available in English. The search strategy in PubMed is supplied in Appendix 1. Similar search strategies were used in EMBASE and Web of Science. Conference abstracts, review articles and references of journal articles were perused for any further articles not identified in the search.

Inclusion and exclusion

All identified articles were downloaded to Reference Manager and sifted for duplicates. There were two stages of review which followed, based on a set of inclusion and exclusion criteria which are listed in the Table 2 overleaf. Titles and abstracts were reviewed first, and those which fulfilled the criteria then had the full text reviewed.

Table 2 Inclusion and exclusion criteria for article selection for systematic review

	Inclusion	Exclusion
Population	Women with clinical indication for antiepileptic drugs (e.g. epilepsy, bipolar disorder)	

Comparisons groups of interest	Eight specific comparisons of interest were:
	- Compared to women who did NOT take antiepileptic drugs in the first trimester of pregnancy:
	  o Any monotherapy
	  o Any polytherapy
	  o Carbamazepine monotherapy
	  o Sodium valproate monotherapy
	  o Lamotrigine monotherapy
	- Pairwise comparisons of three common monotherapies - sodium valproate, carbamazepine and lamotrigine - giving the following comparisons:
	  o Carbamazepine monotherapy vs. sodium valproate monotherapy
	  o Carbamazepine monotherapy vs. lamotrigine monotherapy
	  o Sodium valproate monotherapy vs. lamotrigine monotherapy
		- No comparison group
		- Other antiepileptic drug regimens

Outcome	Major congenital malformations	Minor congenital malformations
Type of study	Case-control, cohort, randomised controlled trials	
Other	Human English language	

Analyses

It was made clear reading the published review by the American Academy of Neurology and American Epilepsy Society that the degree of heterogeneity amongst previous studies prevented a useful meta-analysis.[63] The studies varied greatly in their populations, exposures and outcome measures and types therefore descriptive accounts of groups of comparable studies are given, which was the same approach used previously.[63]

In the next section, I present the results of both reviews. Firstly, a summary of the characteristics of each review is given. Secondly, results are grouped between the two reviews according to the pairwise exposures being compared, as listed in Table 2 and described.

1.5.2. Results

Overview of the systematic review in the report of the Quality Standards Subcommittee (QSS) and Therapeutics and Technology Assessment (TTA) Subcommittee of the American Academy of Neurology (AAN) and American Epilepsy Society (AES)

In 1998, a group of experts in the US published on various issues related to managing women with epilepsy aimed at the health care professional.[64] Ten years later, another panel of experts in epilepsy were brought together to reassess the literature to date and consequently, three “practice parameter” updates were published and offered to health care professionals. Each one had a different focus – obstetrical complications and changes to seizure frequency;[65] vitamin K, folic acid, blood levels, and breastfeeding;[66] and teratogenesis and perinatal outcomes.[63] Discussed here is the latter report on antiepileptic drug teratogenesis and perinatal outcomes. This practice parameter update was based on a systematic review which addressed a number of questions, however in this thesis I will focus on aspects of the review relating to the risk of major congenital malformations associated with *in utero* antiepileptic drug exposure.

Their search strategy was similar to that I adopted for the updated literature review. The review was based on research published between 1985 and 2007. They supplemented their search by interrogating other reviews for missed references. The filtering and review process involved two panel members performing initial screening and four panel members reviewing full-text articles for relevance. Identified articles were categorised into classes dependent on their risk of bias using criteria developed by the American Academy of Neurology which assesses studies for evidence of causality particularly in situations where clinical trials are not practical. Evidence was classed from I to IV, with Class I representing optimal study designs for causal inference including requirements such as prospective, representative, comparison groups matched for confounders, defined and validated risk factors and outcomes. Class IV on the other hand represented poor quality – non-comparative, unrepresentative, major biases etc. Only studies which achieved Class III rating or above were included in their review. Studies were only classified as class I and II if they accounted for confounding.

The outcome sought in their review was major congenital malformations which were defined as structural anomalies with surgical, medical or cosmetic importance. The exposure was restricted to the first trimester, which is the period of organ formation and a vulnerable time for the growing foetus. The control group was restricted to women with untreated epilepsy to account for possible effects of epilepsy.

In total, only nine studies were identified. Four studies were classified as Class III,[15;18;67;68] three as Class II,[4;11;69] and two Class I.[17;20] Six studies were prospective,[15;17;18;20;67;68] most of them from early pregnancy when women were taking antiepileptic drugs in the first trimester. The remaining studies were retrospective and based on medical records – one study was prospective in terms of outcome but women were enrolled in labour or delivery therefore retrospective in terms of exposure.[4] Settings were varied – three from pregnancy registries,[17;18;68] two from epilepsy centres,[15;67] one from hospital,[4] and the remaining through medical records.[11;20;69]

Six studies had a sample size of over 1,000 pregnant women.[4;11;17;20;68;69] There were 333 women in another study,[15] 565 women in a further study[18] and one study did not provide this information.[67] The number of children with exposure to a specific monotherapy was over 100 in all but one study.[4] Five studies included children born to women with epilepsy who were untreated during pregnancy – one study had less than 50 children,[67] whilst more recent studies were larger yielding sample sizes of 235,[17] 606[4] and 939[11] pregnancies with no treatment in the first trimester and one study with over 1000.[69] The remaining four studies only made pair-wise comparisons between specific monotherapies.

All studies separated antiepileptic drug treatment as monotherapy and polytherapy as well as providing information on rates of major congenital malformations according to a specific monotherapy exposure, the most common form of monotherapy being carbamazepine.

Outcome definitions were slightly varied. Two studies grouped together major and minor congenital malformations,[11;67] and a further two studies reported on serious adverse outcomes which comprised major congenital malformations or foetal death.[4;15] Some studies did not give a definition,[18;20] and of those which did, four specified a time period during which major congenital malformations were defined – two studies measured major congenital malformations which were detected within the first six weeks since birth,[17;69] whilst the other two studies used five days as the cut-off.[67;68] Three studies further classified major congenital malformations by the affected organ system.[11;15;17]

Two studies only included pregnancies which ended in live birth,[11;20] three had the potential to record other pregnancy outcomes but did not describe any other than live born babies,[4;15;17] whilst the rest of the studies described alternative pregnancy outcomes such as still birth, spontaneous abortions and elective abortions. Results of prenatal screening after enrolment were captured in four studies.[15;17;67;69]

The authors of the review looked at the research question in two parts – 1) do antiepileptic drugs taken in the first trimester of pregnancy increase the risk of major congenital malformations in the offspring of women with epilepsy compared to the offspring of women with epilepsy not on antiepileptic drugs? 2) Is exposure to a specific antiepileptic drug during the first trimester of pregnancy associated with an increased risk of major congenital malformations compared to exposure to other antiepileptic drugs (i.e. pair-wise comparisons)? In Part 1) they examined antiepileptic drugs in general as well as specific antiepileptic drugs sodium valproate, carbamazepine and lamotrigine and concluded possible increased risks associated with sodium valproate monotherapy and probable increased risks with sodium valproate polytherapy and carbamazepine, however there was insufficient data on lamotrigine to make any conclusions. In Part 2) sodium valproate was compared with carbamazepine, lamotrigine and phenytoin monotherapy. Sodium valproate was concluded as being very likely to be related to major congenital malformations in comparison with carbamazepine, and possibly contributory to the development of major congenital malformations in comparison with phenytoin and lamotrigine monotherapy.

The overall conclusions of their review were limited by the small number of studies which were eligible for inclusion. The recommendations were generally around avoidance of sodium valproate in the first trimester, if possible.

Overview of updated literature search

The search strategy detailed in the methods section of this current review was used to identify the literature in this area which was available since 2007. After removal of duplicates, 57 articles were identified from electronic journal databases and screened for meeting the inclusion and exclusion criteria set out in Table 2. An additional inclusion criterion was used in that the exposure had to be during the first trimester. On review of the title and abstracts, 11 were retained and had their full text reviewed. One study did not have a comparison group,[70] another did not report risks in the comparison group,[71] two compared to the general population instead of to offspring of women with epilepsy[72;73] and one did not report adequately on the risks

in the exposed population.[74] There were two conference abstracts from the UK and Ireland Epilepsy and Pregnancy Register study group which were updates from the material published in 2006,[17;75;76] and is covered in the AAN review. Since both abstracts reported on the same cohort I took the latest abstract which contained the most up to date data.[75] Five articles therefore remained which are included in this current review of the literature since 2007 to 2010.

Of the five studies, there were five independent cohorts. Participants were enrolled through pregnancy registers in three studies including the Kerala Registry of Epilepsy and Pregnancy and the Australian Pregnancy Registry.[19;75;77] One study was based on medical records[78] and one from the prospective LMNDG cohort.[5] Four cohorts were prospectively followed.[5;19;75;77;79]

All studies included more than 200 pregnancies, and three of which contained over 1000.[19;75;78] Only one study did not report specific antiepileptic drug monotherapy risks,[78] but of those which did, carbamazepine was generally the most popular and numbers varied from 74 to 302.[5;19] One study examined exposure to one antiepileptic, lamotrigine.[19] The conference abstract on the UK Epilepsy and Pregnancy Register did not quote the number of children exposed sizes, but made pair-wise comparisons of antiepileptic drugs and reported the relative risks.[75] Effects of any monotherapy were reported in three studies[5;75;77] and effects of polytherapy in four studies.[5;75;77;78] Children born to women with untreated epilepsy was used as a comparison group in four studies,[5;19;77;78] and numbers ranged from 46 to 1900.[5;78]

Major congenital malformations were the measured in four out of the five studies. One study specifically sought cardiac malformations.[77] The exact definition of major congenital malformations was not given in one study.[19] In those which did provide a definition, the threshold for time since birth in which a major congenital malformation was defined varied between six weeks and a year for most studies, and in one study major congenital malformations could be identified at any point in the follow-up period of six years.[5] Categories of major congenital malformations were described in two studies.[5;78]

Spontaneous abortions were noted in three studies,[19;77;78] and stillbirths in two studies.[77;78] Results from prenatal scans performed after enrolment was reported in two studies.[5;78]

Descriptive summaries of studies from AAN review and updated literature search

The following sections describe the studies which make each of the eight comparisons of interest. Results from the published review were collated with those found in the updated search of the literature to give an overall view of the current literature. Table 3 lists all studies in each section along with their characteristics.

1) Any antiepileptic drug monotherapy versus no antiepileptic drugs in women with epilepsy

Summary of AAN findings

Three studies reported on the risk of major congenital malformations associated with exposure to any monotherapy in comparison with children born to women with epilepsy who were not taking antiepileptic drugs during the first trimester.

In 2001, Holmes *et al* conducted a study in the U.S across five maternity units where women were recruited during labour or delivery.[4] A total of 128,049 pregnant women were screened for inclusion and 386 women were found to have taken antiepileptic drug monotherapy during pregnancy and 98 women who had taken none but had a history of seizures. Only 223 monotherapy exposed children and all 98 unexposed children were eventually included in the analysis. The primary outcome was a pattern of antiepileptic drug related embryopathy which included major malformations, hypoplasia of the mid face and fingers, microcephaly and small body size and was determined blindly by a physician, although it is not described when after birth the examination took place. Questionnaires were used to collect data retrospectively on exposure and possible confounders. In their study, the authors reported 10 of 223 (4.5%) monotherapy exposed children and none of the 98 unexposed had a major congenital malformation. From this, the authors of the AAN review derived an

unadjusted odds ratio (OR) of 4.40 (95% confidence interval (CI) 1.29-11.90) showing a possible increased risk of major congenital malformations in the monotherapy exposed group of children.

However, two studies did not support this finding. A retrospective study of a Finnish population was conducted by Artama *et al* using medical records held in the Medical Birth Register and prescription reimbursement records.[11] In Finland, everyone is entitled to reimbursement from prescriptions, and those with epilepsy are entitled to a full reimbursement provided they hold a medical certificate from the neurologist, which shows that the person has been clinically diagnosed. A total of 6,535 women with epilepsy taking antiepileptic drugs were identified from this population between 1985 and 1994 and their records linked with birth data to further identify 2,350 children born between 1991 and 2000. Information on first trimester exposure to antiepileptic drugs was taken from hospital data and malformations classified according to the International Classification of Diseases (version 9). Minor and major congenital malformations were pooled into one group due to lack of detail in the medical records. Of 857 women with first trimester antiepileptic drug exposure, 1,411 babies were born and of 561 untreated women with epilepsy, 939 babies were born. Of 1,231 children who were exposed to antiepileptic drug monotherapy, most had been exposed to carbamazepine (n = 805) and sodium valproate (n = 263). Amongst all children in the study, malformations of the cardiovascular system, cleft lip and palate and malformations of the genital organs were commonly featured. In total, 52 of 1,231 (4.2%) exposed children, and 26 of 939 (2.8%) unexposed children were found to have either minor or major congenital malformations. The adjusted OR was 1.55 (95% CI 0.94-2.60) deeming the results to show no evidence of an association between antiepileptic drug monotherapy exposure and congenital malformations. Morrow *et al* had similar findings in their prospective study of women enrolled in the UK and Ireland Epilepsy and Pregnancy Register.[17] Here, women were referred to the register by health care professionals and information was collected at registration from the women themselves as well as the referee. Women were eligible if the outcome of pregnancy was not known. Information on major congenital malformations and pregnancy details and outcomes was requested by questionnaire

three months after expected date of delivery from the woman's general practitioner as well as any other health care professionals identified during the woman's pregnancy. Major congenital malformations were limited to those present at birth or discovered within six weeks of birth. Overall, 2,598 births were exposed to antiepileptic drug monotherapy, and 227 unexposed in women with epilepsy. Carbamazepine (n = 900) and sodium valproate (n = 715) were the most common monotherapies and some newer antiepileptic drugs were also present including lamotrigine (n = 647) and gabapentin (n = 31). In total, eight children (3.5%) in the unexposed group and 91 children (3.5%) in the exposed group were born with major congenital malformations, which is equivalent to an OR of 1.03 (95% CI 0.49-2.17) after adjusting.

Updated search

No further studies were found which compared these two groups. However, two studies reported the outcome in exposed and unexposed groups, but no OR or relative risk (RR) was provided by the article, I therefore calculated unadjusted ORs for the purposes of this review. Mawer *et al* of the Liverpool and Manchester Neurodevelopment Group (LMNDG) studied major congenital malformations in the children of women enrolled in their prospective study of women with epilepsy.[5] The outcome here was major congenital malformations identified at any point in the six years of follow-up and were classified between major and minor using the EUROCAT definitions. EUROCAT is a European surveillance system of congenital anomalies collecting data from 43 countries on approximately 30% of all cases (http://www.eurocat-network.eu/). In this study, 185 babies were exposed to antiepileptic drug monotherapy *in utero*, most commonly to carbamazepine and sodium valproate as well as 40 children with lamotrigine monotherapy exposure. Forty six children were unexposed to antiepileptic drugs and were born to mothers with epilepsy. Only one (2.2%) unexposed child and 10 (5.4%) exposed children had a major congenital malformation, equivalent to an unadjusted OR of 2.57 (95% CI 0.32-20.6) indicating no difference between the two groups. In support of this, a study from the Kerala Registry of Epilepsy and Pregnancy, Thomas *et al* studied the presence of cardiac malformations in children born to mothers with epilepsy.[77] Of

462 babies born to women with epilepsy, 262 were exposed to monotherapy, whilst 75 were not exposed. Three months after birth, babies were examined blindly by a cardiologist for cardiac malformations. No ORs were reported but 8.0% of the unexposed children and 6.5% of monotherapy exposed children had cardiac malformations, equivalent to an unadjusted OR of 0.80 (95% CI 0.30-2.10).

Section summary

The results are conflicting. Although four out of five studies suggest no increase in risk of major congenital malformations associated with antiepileptic drug monotherapy but one study reports a four-fold increase in risk. One of the studies which found no difference pooled together minor and major malformations, which may have biased the results. The studies were not entirely comparable given the definition of outcome, composition of different antiepileptic drugs in the monotherapy group and lack of adjusting for confounders, therefore one cannot conclude antiepileptic drug monotherapy leads to higher rates of major congenital malformations compared to no use of antiepileptic drugs in the first trimester of pregnancy.

2) Any antiepileptic drug polytherapy versus no antiepileptic drugs in women with epilepsy

Summary of AAN findings

The three studies which examined monotherapy in the last section, also examined polytherapy exposure in comparison with no antiepileptic drug exposure in children born to women with epilepsy.

Holmes *et al* examined 93 babies born to women receiving polytherapy in pregnancy and found eight (8.6%) to have major congenital malformations but none in the unexposed group - the authors of the AAN review calculated an unadjusted OR of 8.34 (2.05-34.64).[4] In support, the study by Artama *et al*, there were 180 babies with polytherapy exposure, the majority of which had been exposed to carbamazepine (n = 114) and sodium valproate (n = 98).[11] Of these, 13 (7.2%) babies were born with minor or major congenital malformations giving an adjusted OR of 2.73 (95% CI

1.26-5.64) compared to babies unexposed to antiepileptic drugs of mothers with epilepsy. Notably, the subset of the exposed group whose mothers were receiving polytherapy excluding sodium valproate, the OR compared to unexposed babies fell to 1.80 (95% CI 0.45-5.38) indicating no increased risk of minor or major congenital malformations. Morrow *et al* also found that polytherapy excluding sodium valproate did not lead to an increase in risk of major congenital malformations (OR 1.10, 95% CI 0.48-2.52) however they also found this true for polytherapy in general.[17] Amongst 718 babies exposed to polytherapy, 43 (6.0%) were identified as having major congenital malformations and after adjusting for maternal age, parity, family history of major congenital malformations, periconceptional folic acid exposure and sex of baby, there was no evidence of a difference in the two groups (OR 1.76, 95% CI 0.80-3.86).[17] However, they did find that polytherapy including sodium valproate increased the risk two-fold compared to no therapy (OR 2.52, 95% CI 1.17-5.44).[17]

Updated search

No studies were identified which compared the two groups, however three studies reported the rate of major congenital malformations for both groups, and ORs were calculated for the purposes of this review. Mawer *et al* found 4 out of 46 children with polytherapy exposure to have major congenital malformations, and sodium valproate was included in the polytherapy regimen for the mothers of each of the four children.[5] One child of the 46 unexposed children had a major congenital malformation, and the rates of major congenital malformations were no different (unadjusted OR 4.29, 95% CI 0.46-39.9). Similarly, Thomas *et al* of the Kerala Registry of Epilepsy and Pregnancy found comparable rates of major congenital malformations in had 125 children with polytherapy exposure, of which 10.4% had cardiac malformations compared to 8.0% in 75 unexposed children (unadjusted OR 1.33, 95% CI 0.48-3.67).[77] Slightly lower absolute rates were observed by Veiby *et al* in their study of Norwegian births, however, they found significantly higher risks in the polytherapy exposed children.[78] This study used data from the Medical Birth Registry where details on pregnancy, including medication, are collected at delivery for entry into the register. All births at 12 weeks gestation or more were entered into the register in Norway, and information on congenital malformations was collected within a year of

birth. Between 1998 and 2005, 2,861 children were born to women with epilepsy. In contrast to other studies, here the majority of women were untreated (n = 1,900) but 135 were receiving polytherapy. Major congenital malformations were found in 8 (6.1%) of exposed children and in 49 (2.6%) of unexposed children indicating a two-fold increase in risk (unadjusted OR 2.38, 95% CI 1.10-5.13).

Section summary

Although three studies show some evidence of a difference in rates of major congenital malformations between babies with and without polytherapy exposure, the largest study which also captured the effects of confounders, did not find a difference. There is a suggestion that polytherapy without sodium valproate may not increase the risk of major congenital malformations but that polytherapy *with* sodium valproate does. The balance of different polytherapy regimens will vary between studies therefore comparability of these studies may be questionable.

3) Carbamazepine monotherapy versus no antiepileptic drugs in women with epilepsy

Summary of AAN review

Two studies were found described in the AAN review. Holmes *et al* found three out of 58 children (5.2%) with carbamazepine monotherapy exposure had major congenital malformations and found this rate to be no different to that amongst the unexposed children (0/98 children with outcome).[4] Similar conclusions were made in the study of the Australian Pregnancy Registry cohort by Vajda *et al*.[18] This is an ongoing registry which enrols women prospectively before the outcome of birth is known, as well as retrospectively after the birth. The purpose of the registry is to determine the incidence of adverse pregnancy outcomes in women with treated and untreated epilepsy and in women who are treated with antiepileptic drugs for non-epileptic conditions.[80] Women enrolled are interviewed by telephone up to four times between first trimester and a year after delivery to obtain details on medication, pregnancy, and birth outcome. To support the interview data, their medical records are also obtained from health care professionals. At the time of the study, 630 pregnant women had enrolled and 565 had known pregnancy outcomes. There were

40 births to untreated epileptic women and 155 births to women who received carbamazepine monotherapy in the first trimester. One (2.5%) unexposed baby and six (3.8%) exposed babies were identified with major congenital malformations, and no difference in rates of major congenital malformations was detected.

Updated search

Only one study since 2007 has been identified. This is a later follow up on the Australian Pregnancy Registry from the 2006 study, hence there is some overlap of women and children. [18] By 2010, Vajda *et al* had recruited over 1000 women to their registry, with 302 babies exposed to carbamazepine monotherapy and 118 with no antiepileptic drug exposure.[19] They reported major congenital malformations using two definitions - within one month of birth and within one year. Using the first definition, a major congenital malformation had to be detected within a month of the child being born. There were four unexposed and eight exposed babies diagnosed with a major congenital malformations by one month. The second definition captured major congenital malformations up to one year after birth. The total number in the exposed group increased to 16, giving an unadjusted OR of 1.59 (95% CI 0.52-4.97) indicating no difference.

Section summary

Only three studies are presented here which examine major congenital malformations rates in carbamazepine monotherapy exposed children and in unexposed children, two studies with overlapping populations. The results are consistent and suggest that carbamazepine monotherapy exposure does not increase the risk of major congenital malformations, however the overlap in these studies, lack of control for confounders and few studies in number prohibit a definitive conclusion.

4) Sodium valproate monotherapy versus no antiepileptic drug use in women with epilepsy

Summary of AAN findings

Of the studies included in the AAN review, there were two studies which compared major congenital malformations in babies exposed to sodium valproate monotherapy in the first trimester with those with no antiepileptic drug exposure born to women with epilepsy.

Artama *et al* found 28 babies with minor and major congenital malformations amongst the offspring of 263 women who were taking sodium valproate in the first trimester of pregnancy, and in comparison with 26 out of 939 babies not exposed to antiepileptic drugs, the chances of minor and major congenital malformations in the exposed group was four times that in the unexposed group (OR 4.01, 95% CI 2.32-7.01)[11]. After adjusting for maternal age and number of previous births, the risk estimates were unaffected. Vajda *et al* showed some support for this finding.[18] In the exposed group, 19 out of 113 babies (16.8%) were born with major congenital malformations. The incidence rate was significantly higher than in the unexposed group, where one in 40 (2.5%) was born with a major congenital malformation.

Updated search

Only the follow up study of the Australian Pregnancy registry was identified in our updated search. This later study by Vajda *et al* reinforced their findings in the earlier study described above - 34 out of 224 (15.1%) exposed babies had a major congenital malformation within a year of birth, which equated to a five-fold increase in risk compared to babies with no antiepileptic drug exposure (OR 4.99, 1.73-14.44).[19]

Section summary

The three studies suggest that there is higher risk of major congenital malformations in sodium valproate monotherapy exposed babies, and that the rate is around four or five times higher when compared to unexposed children. Bearing in mind that two of these studies overlap, one of which did not quantify the magnitude of the increased risk and both studies did not account for confounding, further studies would still be needed to further evaluate these findings.

5) Lamotrigine monotherapy versus no antiepileptic drug use in women with epilepsy

Summary of AAN findings

The AAN review only found one study comparing these two groups. In the UK Epilepsy and Pregnancy Register study by Morrow *et al*, 647 babies with lamotrigine monotherapy exposure, 21 (3.2%) of which had major congenital malformations.[17] Eight out of 227 (3.5%) babies with no antiepileptic drug exposure had major congenital malformations and the AAN review authors derived an unadjusted RR of 0.92 (95% CI 0.41-2.05) indicating no difference in the rate of major congenital malformations between the two groups.

Updated search

A study of the Australian Pregnancy Registry focussed on lamotrigine monotherapy, comparing it with other antiepileptic drugs as well as no antiepileptic use in pregnancy[19] Of 243 babies exposed to lamotrigine and 12 (4.9%) had major congenital malformations present within a year of birth. Compared with the unexposed group (3.4%, n = 4/118) this resulted in an unadjusted OR of 1.48 (95% CI 0.47-4.69)

Section summary

Both studies suggest that lamotrigine monotherapy does not pose any greater risk of major congenital malformations than no antiepileptic drug therapy. Although both studies agree, and both have reasonably large sample sizes, more studies are needed to verify the findings.

6) Carbamazepine monotherapy versus sodium valproate monotherapy

Summary of AAN review

There were four studies which compared major congenital malformations in children with carbamazepine monotherapy exposure and those with sodium valproate monotherapy exposure.

Morrow *et al* found sodium valproate monotherapy exposure was associated with three-fold increase in risk of major congenital malformations compared to carbamazepine monotherapy (OR 2.97, 95% CI 1.65-5.35) after adjusting for maternal age, parity, family history of major congenital malformations, periconceptional folic acid use and sex of baby.[17] Vajda *et al* found 19 in 113 (16.8%) babies with sodium valproate exposure, and 6 in 155 (3.9%) babies with carbamazepine monotherapy exposure to have major congenital malformations.[18] The AAN review authors derived an unadjusted RR of 4.34 (1.79-10.53). A population-based study of medical records in Sweden was conducted by Wide *et al*, comparing carbamazepine and sodium valproate.[20] The Swedish Medical Birth Registry was used to identify children born between 1995 and 2001 whose mothers had reported antiepileptic drug use in pregnancy. Information on major congenital malformations was obtained from the birth registry and from the linked Swedish Register of Congenital Malformations. A total of 1398 children were exposed to antiepileptic drugs during early pregnancy, of which 268 exposed to sodium valproate monotherapy and 703 to carbamazepine monotherapy. Amongst those in the sodium valproate group, 26 (9.7%) had major congenital malformations whilst 28 (4.0%) children in the carbamazepine group also had major congenital malformations, and this gave an adjusted OR of 2.51 (95% CI 1.43-4.86). The variables adjusted for were not given. Another study supported a greater risk associated with sodium valproate monotherapy exposure compared to carbamazepine monotherapy exposure.[15] This was using data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) investigation, which is a multicentre study with centres in the US and UK. The NEAD study was a prospective study enrolling women taking carbamazepine, sodium valproate, lamotrigine and phenytoin during the first trimester of pregnancy between 1999 and 2004. The primary outcome of this study by Meador *et al* was serious adverse outcomes including foetal death and major congenital malformations.[15] In 333 children, 110 had carbamazepine monotherapy exposure and 69 with sodium valproate exposure. Five (4.5%) children in the carbamazepine group and four (5.8%) in the sodium valproate group had major congenital malformations and the AAN review authors

derived a RR of 3.83 (95% CI 1.41-10.39) indicating a higher rate of major congenital malformations in sodium valproate exposed children.

Updated search

Only one article was found which compared sodium valproate monotherapy with carbamazepine monotherapy, and that was an update on data from the UK Epilepsy and Pregnancy Register, presented in a conference abstract and hence details are limited.[75] Data were captured up to 2009 which gave rise to 5,802 pregnancies of which 5,376 were treated with antiepileptic drugs during pregnancy. The numbers in each exposure group are not given, but the relative risk of major congenital malformations in sodium valproate exposed babies compared to carbamazepine exposed babies was 2.35 (95% CI 1.57-3.57).

Section summary

There were in total five studies of four independent cohorts which compared major congenital malformation rates in sodium valproate exposed children with carbamazepine exposed children. Two studies accounted for confounding variables and both found a two- to three-fold increase in major congenital malformation rates amongst children in the sodium valproate exposed children. The cohorts from the NEAD study and the Australian Pregnancy Registry found an increase of around four times associated with sodium valproate exposure compared to carbamazepine exposure, however both of these studies had much smaller samples and did not account for confounding. Findings from Kennedy *et al* reflect those from their earlier UK Epilepsy and Pregnancy Register study by Morrow *et al*, but have greater precision likely from an increase in numbers.[17;75] Overall, the study findings indicate a higher risk associated with sodium valproate monotherapy compared to carbamazepine monotherapy.

7) Carbamazepine monotherapy versus lamotrigine monotherapy

Summary of AAN findings

The AAN review does not cover the comparison between carbamazepine and lamotrigine, however one study in their review contained relevant details. Morrow *et*

al compared 647 babies with lamotrigine monotherapy exposure and 900 babies with carbamazepine monotherapy exposure and found 21 (3.2%) and 20 (2.2%) babies had major congenital malformations in the lamotrigine and carbamazepine group, respectively.[17] They concluded no difference in rates of major congenital malformations between the two antiepileptic drugs groups (adjusted OR 1.71, 95% CI 0.88-3.32).

Updated search

My updated search found no studies making this comparison.

Section summary

Based on one study, we cannot be certain on the risk of lamotrigine monotherapy relative to carbamazepine monotherapy.

8) Sodium valproate monotherapy versus lamotrigine monotherapy

Summary of AAN findings

Studies from the Australian Pregnancy Registry and the UK/US NEAD cohort compared major congenital malformations in children with sodium valproate monotherapy exposure to those with lamotrigine monotherapy exposure. In the study by Vajda *et al*, 19 in 113 babies (16.8%) with sodium valproate monotherapy exposure had major congenital malformations recorded, whilst none of the 61 children with lamotrigine monotherapy exposure had major congenital malformations.[18] The AAN review authors derived an unadjusted RR if 5.58 (95% CI 2.06-15.09). Meador *et al* of the NEAD study found 12 out of 69 children (17.9%) with sodium valproate monotherapy exposure had major congenital malformations and one child had major congenital malformations out of 98 children (1.0%) with lamotrigine monotherapy exposure, giving a much higher RR of 17.04 (95% CI 2.27-128.05).[15]

Updated search

The only article which reported results examining this area was the previously mentioned conference abstract by Kennedy *et al* of the UK Epilepsy and Pregnancy

Register.[75] As mentioned before, the number of children in each antiepileptic drug group is not given, but they reported the RR of major congenital malformations in sodium valproate monotherapy exposed children compared to lamotrigine monotherapy exposed children was 2.40 (95% CI 1.57-3.68).

Section summary

There was a general consensus in that sodium valproate monotherapy is associated with a greater risk of major congenital malformations compared to lamotrigine monotherapy. However, the three studies disagree on the magnitude of increase in risk, and the confidence intervals suggest a lack of precision in the estimates except in the work by Kennedy *et al*.[75] Further large studies need to be conducted to clarify the increase in risk.

1.5.3. Discussion

Summary

There are 11 studies presented here which stem from nine independent cohorts. Unfortunately, not all 11 studies make the same comparison resulting in only three studies, on average, to draw conclusions for each comparison. The comparison between carbamazepine and sodium valproate monotherapy was conducted across the most studies, five studies in total. The conclusions made are limited by the small number of studies. Nevertheless, their strengths along with the weaknesses of these studies, should be borne in mind in interpreting the conclusions set out at the end of this section.

Strengths & limitations

Size

The total number of children was over 200 in every study and there were over 1000 antiepileptic drug exposed children in six studies. Even when specific monotherapies were examined, the number was mostly greater than 100. The largest study used data from the UK Epilepsy and Pregnancy Register.[17] This was a good quality study with the highest number of foetuses exposed to specific monotherapies – 900 births

were exposed to carbamazepine, 715 to sodium valproate exposure and 647 to lamotrigine. The smallest numbers arose from the NEAD cohort in the study by Meador *et al* where around 100 babies were examined in each antiepileptic drug monotherapy group.[15]

Setting

Most studies were based on data from pregnancy registries, few from medical records, one from antenatal clinics and one from epilepsy clinics. Only one study was population based – Wide *et al* performed their study using data from the Swedish Medical Birth Register where it is compulsory for health care providers to submit data on deliveries, therefore capturing most of the population.[20] Pregnancy registries on the other hand, have large numbers but are not necessarily representative of the population. Self-enrolled or women who are referred may have been enrolled on the register because they have a prenatal diagnosis of a malformation, or they have reason to believe that their risk is high – for example, if previous pregnancies have been affected. In a similar manner, women from epilepsy clinics are not likely to be representative of the population as they may be those who suffer more severely from epilepsy compared to those whose conditions are controlled.

Ascertainment of exposure

The details on the type and timing of antiepileptic drug medication was mostly gained through interviews conducted in retrospect. Information gained in this way is biased because it depends on accurate recall – important in these studies for first trimester exposure to be attributed to major congenital malformations. Some studies also used medical records or contacted the woman's health care professionals to support the details given in interview. However the accuracy of medical records also depends on the quality of recording. Furthermore, adherence to prescribed medication was rarely described – this may have been obtained through interviews but is unlikely to be ascertained in medical records.

Exposure definition

The most conflicting results were amongst studies comparing any monotherapy and any polytherapy with no antiepileptic drug exposure. One study may have included mainly carbamazepine monotherapy exposed children in their "any" monotherapy group, whereas another may be dominated by a different drug e.g. sodium valproate. In the study by Holmes *et al* phenytoin was the common monotherapy, whereas in the study by Morrow *et al* the most common drug was carbamazepine, and this study was the only one to include newer antiepileptic drug lamotrigine.[4;17] These two studies differed in their conclusions. Similarly with polytherapy, there is a suggestion that polytherapy with sodium valproate is associated with a higher risk of major congenital malformations – therefore risk of major congenital malformations in a group of "any" polytherapy exposure may depend on the presence of sodium valproate amongst the polytherapy regimens. Some studies analysed polytherapy with sodium valproate separately from polytherapy without sodium valproate, but to fully account for differing regimens, specific antiepileptic drug combinations should be examined.

Outcome definition

The primary outcome in almost all of these studies was major congenital malformations. One study pooled minor and major malformations, another included foetal death with major congenital malformations to create a composite outcome.[15] The latter study provided a breakdown so I was able to obtain results only for major congenital malformations, however the former study by Artama *et al* highlights one of the difficulties with using medical records in that it can be difficult to distinguish between minor and major malformations without a clinical review of the case.[11]

The time limit for detecting major congenital malformations varied, and in some studies not specified. The longest was throughout an entire follow-up period of six years. The shortest was five days. In one study, major congenital malformations were counted twice - those recorded within one month of birth and those within one year and in some cases, the number of children with major congenital malformations was doubled by extending time to one year.[19] There is not a general consensus on

when a major congenital malformation should be detected, but this study shows that some may be missed if the cut-off is too short, hence the absolute risks would be underestimated.

Where possible, studies have excluded women who have had prenatal scans showing evidence of malformations because these women could be more likely to participate in a study if they think they will receive more monitoring and care during pregnancy. However, this does exclude an important group of women – major congenital malformations can be detected early in pregnancy through such scans, some will not survive and some may be terminated. These may even be the most severe cases that will not be counted in these studies. Ideally, women should be enrolled into a study before any prenatal scans have taken place and all major congenital malformations detected through scans should be recorded.

Birth outcome

Similarly, all birth outcomes would ideally be known. Live births are generally a convenience sample since it is difficult to obtain data on some non-live births, particularly terminations. Some studies included pregnancies which had not ended in live birth, however little information was known on whether or not those babies suffered from malformations. This information is understandably difficult to gain, and impossible if no prenatal scans have been performed.

Confounders

Almost all studies collected data on potential confounders. However, only three studies adjusted for confounding. Even if the others had done so, they did not state this in their results [11;17;20] For some studies, the comparisons made in this current review were not the primary comparisons of the study hence confounding was neglected and although the AAN review authors derived some of the risk rates, they were unable to calculate adjusted risks. Potential confounding should be accounted for in observational studies because the exposed and unexposed groups are likely to unbalanced by factors which are related to the exposure and the outcome.

General findings

One of the major conclusions drawn from this review is that on carbamazepine monotherapy versus sodium valproate monotherapy. The review suggest that there is a higher risk of major congenital malformations in babies born to women receiving sodium valproate monotherapy in the first trimester compared to those receiving carbamazepine monotherapy. The size of the increased risk not as clear from these studies but may be somewhere between two and five times.

Sodium valproate monotherapy possibly also increases the risk of major congenital malformations in comparison to lamotrigine monotherapy and in comparison with no antiepileptic drug exposure in the first trimester.

Carbamazepine and lamotrigine monotherapy possibly do not increase the risks of major congenital malformations compared to no antiepileptic drug treatment in the first trimester of pregnancy.

No firm conclusions can be made with regards to major congenital malformation risks amongst any monotherapy or any polytherapy.

These conclusions are limited by the few good quality controlled studies which examine major congenital malformations and antiepileptic drug exposure in pregnancy. Treatment decisions in pregnancy can have major consequences for the woman and her child therefore, in my view, recommendations and advice should be given based on large, well conducted studies which consistently agree in their findings. In this area, there is a need for more studies in general, but studies need to be large, preferably prospective and with accurate recording of medication details and major congenital malformations need to be well defined and diagnosed. Risk estimates for specific monotherapy and polytherapy regimens are more useful than broad groups of exposure such as “any” monotherapy. There is also an urgent need for studies examining newer antiepileptic drugs – lamotrigine is fast becoming a popular treatment, therefore its effect in pregnancy must be established. Ideally we should know about major congenital malformations which are detected at any stage

in pregnancy regardless of birth outcome, and it may be beneficial to extend the period of follow-up after birth to capture major congenital malformations not detected in the early months of life. Lastly, confounding variables should be considered in any observational study design, notably alcohol and tobacco use in pregnancy, maternal age and epilepsy type/severity.

Table 3 Summary of selected articles

Authors	Country	Exposed	Unexposed	Outcome
Comparisons with women with untreated epilepsy				
1) Any antiepileptic drug monotherapy				
Artama et al (2005)	Finland	1231	939	All congenital malformations
Holmes et al (2001)	U.S	223	98	Major congenital malformations
Morrow et al (2006)	U.K	2598	227	Major congenital malformations
Mawer et al (2010)	U.K	185	46	Major congenital malformations
Thomas et al (2008)	India	262	75	Cardiac malformations
2) **Any antiepileptic drug polytherapy**				
Artama et al (2005)	Finland	180	939	All congenital malformations
Holmes et al (2001)	U.S	93	98	Major congenital malformations
Morrow et al (2006)	U.K	718	227	Major congenital malformations
Mawer et al (2010)	U.K	46	46	Major congenital malformations
Thomas et al (2008)	India	125	75	Cardiac malformations
Veiby et al (2009)	Norway	135	1900	Major congenital malformations
3) Carbamazepine monotherapy				
Holmes et al (2001)	U.S	58	98	Major congenital malformations
Vajda et al (2006)	Australia	155	40	Major congenital malformations
Vajda et al (2010)	Australia	302	118	Major congenital malformations
4) Sodium valproate monotherapy				
Artama et al (2005)	Finland	263	939	All congenital malformations
Vajda et al (2006)	Australia	113	40	Major congenital malformations
Vajda et al (2010)	Australia	224	118	Major congenital malformations
5) Lamotrigine monotherapy				
Morrow et al (2006)	U.K	647	227	Major congenital malformations
Vajda et al (2010)	Australia	243	118	Major congenital malformations

Authors	Country	Exposed	Unexposed	Outcome
Comparisons between antiepileptic drug monotherapies				
6) Carbamazepine vs. sodium valproate				
Meador et al (2006)	U.K & U.S	110	69	Major congenital malformations
Morrow et al (2006)	U.K	900	715	Major congenital malformations
Vajda et al (2006)	Australia	155	113	Major congenital malformations
Wide et al (2004)	Sweden	703	268	Major congenital malformations
Kennedy et al (2010)	U.K	unspecified	unspecified	Major congenital malformations
7) Carbamazepine vs. lamotrigine				
Morrow et al (2006)	U.K	900	647	Major congenital malformations
8) Sodium valproate vs. lamotrigine				
Meador et al (2006)	U.K & U.S	69	98	Major congenital malformations
Vajda et al (2006)	Australia	113	61	Major congenital malformations
Kennedy et al (2010)	U.K	unspecified	unspecified	Major congenital malformations

1.5. Summary

The safety of drugs in pregnancy has been an ongoing concern since the thalidomide scandal highlighted the potential devastation that foetal exposure to maternal medications can cause. Antiepileptic drugs are teratogenic but some of the conditions for which they are prescribed are difficult to manage without drug treatment. Thus, a clearer understanding of the safety of antiepileptic drugs in pregnancy is much sought after. Decades of research have suggested increased risks associated with certain antiepileptic drugs – namely sodium valproate – but there are unknowns with respect to the magnitude of risk for different antiepileptic drug regimens. This paucity of knowledge was highlighted in the literature review which furthermore showed that there are only a handful of studies which have compared the risk between different antiepileptic drug treatments – information which clinicians can use to provide a quantitative framework around the advice given to women about the risks and benefits of antiepileptic drugs in pregnancy.

The main research question in this thesis will focus on the relative risk of major congenital malformations associated with different antiepileptic drug regimens in pregnancy. This PhD study provides access to a large clinical database of routinely collected UK primary care data, known as The Health Improvement Network (THIN) which contains historical medical records for a large number of patients from 1994 onwards. In the forthcoming chapters, I describe why THIN is an ideal data source for this research by exploring the recording of information pertinent to conducting this research.

1.6. The next chapter

The limitations in the studies discussed in this chapter emphasise the difficulty in conducting drug safety in pregnancy studies. In the next chapter, an overview is given of the typical study design adopted in such studies explaining their strengths and limitations. The chosen data source for this research project is then introduced and described in the context of these relative strengths and weaknesses to demonstrate the appropriateness of THIN data for this study.

Chapter 2

Methodological challenges of studying teratogenicity

2.1. Aim of the chapter

At the end of Chapter 1, several challenges in studying teratogenicity were raised through the literature review. In this Chapter, I give an overview of how the choice of study design and data source can overcome some of these challenges. More specific to this project, I describe examples of different data sources that have been used in the study of antiepileptic drugs in pregnancy. This demonstrates the variety of sources of available and their relative strengths and weaknesses. This leads to an introduction of the data source chosen for this PhD which is The Health Improvement Network.

2.2. Background

Studies examining adverse effects of medication given in pregnancy are conducted post marketing i.e. after the drug has been licensed for use and is prescribed in the general population. In an ideal world, all side effects would be known prior to licensing, in the development stages of a drug. However, some side effects are rare and would require a very large group of volunteers to be involved in testing in order that the effect is observed in pre-clinical trials. Furthermore, if studying the side effects of drugs in pregnancy, one would need pregnant women to participate in clinical trials. The repercussions of the thalidomide disaster make it undesirable to involve pregnant women in clinical trials, from both the pharmaceutical and the woman's point of view.

Our knowledge of a drug's teratogenic potential is therefore derived from animal studies and post marketing observational studies. Animal studies are commonly used to flag possible human teratogens; however, animal models are not perfectly representative of humans thus it is possible for humans to be affected but not animals. Reliance is therefore placed on observational studies to uncover drugs which may elevate the risk of major congenital malformations if taken in pregnancy.

2.3. Observational study designs

The studies in Chapter 1 show that teratogenic effects are mostly examined after the drug has been marketed. These are observational studies – studies which examine populations of interest in their natural course without intervention from the researcher. The next section describes the commonly used observational study designs, particularly for investigating antiepileptic drugs in pregnancy.

Cohort study

In a cohort study, a group of people are observed either forwards (prospectively) or backwards (retrospectively) over time. The group are divided into natural sub groups according to their levels of exposure – e.g. whether or not they are on antiepileptic drug medication. The outcome is measured in each group, information on confounders collected and analysed using various methods. One major advantage of cohort studies is that they involve a population at risk of an outcome, and therefore incidence and prevalence rates of the outcome can be obtained and absolute risks can be estimated

A cohort study design is useful when one wishes to examine multiple outcomes from a single exposure, particularly if the exposure is rare, and is therefore a common choice of design for newly marketed drugs since it may take some time for these drugs to become commonly prescribed.

Case-control studies

Case-control studies are retrospective studies examining a group of individuals with an outcome (i.e. cases) and a group of individuals without the outcome (i.e. controls) back in time, looking for differences in exposures. Particular situations lend themselves well to case-control studies - studying multiple exposures to a single outcome, rare outcomes and if there is an urgent need for a study – say in an outbreak situation – because there are a fixed number of cases made available at the beginning of the study. However, the total population at risk of an outcome is not available absolute risks cannot be obtained. Odds ratios are

instead reported which are a close estimate of the relative risk if the outcome is rare.

Neither study design perfectly addresses all challenges in studying teratogenicity. Below, I outline some of the shortfalls of observational study designs.

- Both designs are subject to confounding. Measured confounders can be accounted for, but unmeasured and unknown confounding is always an issue in any type of observational study.
- Selection bias – where the study population is not representative of the general population – is potentially an issue for both designs but depends on the data source, which is discussed next.
- Recall bias affects either study design, but is more commonly an issue in case-control studies. If information on exposure and risk factors is ascertained retrospectively after the outcome is known – the knowledge of the outcome may affect the level and/accuracy of recall.
- Observer bias also affects studies if the observer expresses a differential effort to obtain data on exposure and risk factors depending on the outcome.

These are only some of the major challenges – more are discussed in the next section on data sources. Table 4 summarises the main strengths and limitations associated with cohort and case-control studies.

Table 4 Advantages and disadvantages of study designs

	Advantages	Disadvantages
Cohort design	✓ Can examine multiple outcomes ✓ Ideal for rare exposures ✓ Wide range of risk estimates can be calculated ✓ Prospective studies minimise recall bias ✓ No additional selection of a control group as there is with case-control studies	× Can be large, expensive and labour intensive × Loss to follow up can invalidate results × Open to selection bias × Open to recall bias if retrospective × Not ideal for rare outcomes × Prone to confounding × Open to exposure misclassification × Open to observer bias if retrospective
Case-control design	✓ Can examine more than one exposure to a single outcome ✓ Ideal for rare outcomes ✓ Ideal for generating hypotheses for further larger studies ✓ Ideal for urgent studies (e.g. outbreaks) ✓ Ideal for delayed outcomes	× Open to recall bias if information obtained through retrospective interviews or questionnaires × Can be difficult in selecting a control group × Estimates are limited to odds ratios × Prone to confounding × Open to exposure misclassification × Open to observer bias × Limited to one outcome

2.4. Observational sources of data

The choice of study design can be informed by the available sources of data. In studies of medication safety in pregnancy, there are some common types of data sources used in research.

2.4.1. Pregnancy registry

A pregnancy registry is usually established to monitor adverse outcomes associated with the use of specific drugs, or a class of drugs, in pregnancy. Pregnant women are enrolled if they have a certain condition or are prescribed certain drugs in pregnancy. Data is generally on pregnancy, delivery and post-natal states and events in the mother and baby. This is usually collected in a prospective manner throughout their pregnancy and for some length of time after the birth of the baby, depending on the outcome of interest (e.g. an interest in child development might necessitate years of follow up). The exact methods of data collection vary between registries but can involve telephone interviews, questionnaires and access to medical records.

Registries can be established by any interested party (e.g. industry, academic research group, independent physician) though participation is always voluntary. It is sometimes made mandatory for the manufacturer of a new drug to establish a pregnancy registry as a “post–marketing requirement” or “commitment” - written agreements between the manufacturer and the regulatory agency made before or after marketing approval.

Example: The UK and Ireland Epilepsy and Pregnancy Register

As was evident from the literature review in Chapter 1, there are several epilepsy and pregnancy registries around the world. The prominent ones which have made major contributions to our understanding of the teratogenic effects of antiepileptic drugs include:

- the International Registry for Antiepileptic Drugs in Pregnancy (EURAP),
- the North American Antiepileptic Drugs in Pregnancy Registry,
- the Australian Pregnancy Registry,
- the UK and Ireland Epilepsy and Pregnancy Registry, and

- the Lamotrigine Pregnancy Registry.

I describe in more detail the UK Epilepsy and Pregnancy Register which has published several studies in this area since its initiation. The UK arm of the UK Epilepsy and Pregnancy Register was first established in 1996 and was joined with the Irish Epilepsy and Pregnancy Register in 2007 to form the registry as it stands today.[81] The aim is to observe which antiepileptic drugs are used in pregnancy and to determine their relative safety.[81;82] Women are referred to the register by themselves or through a health care professional and included if they are pregnant with epilepsy regardless of whether or not they are taking antiepileptic drugs, and before the pregnancy outcome is known. They are excluded if:

  - prenatal tests have found any major congenital malformations, or
  - they did not take antiepileptic drugs in the first trimester but did take them in the subsequent trimesters.[17]

Baseline and exposure information is collected from the referring source (i.e. the woman herself or the health care professional), medical records and liaison with other health care professionals. Outcome data is collected three months after the expected delivery date via a questionnaire to the woman's general practitioner.[17] In August 2013, over 10,000 women had joined the register which is funded by UCB Pharma Ltd.[17;82]

A recent study

In January 2014, *Campbell et al* published recent findings from the UK Epilepsy and Pregnancy Register.[81] They conducted a retrospective cohort study of 5,206 pregnancies observed between 1996 and 2012, in which women took one of three monotherapies in the first trimester (sodium valproate (n = 1,290), carbamazepine (n = 1,718) or lamotrigine (n = 2,198)). The outcome of interest was a major congenital malformation which they defined as "an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered in the first six weeks of life according to the definitions and list of

disorders in the EUROCAT* registry." The outcome was ascertained three months after birth using information gathered from health care professionals associated with the woman's care. One of the study authors classified pregnancies according to outcomes as:

- without congenital malformations,
- with major malformations, or
- with other malformations.

The major malformation rate in each of the three antiepileptic drug exposed groups was compared to generate odds ratios. Logistic regression methods were used to account for a number of potential confounders. As a sub study, they also reported odds ratios comparing the rate of *specific* malformations between different exposures – for example, one of their findings was that neural tube defects and facial clefts were more likely in babies exposed to sodium valproate compared to carbamazepine.

Strengths and weaknesses of pregnancy registries

A large sample size is advantageous in studying teratogenicity due to the rare incidence of major congenital malformations. A larger sample is more likely detect moderate differences in risk of major congenital malformations between groups and may also allow confounding to be examined in more detail. Pregnancy registries have provided large samples – UK Epilepsy and Pregnancy Register is the largest national registry in the UK and in the latest study, analysed over 5,000 pregnancies. This is a major strength, however, the downside is that for a condition such as epilepsy which affects around 1% of the UK population, it can take a long time to accumulate such numbers, which may have cost implications.

Pregnancy registries are usually set up with a research question in mind. This means that risk factors of interest can be captured and measured appropriately for analysis unlike in administrative databases where analysis is limited to data

* EUROCAT is a European surveillance system of congenital anomalies collecting data from 43 countries on approximately 30% of all cases of major congenital malformations (http://www.eurocat-network.eu/).

which has already been collected. Data is mostly captured prospectively if possible, though some registries will enrol patients in retrospect (and therefore ascertain some details after the event). Where this occurs, some registries acknowledge potential differences between prospectively and retrospectively enrolled women by presenting separate analyses.

The main drawback of pregnancy registries is the potential for selection bias, although this limitation is not restricted to pregnancy registries. Firstly, women enrolled in a registry may be different from those who do not enrol. Secondly, if pregnancy losses are not collected, the registry may underestimate the rates of major congenital malformations as some, but not all losses may associated with these.

2.4.2. Congenital malformation registry

A congenital malformation registry collects data on the women whose babies are diagnosed with a major congenital malformation. Many countries have these registries for surveillance purposes so that, should there ever be another drug like thalidomide, these registers can provide valuable early signals. However, the breadth of information in these registries has meant that over time, they have also been used to inform planning of health services and conduct epidemiological studies to help understand the causes and consequences of major congenital malformations.[83]

Notifications to a congenital malformations registry are either through self-enrolment or from clinical sources including pathology labs, ultrasound labs and delivery suites. Notifications are made retrospectively after a pregnancy has ended and a major congenital malformation diagnosed, or when diagnosis has been made following a prenatal scan.

Once a registry is notified of a case, further data can be collected from medical records and through questionnaires and interviews. The information collected is broader in terms of exposures compared to pregnancy registries because the goal is to identify potential teratogens (as opposed to pregnancy registries where the goal is to identify outcomes associated with specific drug exposure in

pregnancy). For comparisons, some registries also collect data on “healthy” babies - a group of unaffected babies to compare exposures against.

National congenital malformation registries can also contribute to international collaborations, such as EUROCAT which collects data on congenital malformations from 43 registries in 23 countries. This pooled dataset greatly increases the size of studies conducted using this data, which for studying rare outcomes is a strong advantage. However, there is likely to be heterogeneity between different countries and possibly different registries which have to be considered in analyses.

Example: Spanish Collaborative Study of Congenital Malformations (ECEMC)

In antiepileptic drug research, congenital malformation registries have been less often used than pregnancy registries. However, congenital malformations registries have their strengths – described below is a case-control study from the Spanish Collaborative Study of Congenital Malformations (ECEMC) who have addressed some of the major issues usually associated with congenital malformations registries.

Established in 1976, the ECEMC is a hospital based registry of congenital malformations across Spain. The objective of the registry is surveillance of congenital malformations in Spain and epidemiological research to understand the characteristics, clusters and causes of congenital malformations.[73;84] The network involves over 400 paediatricians working in one of 80 participating hospitals.[84] They are trained to follow strict methodology to examine new born babies within three days of birth and assess whether or not there are major or minor malformations. Control babies born without any congenital malformations are also recruited at this time by the same set of paediatricians. Once the status of a case is determined and data on the infant has been collected, the paediatrician interviews the mother using a predefined protocol to collect the same data from both the cases and the controls. The data are then sent to and analysed by a separate, central co-ordinating group of experts in congenital defects epidemiology, clinical teratology, dysmorphology, clinical genetics and cytogenetics.[73] They are responsible for performing diagnostic tests to confirm

the initial diagnosis made by the local paediatrician as well as conducting research studies. The registry captures between 20 and 25% of all births in Spain.[84]

A recent study

The ECEMC published a case-control study looking at a specific type of major congenital malformation – hypospadia – and its association with specific antiepileptic drug exposure – valproic acid (a form of sodium valproate) - in the first trimester.[73]

Hypospadia is a rare malformation which affect males – it is the incorrect positioning of the opening of the urethral tube in the penis. According to EUROCAT, it is estimated to affect approximately 13 per 10,000 births in the UK http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. The ECEMC identified 2,393 babies with hypospadia (cases) and 12,465 males without (controls). Cases were initially identified by the paediatrician, and confirmed using other methods which include blood samples, photos, imaging studies and pathology reports. Controls were selected as the next male infant born in the same hospital but without any congenital malformations. Exposure information was ascertained via structured interview, gathering information on timing, dose, and type of drug use as well as risk factors information. Exposure was defined as use of valproic acid in the first trimester of pregnancy – an infant was unexposed if valproic acid was not taken in this time period. Odds ratios were calculated and conditional regression analysis used to control for confounders. The results of the study suggested a substantial increased risk of hypospadias.

Strengths and weaknesses of congenital malformation registries

One advantage which is made clear in this study is that congenital malformations registries can be ideal if one wishes to examine specific major congenital malformations. Hypospadias are one of the most common types of major congenital malformations, but are rare in the population. This study identified over 2,000 cases – using a registry which is based on the outcome of an event, one is more likely to ascertain large numbers of outcomes.

The ECEMC also show how a congenital malformation registry can capture an internal control group of babies without major congenital malformations. Other congenital malformations studies have used external reference populations in order to make comparisons with a group of “healthy” controls. But these have questionable comparability since they are usually selected in a different setting or location and they are not assessed by the same paediatrician or other persons diagnosing major congenital malformations potentially introducing information bias.

A strength specific to the ECEMC is that they have tried to reduce outcome misclassification by conducting diagnostic tests as well as training a paediatrician to use standardised methodology to diagnose the condition themselves.

In general for congenital malformations registries, steps to reduce exposure misclassification should be taken since this is always information collected retrospectively. The use of medical records, although collated retrospectively, can offer a method which has a lower likelihood of misclassification if the records were made prospectively. However, women interviewed after the birth of their child, and after they join the registry, may report details of drug use in pregnancy differently depending on the whether or not their baby was affected i.e. recall bias may have been an issue.

Congenital malformation registries are restrictive in that only case-control studies can be performed using their data. However, the ECEMC have shown how rigorous methodology can be used to conduct case-control studies that provide valuable observations.

2.4.3. Population based birth registers

National birth registers exist in a number of countries – they collect information on nearly all births in hospital and at home. Similar to congenital malformation registries, they were first established in the wake of the thalidomide disaster as a means of surveillance of major congenital malformations and other perinatal health problems, but are now commonly used for research purposes.

The registers collate information from medical records, antenatal forms and maternity wards and are usually notified to the registry by the midwife or other health care personnel as part of their duties. Data is collated retrospectively, but it is prospective in that the data was recorded before the outcome is likely to have been known (e.g. antenatal information is filled out on forms during antenatal visits prior to pregnancy outcome).

Information is obtained on mothers and fathers, demographics, health of parents, health in pregnancy, complications in pregnancy and delivery and information on the baby including major congenital malformations and perinatal health problems.[85]

Example: Danish Medical Birth Registry (DMBR)

Described here is an example of a study from the Danish Medical Birth Registry (DMBR). Established in 1968, the DMBR was set up to monitor perinatal health and the quality of antenatal and delivery services in Denmark.[86] All births in hospital and at home are recorded making the registry representative of the population. The information is made available to the registry via the midwife at the point of delivery, or by the doctor when the mother is discharged from hospital, using a standard form.[87] The data is typical of other birth registries – demographics, reproductive history, health in pregnancy and delivery details,[87] along with a unique identifier which allows the registry information to linked across to other national registers.

A recent study

In 2011, Molgaard-Nielsen *et al* used data from the DMBR to examine first trimester use of newer antiepileptic drugs in relation to the risk of major congenital malformations. A retrospective cohort study was performed using 837,795 live births from 1996 to 2008. Births were linked to another national registry, the Registry of Medicinal Products Statistics, which provides information on all prescriptions in Danish pharmacies since 1994. Women prescribed antiepileptic drugs in the first trimester of pregnancy were defined as exposed. Further linkage was made to the National Patient Registry which contains individual level data on inpatient stays and outpatients visits at hospitals. This was used to identify cases of major congenital malformations, which were defined according to EUROCAT

guidelines and had to be recorded within a year since birth. Information on several confounding variables was obtained through linkage with other national registers. Odds ratios were calculated comparing the antiepileptic drug groups with a group of births for without antiepileptic drug exposure in the first trimester of pregnancy.

Strengths and weaknesses of birth registers

One of the main strengths of birth registries is that some countries are able to link their birth registry data to a number of other national registries – for example, hospital discharge data. This additional resource can be used to validate diagnoses, increase sample sizes and simply to provide additional factors of interest. The linkage to pharmacy data is major advantage since the details are an accurate copy of the filled prescription providing information on the type of drug, its strength and daily dose as well as providing a point in time which is a close proxy for when the dispensed drugs should have been consumed. This is a more reliable source of pharmacological information than interviews with the mother who may be biased or may not remember all of the details correctly.

However, questions have in the past been raised over the quality of the data from some birth registries.[87] It has been suggested that there poorer accuracy if those inputting the data have little knowledge of how the data is used for research.[87] Usually, data is routinely entered by personnel who have no involvement in the secondary uses of the data, some seeing it as a burden.[88] The lack of inclusion may lead to disinterest in the importance of accuracy of details. By involving the staff who routinely collect the data in research, a better quality of data is possible.[88]

Selection bias can continue to be a challenge in birth registry data if there is a lack of information on non-live outcomes in pregnancies.

2.4.4. Administrative databases

These are databases which hold routinely collected health care data and whose primary purpose is administrative - not for research. However, the data are increasingly being used for research purposes primarily due to large sample sizes held in such databases, and the relatively faster speed at which studies can be

conducted compared to studies which involves data collection. They have been valuable for research into health service planning and monitoring, economic analyses as well as epidemiological research.[89] I describe here two types of administrative databases – insurance claims databases and electronic medical records.

Claims databases

Claims databases provide a longitudinal record of billable health interactions with medical services and pharmacy. Information is collected by submission of claims from the care provider (e.g. hospital or pharmacy) to the insurer. Details can include information on diagnoses, operations, inpatient stays, the care provider, treating physician's profile, and prescriptions. These databases are a popular choice for research studies in the United States since healthcare is not free but paid for through health insurance plans. Some are state funded, while others are private insurance plans paid for by individuals themselves or possibly employers who offer health insurance as employee benefits. This diversity in health plans means there are likely to be differences in the type of people enrolled in different health plans, and therefore the use of data from just one health plan may not reflect the population. For example, Medicaid is a government funded health plan in the U.S for those on low income, while Medicare is another government funded plan aimed specifically at those over 65 years of age – thus there are at least differences in age and wealth between the members of these two plans.

Example of claims databases in the U.S.

Described here is a recent study which used insurance claims data to study the specific relationship between topiramate, a newer antiepileptic drug, and the risk of oral clefts.[90] This was a retrospective cohort study was carried out on pregnancies linked to a child who was born in the period 1997-2010. The data was collated from across four databases – three were insurance claims, the remainder was an electronic health record system. Two of the claims databases used in this study are derived from private health insurance claimants, whilst another used claims data from a government funded health insurance plan for people on low incomes (Medicaid). The remaining database contained the medical records of members who receive private health care through Kaiser Permanente Northern California health plan. Each of the data sources followed a

standardised protocol to collect the same information which was pooled and analysed centrally. However, the methods for identifying the study population varied with each data source, due to differences in the information captured on the linkage between a mother and baby.

The authors compared the prevalence of oral clefts between three cohorts – women with first trimester topiramate use, women with any antiepileptic drug use prior to pregnancy but not during the first trimester or the four months before conception, and women with similar medical indications for topiramate to the first cohort but with no use of topiramate in the first trimester or four months prior to conception.

The dates of the first trimester in this study were derived from the date of delivery, gestational age at birth and the number of babies born. Prescription claims and dispensing data was used to identify exposure, and timing of exposure, to topiramate. Oral clefts were searched for using diagnosis codes and those identified in the claims databases were further verified by two paediatricians, whilst those found in the medical records were assumed valid. To build a longitudinal medical profile of the cases, medical records of the cases found in the claims databases were requested and these claims were joined together to track the medical history of the mother and her pregnancy.

Strengths and limitations of claims databases

One of the strengths of claims databases, is that most offer accurate reporting of dispensing data – claims from pharmacies for reimbursements are generally accurate due to government audits which are regularly carried out to prevent fraudulent claims being made.

Claims databases offer information on the health of a large number of individuals, but their data quality has been questionable in the past.[89;91-94] Below I outline some of the criticisms. Diagnoses made in hospitals use the International Classification of Diseases (ICD) to code symptoms and diagnoses. For a claim, these ICD codes have to be translated to Diagnosis Related Group (DRG) codes. Hospitals have been known to use the DRG code which offers the highest financial reimbursement, rather the most clinically important.[95] This highlights

another general weakness of administrative databases, in that they are not designed for specific research questions. A researcher is limited to the information which is available. In this study the authors requested medical records to supplement the information available from claims data, however even this combined administrative data may not provide all of the desired information.

Further limitations to claims data include the need for extensive data cleaning, the need to understand recording behaviour (e.g. what does a missing smoking status mean? Is recording of certain information such as BMI only given if the claimant has a particular condition?) and therefore whether or not the claimant population is representative of the general population.

Electronic medical records

Electronic medical records provide a history of interactions with the healthcare system such as prescribing and diagnosis information, test results and referrals, as well as a demographic profile of the individuals held on the database. The aim of the database is to provide a complete picture of the health of an individual in order to promote the correct course of care for that individual.

Described next is an example of an electronic medical records database, The Health Improvement Network (THIN). This is the data source which is used in the studies contained in this PhD, and here I provide details on the database itself as well as its strengths and weaknesses.

2.5. The Health Improvement Network

2.5.1. Background

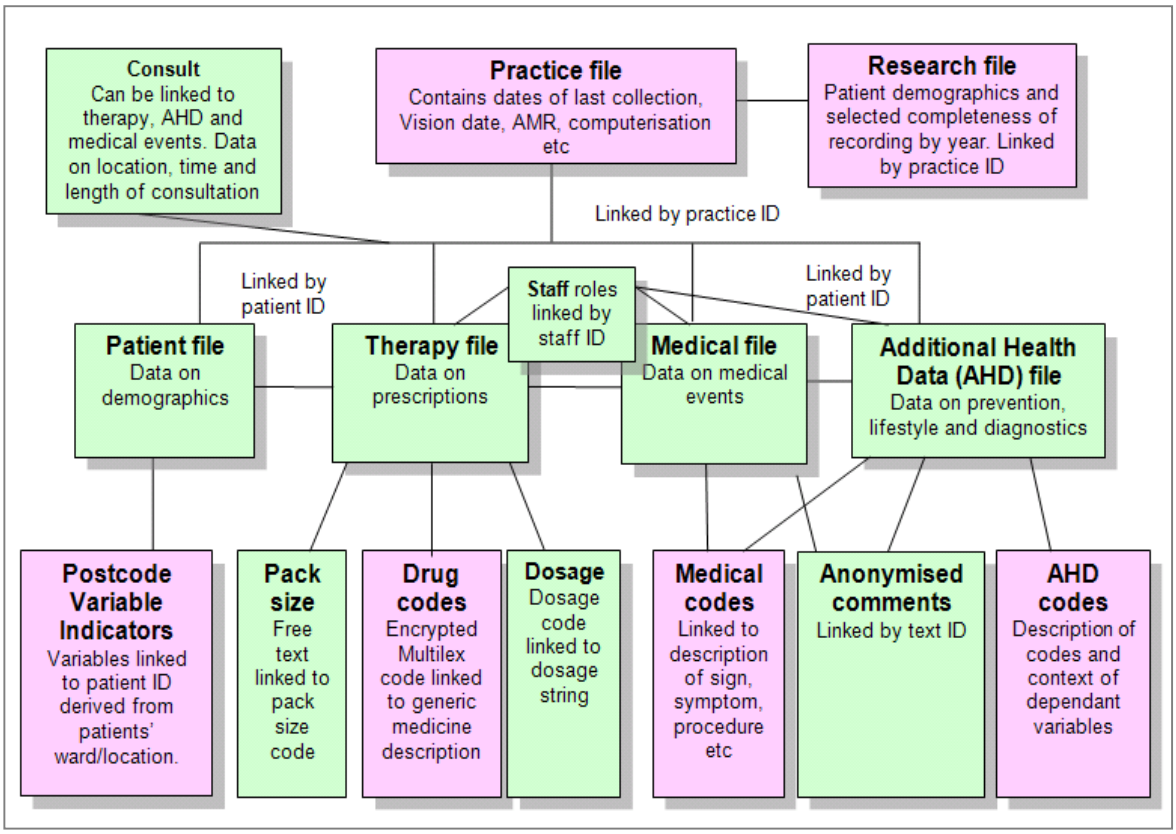
In the UK, primary care is the first point of contact for medical care (unless in an emergency situation). The general practitioner (GP) can conduct or order tests, prescribe drugs and provide some diagnoses, although many diagnoses may require confirmation from specialists. They also act as the gatekeeper to further specialist care – for example – if an individual presents with symptoms of epilepsy (e.g. recent seizures), the GP may refer the individual for further tests to be performed in a hospital setting (such as an EEG and MRI scan) and refer them

to a neurologist for specialised consultation. Generally, a specialist can only be seen through a referral from primary care (the exception being through emergency care) and therefore primary care data should at least capture the initial consultation from which a referral was made.

The Health Improvement Network (THIN) is one of the UK's largest primary care databases. In 2014, the database contained information on over 12 million patients attending 587 practices (http://csdmruk.cegedim.com/). Data in THIN is collected through an interface (provided by Vision software) which is used by the GP practice to input medical information. When the data is collected out of the system every quarter, it is anonymised to protect patient confidentiality. The data are extracted, cleaned and then structured into tables ready for researchers to analyse. Updates on THIN data are available twice a year.

Researchers receive THIN data in four main data blocks – patient, therapy, medical and additional health data (Figure 1) which collate information recorded during a patient's visit to their GP as well as information received from other parts of the health system e.g. hospital discharge letters. This includes medical diagnoses and symptoms (based on the hierarchical Read code system),[96;97] additional health data on health measures, test results and immunisations, prescriptions, referrals to secondary care and free text information. It also includes demographic information such as the patient's year of birth and sex, and a marker of social deprivation, the Townsend score. The Townsend score is a postcode based index of deprivation which uses information from the 2001 Census. The score is based on the percentage of unemployment, overcrowded households, no car/van ownership and non-home owners.[98;99] The THIN data files are linked by an anonymous patient identifier. The database also includes a family identifier as well as dates on registration, death and transfer to another practice.

Figure 1 THIN data structure (Redrawn from Source: CSD-EPIC Research Format THIN data (Version 2.0), 2010)



Data quality indicators have been created which help researchers determine when practices were providing good quality data. The Acceptable Mortality Rate (AMR) date was developed by Maguire *et al* in 2009 after it was observed in that data that some GP practices had low mortality rates indicating that mortality was not being adequately recorded.[100] The AMR date measures the year in which the death rate in the practice was deemed acceptable in comparison with age/sex adjusted national rates. For research purposes, the use of data only from this date onwards removes under-reporting of deaths and other biases associated with record updating.[100] A further measure was derived by Horsfall *et al* - the Acceptable Computer Usage (ACU) date which defines when the practice on average was entering at least two therapy records, one medical record and one additional health data record per patient per year.[101] Both dates can be used to define a point in time from which good quality data is likely to have been recorded in a practice.

Research studies using THIN data cover a broad range of conditions, drugs and epidemiology. Studies have included estimation of incidence rates such as for

pancreatic and biliary tract cancer, description of prescribing patterns such as mood stabiliser treatment in people with bipolar disorder, and studies of association such as serum bilirubin and the risk of respiratory disease and death.[34;102-105] Other uses of THIN data have been in health care planning, assessment of current clinical practices, and for methodological research.[106;107] Outlined below are the general strengths of THIN data for research, and in balance to this, some of its limitations, which have to be borne in mind and addressed in any research study. As THIN is the data source chosen for use in this PhD, the further details of advantages and disadvantages specific to studying medication safety in pregnancy are covered in the next chapter which presents how THIN can be used to identify a mother-child cohort.

2.5.2. Strengths of THIN data for research

- *Designed for research*

  One of the major differences between THIN and insurance claims databases is that THIN is intended for use in clinical research, secondary to clinical management. Thus the data captured is designed to benefit and inform primary care research. Furthermore, the providers of THIN data are continually improving their data and consulting both GP practice users and researchers on how the system and the data can be improved to meet their needs.

- *Large sample size*

  As mentioned, the database holds information for 12 million patients across the UK providing access to potentially large sample sizes for study.

- *Representative of general population*

  All data are anonymised, and are broadly representative of the UK population in terms of sex, age, size of practice and geographic distribution.[108]

- *Prospective data collection*

Studies of routinely collected data are retrospective however, more importantly, they use prospectively recorded data. This reduces the potential for recall bias whereby the level of exposure information recalled differs depending on whether or not an outcome occurred.

- *Real world clinical data*

  The data is a reflection of clinical practice in the real world amongst a population of individuals who differ in all manners of their health and socio-demographic factors. It reflects real GP behaviours which are also likely to differ but are a true representation of medical care in real time - a stark contrast to the regimented medical care recovered in clinical trials where participants are tended to at specific time points.

2.5.3. Weaknesses of THIN data for research

- *Uncollected or poorly recorded information*

  The main disadvantage in using a database of retrospectively collected routine data is that the data is not collected for a specific research study. Thus, there may be factors which are of interest to a study which are not collected, or are poorly measured. For example, there is limited information on severity the underlying conditions associated with prescribing of antiepileptic drugs.

- *Lack of information outside of primary care*

  Despite the breadth of clinical information collected in THIN, any events such as prescriptions, diagnoses, inpatient stays, which happen outside of primary care may not be well-recorded although discharge letters are sent from hospitals to GPs. This depends on efficient communication of such information to primary care and further accurate input of relevant clinical details into the computer system.

Electronic medical records databases are a powerful source of real world clinical data due to the large number of patients and wide breadth of clinical information contained in such databases. THIN is an excellent example, and furthermore

shows how routinely collected electronic medical records can serve both as a clinical management system and for use in research.

2.6. Summary

Designing a study to examine the teratogenicity of drug is challenging. Randomised controlled trials are not a favourable design for concerns over the involvement of pregnant women and the study sample required to study rare outcomes, meaning that research must depend on observational studies. Despite having to address issues around bias, confounding, and access to relevant information, observational data has the capability to provide large samples of women taking drugs in pregnancy, as well a wide range of other health and clinical information. Every observational study has to consider the aforementioned issues and additionally other issues specific to the research question in mind. In this PhD, I will conduct a retrospective cohort study of pregnant women using data from The Health Improvement Network primary care database. Some of the reasons for this choice have been alluded to in the above section on the general merits of THIN. The next chapter expands on why THIN was chosen specifically for this study of pregnant women.

Chapter 3

Using The Health Improvement Network to Identify a Mother – Child cohort

3.1. Aim of chapter

The previous chapter introduced the various data sources which can be used to study major congenital malformations and their association with *in utero* exposure to medication. The chapter concluded with the introduction of The Health Improvement Network (THIN) as the selected data source or this PhD. In this chapter, I discuss The Health Improvement Network in greater detail, with particular emphasis on how the data is used to create a cohort of pregnancies which can be linked to a child. Finally, a further review of THIN in terms of its strengths and limitations specific to this research study is given, justifying the decision to use this data source.

3.2. Cohort of pregnancies in THIN

In the UK, primary care is often the first point of contact for pregnant women for advice and referral to antenatal services.[109] Thus, a large number of pregnancies are recorded in primary care databases such as THIN which are likely to be representative of the UK population. The cohort of pregnancies derived from THIN is described in the next section. Firstly, the algorithm used to extract pregnancy data and link the pregnancy to the subsequent child's medical record, and secondly a summary of the characteristics of the cohort.

3.2.1. Method

The algorithm for identifying pregnancy information in THIN has been developed by Dr Irene Petersen (University College London) in her research on antidepressants in pregnancy.[110] Further validation techniques were developed Dr Rachel McCrea (University College London).[111;112] The pregnancy cohort and linked mother-child cohort created from these methods were used in the studies

for this PhD. Below is a brief description of how these cohorts were extracted from primary care data.

The pregnancy cohort captures women aged 13-55 years who were pregnant and registered at a GP practice contributing data to THIN between 1994 and 2012. A pregnancy was indicated in THIN if there was a Read code in the woman's medical records or additional health data pertaining to the delivery of a baby or an antenatal event. For example, "Z257.11 Normal delivery". Pregnancy start dates were ascertained from the date of the last menstrual period, gestational age of the baby at birth, preterm birth, and free text data. Delivery dates were determined using the date of the record if there was a delivery Read code in the data or derived from Read codes for postnatal visits such as "62R1.00 P/N - first day visit". Otherwise, a record of the estimated delivery date was used. If no information could be found on delivery, then it was assumed to be 280 days after the pregnancy start date (i.e. full term) if present. Similarly, if there was no start date information, and only delivery information, then the start was assumed as 280 days prior to delivery. Pregnancies where no start or end date could be found or estimated were excluded. Pregnancies were included if there was at least six months of acceptable quality data in the woman's records prior to the start of pregnancy – this was needed to determine who was prescribed antiepileptic drugs prior to pregnancy – and similarly, at least six months of follow up after delivery was required to determine who had the relevant outcomes.

A mother-child linkage algorithm links a child in THIN to the pregnancy, thus providing information on child outcomes. The existing THIN variable "famnum" is a family number and is derived based on matching addresses. This is how the initial link was made between mother and child within the same general practice. Further, a mother-child linkage was created associating a child with a pregnancy based on matching the child's month of birth to the date of delivery in the mother's records. As the exact date of birth is not known and some children may be registered sometime after birth (for example if they had been in hospital) children were considered if they were registered from birth up to least six months of age. The family number, however, also capture individuals within the same "famnum" if they lived in a block where the postcode was the same for all residents. Therefore individuals were excluded if there were more than four children

identified in the same household, or more than one mother linked to the same child.

Drs Petersen and McCrea conducted further work on the pregnancy cohort to improve the validity of the identified pregnancies. An algorithm was implemented which extracted five key types of evidence of pregnancy. These were:

- last menstrual period,
- antenatal data,
- delivery data,
- postnatal data, and
- linkage to a child.

If there were at least two different types of evidence from the list above, a pregnancy was deemed valid. An exception was if the pregnancy had only evidence of the last menstrual period and an antenatal record. Here, it was required that the antenatal record was at least 105 days after the date of the last menstrual period so that the pregnancy had at least completed the first trimester. A further exclusion was made if subsequent or previous pregnancies were found to be less than 280 days apart. There is the possibility that this removes valid pregnancies which have ended prematurely. However, the decision to exclude this was based on previous observations that suggest that the outcome for many of these pregnancies were unreliable.

3.2.2. Summary of characteristics

Between 1994 and 2012, there were 353,171 pregnancies belonging to 256,026 women identified using the above method, of which 82% (n = 288,281) could be linked to a child's medical record in THIN. The majority of the pregnancies – over 80% - were recorded from 2000 onwards (Table 5). Around 30% of women had more than one pregnancy recorded in THIN. Women were, on average, 30 years old at the time of delivery (IQR = 26-40). The distribution amongst the five levels of social deprivation measured by the Townsend score fell slightly biased to the lesser deprived groups. Amongst the children identified using the mother-child linkage, the median follow-up time for the child was 4.6 years (IQR= 2.1-8.2) and just over half of the children were boys (Table 5).

Table 5 Characteristics of pregnancies recorded between 1994 and 2012

	Number of pregnancies (N = 353,171) n (%)
Maternal age band (years)	
<20	18,095 (5.1)
20-24	53,426 (15.1)
25-29	92,482 (26.2)
30-34	112,040 (31.7)
35-39	63,679 (18.0)
40-44	12,853 (3.6)
45+	596 (0.2)
Year of delivery	
1994-1999	46,032 (13.0)
2000-2004	92,958 (26.3)
2005-2009	140,835 (39.9)
2010-2012†	73,346 (20.8)
Townsend	
1 (least deprived)	81,256 (23.0)
2	66,691 (18.9)
3	69,195 (19.6)
4	64,902 (18.4)
5 (most deprived)	48,620 (13.8)
Missing	22,507 (6.4)
Number of pregnancies in THIN‡	
1	188,862 (71.3)
2	63,258 (23.9)
>2	12,906 (4.9)
Linked to a child in THIN	
Yes	288,281 (81.6)
No	64,890 (18.4)
Length of follow up time in child (years) *(median [interquartile range])*	4.6 [2.1-8.2]
Sex of child§	
Male	147,766 (51.3)
Female	140,515 (48.7)

† This is smaller than previous years due to the requirement that pregnancies needed six months of data after delivery – pregnancies delivered in the second half of 2012 would therefore not have sufficient data in the current dataset.
‡ Denominator is the number of women (n=265,026), not number of pregnancies
§ Denominator is the number of pregnancies linked to a child (n=288,281)

3.3. Antiepileptic drugs, pregnancy and major congenital malformations recording in THIN

As Table 5 shows, THIN data is a useful resource for providing a large sample of population based pregnancies. The decision to use THIN data for this research study was based on this and a number of other strengths that are outlined below.

- *Well reported prescription data*

  In the UK, the majority of prescribing is conducted through primary care and hence is captured in a primary care database such as THIN. Moreover, the Vision software which collects data for THIN, is devised such that the information entered by the GP onto a computer system to generate a prescription for the patient to take to the pharmacy, is directly captured i.e. not re-entered after the consultation. This reduces the likelihood of errors in reporting the details of the prescription.

- *Minimal recall bias for drug exposure*

  Many studies which examine the use of drugs in pregnancy rely on retrospective methods of exposure status ascertainment. As discussed in Chapters 1 and 2, this can lead to issues around recall bias whereby women recall the exposure details differently depending on outcome status. By prospectively collecting data on exposure before outcome is known, recall bias is minimised.

- *Ideal for rare exposures and outcomes*

  Antiepileptic drug exposure in pregnant women is relatively rare. Holmes *et al* estimated this to be around 1 in 250 pregnant women.[4] Major congenital malformations are also rare – 1-3% in the general population, although possibly as high as 10% in certain antiepileptic drug exposed groups. This is compounded if investigating specific antiepileptic drug exposures, and therefore a large sample size is needed to ascertain sufficient numbers of exposures and outcomes.

- *Comparison to women with untreated conditions*

Comparisons of outcomes with similar individuals is needed is order to attribute an association with the exposure of interest and not a confounding variable. Studies which have used the general population as an unexposed comparison group (i.e. pregnancies in the general population where antiepileptic drugs were not taken in pregnancy) fail to account for the possibility that the underlying condition, such as epilepsy or bipolar disorder and factors associated with these may be confounding the association. Primary care databases are population based, thus enabling a sample of antiepileptic drug unexposed pregnancies to be gathered amongst women with similar conditions as those in the exposed groups. These unexposed pregnancies may, however, be different in that the severity of the underlying condition is milder, allowing them to be untreated – this limitation to the data is referred to later.

- *Validation of primary care data*

  There are several validation studies which have examined aspects of THIN data to see how well recorded particular events are. THIN data has good generalisability to the UK for demographics, diagnoses (including epilepsy and mental illness) and death recording.[108;113;114] THIN has also been used for studies in pregnancy and studies involving antiepileptic drug use. [110;115-117]

Along with the knowledge that pregnancies and prescribing are well recorded, the above strengths justify the choice in selecting THIN to study antiepileptic drug use in pregnancy and the risk of major congenital malformations as part of this PhD. Limitations must, however, be borne in mind throughout the study and in the overall conclusions in this thesis. Some of these are outlined below and will be further discussed in Chapter 8.

- *Adherence to prescribed medication*

  The prescribing of a drug does not necessarily mean that the drug is taken or if the drug is dispensed and therefore we cannot be certain of foetal exposure. A true effect would therefore be diluted as patients who did not consume the prescribed drug would be misclassified as exposed.

- *Lack of information on disease severity*

  Disease severity may not be well recorded for the underlying conditions of women receiving antiepileptic drugs in THIN. For example, epilepsy has a broad scope of severity with some women having many tonic-clonic seizures every day to those who have milder forms with fewer and less intensive seizures. This is important if disease and its severity are confounders i.e. they are associated with both antiepileptic drug exposure and the risk of outcomes. Few studies have captured such information in the past and as such it is unknown the extent of confounding if any.

- *Prescribing outside of primary care*

  Although GPs in the UK are responsible for the majority of prescribing, medication initiated in secondary care (e.g. accident and emergency) or in tertiary care (e.g. neurologist, psychiatrist etc.) will not be present in primary care records unless they are entered appropriately into the computer system by the GP practice in retrospect.

- *Possible under recording of non-live births*

  Table 5 showed that around 80% of the identified pregnancies could be linked to a child. These are children who have been registered at a GP surgery, therefore they were live born babies. The 20% of pregnancies which could not be linked to a child will include women who transferred to a new GP practice shortly after delivery of a live born baby, (thus the baby would be registered at a new practice and could not be linked), and also women whose pregnancies ended in a non-live birth (i.e. miscarriage, termination, stillbirth, neonatal death). These are potentially under recorded in primary care due to them being largely diagnosed outside of primary care and in hospital.

- *Retrospective case ascertainment*

  In this study, major congenital malformations need to be distinguished from minor congenital malformations – for some malformations, it is clear whether or not they are major or minor (e.g. a birth mark is generally minor), however the severity of some and therefore whether or not they are major can be difficult to ascertain from a medical record alone.

3.4. The next chapter

There are limitations to every study design, and there is not one correct method for studying medication use in pregnancy. Primary care data is a useful resource which has been underutilised in the study of antiepileptic drugs in pregnancy despite the strengths it offers. In this thesis, I plan to use to use UK primary care data to conduct three studies on antiepileptic drugs in pregnancy and major congenital malformations. In the next chapter, an overview of these studies is presented.

Chapter 4

Overview of three research studies

4.1. Aim of chapter

The first chapter of this thesis showed there is a current need to continue research into the teratogenic effects of antiepileptic drugs in pregnancy, largely to establish drug specific risks using large samples. The second chapter described various ways of conducting such a study using different designs and data sources, whilst the third chapter focussed on the use of one data source – The Health Improvement Network (THIN) – and its strengths specifically for studying the risk of antiepileptic drug use in pregnancy. Primary care data from THIN was therefore chosen to conduct a cohort study of women taking antiepileptic drugs in pregnancy, and this study is presented later in this thesis. However, prior to that, there are two studies which were conducted and are also presented in this thesis. These studies are an exploration and validation of data that is required from THIN for the main study. In this current chapter, a brief outline of the aims and objectives of each of these studies and the main cohort study is given. More detailed methods, results and discussions relating to each of the three studies are presented in later chapters.

4.2. Study 1: Antiepileptic drug prescribing in pregnancy in primary care

The aim of this study was to understand patterns of antiepileptic drug prescribing in pregnancy in primary care. This helped to verify whether sufficient information on antiepileptic drug prescribing was captured in THIN.

The specific objectives were to:

1. Examine secular trends in the prescribing of antiepileptic drugs during pregnancy;
2. Explore changes to prescribing, specifically discontinuation of antiepileptic drugs, soon after a woman becomes pregnant;

3. Identify factors associated with antiepileptic drug discontinuation in pregnancy.

4.3. Study 2: Prevalence of major congenital malformations and perinatal death in primary care

The aim of this second study was to describe the outcomes of interest for the main study: major congenital malformations and perinatal death using THIN data.

The specific objectives were to:

1. Estimate the birth prevalence of each outcome in the general population using primary care data;
2. Examine secular changes and associated demographic factors.

4.4. Study 3: Antiepileptic drugs in pregnancy and the risk of major congenital malformations or perinatal death in primary care

This is the main cohort study in this thesis which aims to answer the question - what is the risk of major congenital malformations or perinatal death associated with first trimester use of antiepileptic drugs in pregnancy?

The objectives were as follows:

1. In women who were prescribed antiepileptic drugs before pregnancy, determine the absolute risk of major congenital malformations or perinatal death for:
    a. each group of pregnancies prescribed individual antiepileptic drug monotherapy in the first trimester of pregnancy.
    b. pregnancies prescribed sodium valproate polytherapy in the first trimester of pregnancy.
    c. pregnancies where no antiepileptic drug therapy was prescribed in the first trimester of pregnancy.

2. In women who were prescribed antiepileptic drugs before pregnancy, conduct pairwise comparisons of the risk of the major congenital malformations or perinatal death between each of the following first

trimester regimens, adjusting for differences in demographic and clinical characteristics:

a. Lamotrigine monotherapy
b. Carbamazepine monotherapy
c. Sodium valproate monotherapy
d. Sodium valproate polytherapy
e. No therapy

4.5. The next chapters

Studies 1, 2 and 3 are described in full in Chapters 5, 6 and 7 respectively. The thesis concludes with an overall discussion of the collective findings in these studies and how this informs the research area with recommendations for clinical practice and further research.

Chapter 5

Antiepileptic drug prescribing in pregnancy in primary care

5.1. Aim and objectives of the chapter

The aim of this chapter is to gain a broad understanding of antiepileptic drug prescribing in pregnancy in primary care. Antiepileptic drug use in pregnancy is the exposure of interest in the main research study presented later in this thesis. Therefore, it is necessary to explore the recording of such information in the data source which I plan to use. In this exploration, I look at which drugs are prescribed to pregnant women and whether or not women continue to be prescribed following the start of pregnancy.

As set out in the previous chapter, the specific objectives were to:

1. Examine secular trends in the prescribing of antiepileptic drugs during pregnancy;
2. Explore changes to prescribing, specifically discontinuation of antiepileptic drugs, soon after a woman becomes pregnant;
3. Identify factors associated with antiepileptic drug discontinuation in pregnancy.

5.2. Introduction

Women in pregnancy generally seek support from their GP or local midwife service to provide antenatal care. As part of this care, women with chronic conditions may need further support to manage their condition throughout the course of pregnancy, which includes discussions on the use of drugs in pregnancy. Epilepsy and bipolar disorder are chronic conditions that can be treated with antiepileptic drugs and women with these conditions need to be aware of the risks and benefits of continued therapy in pregnancy, ideally before pregnancy occurs.[118;119]

The National Institute of Health and Clinical Excellence (NICE) advise against the use of one specific antiepileptic drug, sodium valproate, in pregnancy if possible because of its teratogenic risk.[24;31] In previous UK guidelines, health care

professionals were advised that women with bipolar disorder should avoid, carbamazepine and lamotrigine if possible.[24] New guidelines published in 2014 go further to state that pregnant women with mental health conditions should cease sodium valproate in pregnancy, consider ceasing carbamazepine and monitor blood serum levels of lamotrigine in pregnancy.[120] These three drugs are, however, popular drugs for treating epilepsy and bipolar disorder,[34;121] thus the dilemma of using these drugs in pregnancy affects many women. A recent survey of women with epilepsy found many of the women did not discuss the risks and benefits of antiepileptic drugs in pregnancy with their GP/neurologist.[118] Women and their health care professionals are hence, forced to face treatment dilemmas in pregnancy, rather than before.[122] Coupled with the misperception of the actual teratogenic risk of drugs,[9] women may be more inclined to stop treatment or switch treatments abruptly in pregnancy, possibly resulting in inadequate management of their underlying epilepsy or bipolar disorder which in itself places the woman at risk during their pregnancy.[51]

There is a clear need for more information on the risks and benefits of antiepileptic drugs in pregnancy. However, the first step is to explore which antiepileptic drugs are commonly prescribed. Treatment choices in pregnancy are likely to have changed in the last 20 years due to the known teratogenicity of older antiepileptic drugs such as sodium valproate and the introduction of newer antiepileptic drugs such as lamotrigine which are favoured on account of their limited side effects profile and better tolerability. Previous studies highlight sodium valproate, carbamazepine and lamotrigine as commonly prescribed antiepileptic drugs in pregnancy. In this chapter, I present my study which aims to further evaluate prescribing of antiepileptic drugs in pregnancy in general practice and furthermore, to examine the influence of pregnancy on discontinuation of antiepileptic drugs.

5.3. Methods

5.3.1. Secular trends in antiepileptic drug prescribing in pregnancy

Using the pregnancy cohort of 353,171 pregnancies described in Chapter 3, the therapy records for each pregnancy were investigated for prescriptions of antiepileptic drugs made during pregnancy. A list of drug ID codes relating to

antiepileptic drugs listed in Chapter 4.8.1 of the British National Formulary (BNF) was created and used to identify the relevant prescriptions of antiepileptic drugs (carbamazepine, ethosuximide, gabapentin, pregabalin, lamotrigine, levetiracetam, phenobarbital, primidone, phenytoin, topiramate, valproate, vigabatrin, lacosamide, rufinamide, oxcarbazepine, tiagabine, valproic acid, clobazam, clonazepam, piracetam, acetazolamide).

For each year between 1994 and 2012, the prevalence of antiepileptic drug prescribing in pregnancy was calculated as the number of pregnancies where two or more prescriptions were given within any three month period in pregnancy divided by the total number of pregnancies delivered in the given year. This attempts to capture repeat users of antiepileptic drugs and thus exclude individuals with just one-off prescriptions. Secular trends are observed for overall antiepileptic drug prescribed, and for individual antiepileptic drugs.

5.3.2. Discontinuation of antiepileptic drugs in pregnancy

Pregnant women prescribed antiepileptic drugs at least once in the three months before pregnancy were identified and stratified into three groups based on the indication for prescribing antiepileptic drugs. These indications were epilepsy, bipolar disorder or depression (identified using Read code lists found in Appendix 2) and no/other indication (for example the treatment of neuralgia) for antiepileptic drugs. Read code lists were derived based on searches for key words, examination of relevant hierarchies and clinical review - a method which has been widely used in other epidemiological studies of THIN data.[96] The prescriptions were traced from three months before pregnancy to their last consecutive prescription. This last prescription was assumed when no other antiepileptic drugs were prescribed within the subsequent three months of the previous prescription. The period of follow-up was from three months before the pregnancy start date and ended at the earlier of the last prescription date or the delivery date if the birth was premature, or two months before the delivery date if the birth was full term.

A group of non-pregnant women prescribed antiepileptic drugs was selected for comparison with pregnant women prescribed antiepileptic drugs. This included

women who had never been pregnant as well as women who had had one or more pregnancies. For the latter group I excluded periods where they were pregnant and excluded periods from two years before pregnancy to one year after a delivery. These periods were designed to exclude the time where planning pregnancy, pregnancy itself or breastfeeding may have an impact on choice of drug treatment. One non-pregnant period per woman was chosen at random. A random index date was assigned in the non-pregnant period as a comparative pregnancy start date. Non-pregnant women were also stratified by the indication for antiepileptic drugs and randomly selected within five year age bands so that the age distribution was similar to that of pregnant women. Two women for every one pregnant woman taking antiepileptic drugs were selected. For non-pregnant women, follow-up started three months before the index date and ended at the earlier of the last prescription date or 280 days after the index date.

Cox's proportional hazards regression model was used to estimate hazard ratios (HRs) comparing the time to last prescription between pregnant and non-pregnant women, stratified by indication for antiepileptic drugs. The proportion of women continuing to receive antiepileptic drug prescriptions was identified at 92 days follow-up (i.e. the approximate start of pregnancy), 134 days (i.e. approximate point of six weeks gestation), and at 288 days follow-up (i.e. approximately beginning of the third trimester). Amongst the women with no or other indication for antiepileptic drugs, it was not possible to select a similar non-pregnant group of women, thus HRs were not estimated for this group.

The following factors were examined using Cox's regression to build a model for the discontinuation of antiepileptic drugs in pregnancy, stratified by indication.

- Maternal age was categorised as younger than 25, 25-34 and 35+ years
- Social deprivation was measured using the Townsend quintile (described in Chapter 2)
- The number of times antiepileptic drugs were prescribed prior to the initiation of follow-up, i.e. in the three to six months before pregnancy, was counted and categorised as 0, 1 or 2+
- Co-medication was measured as the number of different types of drugs prescribed for treatment of conditions affecting the central nervous system

(BNF Chapter 4), excluding antiepileptic drugs and was categorised as 0, 1 and 2+, and measured in the three months before pregnancy

- Amongst women with epilepsy, co-morbidity with bipolar disorder or depression was also analysed as a risk factor.

Univariable analyses of each of these factors and adjusted analyses including all factors in the regression model were performed. The reference category was the largest group for maternal age, number of co-medications, and frequency of antiepileptic drug prescribing prior to pregnancy. Townsend score 1 (least deprived) formed the reference group for examining social deprivation.

As a secondary analysis, the discontinuation rate in pregnant women was compared between pre-pregnancy antiepileptic drugs. Women prescribed sodium valproate in the three months before pregnancy were compared to women prescribed lamotrigine and carbamazepine separately. Hazard ratios were estimated comparing the time to last prescription with sodium valproate as the reference group.

5.4. Results

5.4.1. Secular trends of antiepileptic drug prescribing prevalence

Antiepileptic drugs were prescribed in pregnancy for 1,620 (0.5%) out of 353,171 pregnancies in the cohort. Lamotrigine (0.2%; n = 573), carbamazepine (0.2%; n = 560) and sodium valproate (0.1%; n = 342) were the three most commonly prescribed antiepileptic drugs in pregnancy over the study period (Table 6).

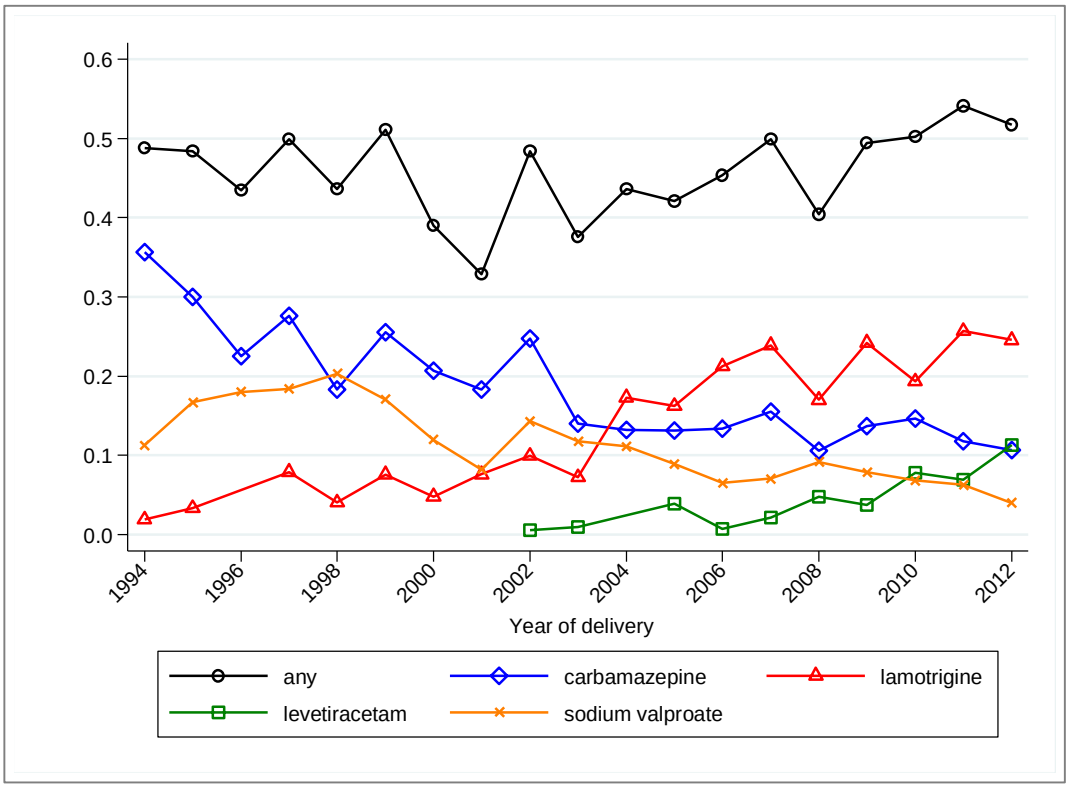
Table 6 Antiepileptic drugs prescribed in pregnancy

Women prescribed antiepileptic drugs in pregnancy (N=353,171)	n (%)
Any	1,620 (0.46)
Lamotrigine	573 (0.16)
Carbamazepine	560 (0.16)
Sodium valproate	342 (0.10)
Levetiracetam	106 (0.03)
Phenytoin	65 (0.02)
Gabapentin	61 (0.02)
Clonazepam	53 (0.02)
Clobazam	44 (0.01)
Topiramate	42 (0.01)
Pregabalin	17 (<0.01)
Phenobarbital	10 (<0.01)
Oxcarbazepine	7 (<0.01)
Ethosuximide	7 (<0.01)
Acetazolamide	5 (<0.01)
Vigabatrin	5 (<0.01)
Zonisamide	3 (<0.01)
Primidone	3 (<0.01)
Lacosamide	2 (<0.01)

Figure 2 below shows the secular changes in antiepileptic drug prescribing in pregnancy for five categories – pregnant women prescribed any antiepileptic drug in pregnancy, and pregnant women prescribed one of four most common antiepileptic drugs in pregnancy - lamotrigine, carbamazepine, sodium valproate and levetiracetam. Between 0.3% and 0.6% of pregnancies delivered each year from 1994 to 2012 were exposed to antiepileptic drugs. Amongst these, carbamazepine was the most commonly prescribed antiepileptic drug in pregnancy in the 1990's; however its use fell from around 0.4% in 1994 to 0.1% in 2012. Sodium valproate use rose for a short period between 1994 and 1998 when it reached its peak (0.2% of pregnancies) before declining to being prescribed in less than 0.05% of pregnancies in 2012. Prescribing of these older antiepileptic drugs was surpassed in 2004 when lamotrigine rose to be the most commonly prescribed antiepileptic drug. In 2012 it was prescribed in 0.3% of all pregnancies.

Newer antiepileptic drug, levetiracetam, was the fourth most commonly prescribed antiepileptic drug in pregnancy, prescribed to 0.03% of all pregnancies and a look at its secular changes shows a slow increase in its use in pregnancy since its introduction to the market in 2000. By 2012 it was as commonly prescribed as carbamazepine in 0.01% of all pregnancies.

Figure 2 Secular changes in prescribing prevalence of antiepileptic drugs in pregnancy



5.4.2. Discontinuation of antiepileptic drugs

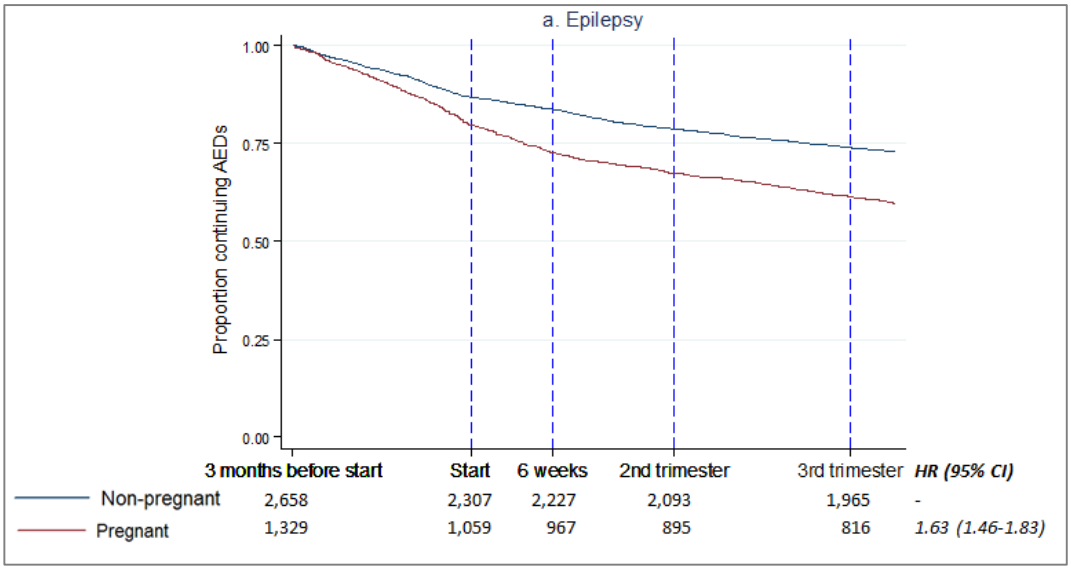
5.4.2.1. Pregnant vs. non-pregnant women

Of the 353,171 pregnant women, there were 1,911 (0.5%) who had received an antiepileptic drug prescription in the three months before pregnancy. Of these 1,329 (69.5%) had a clinical record of epilepsy and 166 (8.7%) of bipolar disorder or depression. The remaining 416 (21.8%) had no indication or other indications for the prescribing of antiepileptic drugs.

Women with epilepsy

Figure 3 shows the discontinuation rate between 1,329 pregnant women and twice as many non-pregnant women (n = 2,658) who were prescribed antiepileptic drugs for epilepsy. After 92 days follow-up (i.e. beginning of pregnancy in pregnant women), 79.6% (n = 1,059) of pregnant women and 86.8% (n = 2,307) of non-pregnant women continued to receive antiepileptic drugs. After 134 days (i.e. six weeks gestation in pregnant women) this fell to 72.7% (n = 967) of pregnant women and 83.7% (n = 2,227) of non-pregnant women. After 288 days (i.e. beginning of third trimester in pregnant women), 61.4% (n = 816) of pregnant women continued to receive antiepileptic drug prescriptions, compared to 73.9% (n = 1,965) of non-pregnant women. Overall, pregnant women with epilepsy were found to be more likely to discontinue antiepileptic drugs in pregnancy compared to non-pregnant women with epilepsy (HR 1.63, 95% CI 1.46-1.83).

Figure 3 Antiepileptic drug discontinuation in women with epilepsy

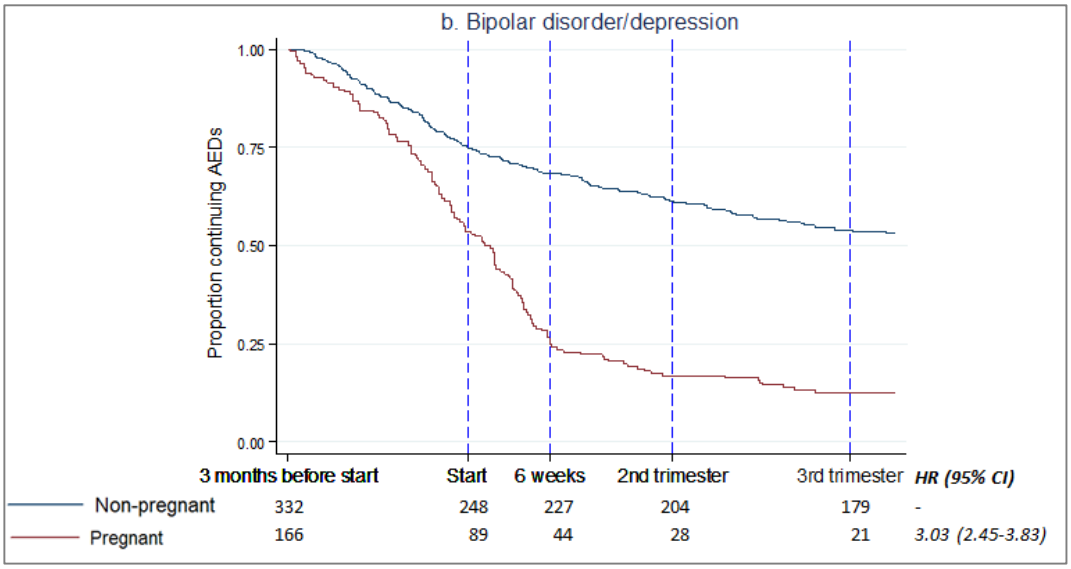


Women with bipolar disorder or depression

Compared to 332 non-pregnant women taking antiepileptic drugs for bipolar disorder or depression, the rate of discontinuation of antiepileptic drugs was much faster in 166 pregnant women (Figure 4). After 92 days follow-up, just over half (n = 89) of the pregnant women continued to be prescribed compared to 74.7% (n=248) of non-pregnant. There was a rapid decline for pregnant women - only

26.5% (n = 44) remained to be treated at 134 days follow-up, compared to 68.4% (n = 227). By the beginning of the final trimester, 12.7% (n = 21) and 53.9% (n = 179) of pregnant and non-pregnant women respectively were prescribed. Overall, pregnant women with bipolar disorder or depression were three times more likely to cease antiepileptic drugs compared to non-pregnant women (HR 3.03, 95% CI 2.45-3.83).

Figure 4 Antiepileptic drug discontinuation in women with bipolar disorder/depression

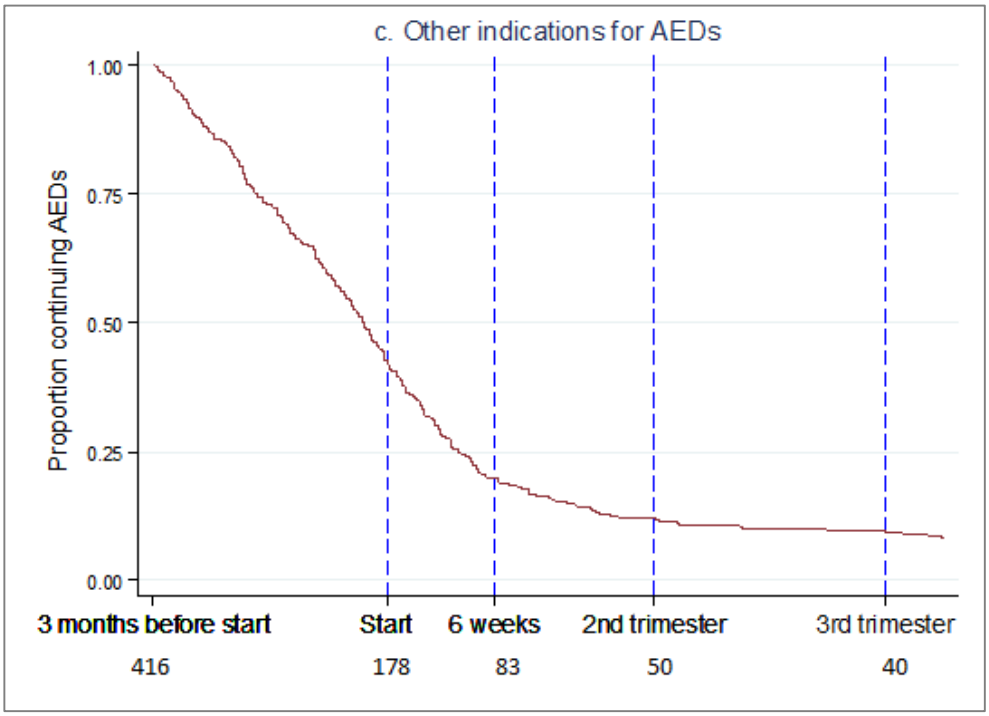


A review of the therapy records of the 122 women who had ceased receiving prescriptions for antiepileptic drugs six weeks into the pregnancy found 66 (54%) women continued on alternative antidepressants/antipsychotics in the first trimester, leaving 56 (46%) women who did not. Only 14 women were found to restart antiepileptic drugs later in pregnancy.

Women with other indications for antiepileptic drugs

A total of 416 women were prescribed antiepileptic drugs in the three months before pregnancy where an indication of epilepsy, bipolar disorder or depression was not entered in the medical records. Figure 5 shows that there is a dramatic decline in the use of antiepileptic drugs in pregnancy for this group. By the start of pregnancy, just under half continue to be treated with antiepileptic drugs (42.8%; n = 178), and falling to 20.0% (n = 83) by six weeks gestation. By the beginning of the third trimester, 90.4% (n = 376) had ceased being prescribed antiepileptic drugs.

Figure 5 Antiepileptic drug discontinuation in women with no/other indications



5.4.2.2. Discontinuation rates by specific antiepileptic drugs in pregnancy

Pregnant women with epilepsy

Of 1,329 pregnant women with epilepsy who were receiving antiepileptic prescriptions in the three months preceding pregnancy, 409 (30.8%) were prescribed lamotrigine, 408 (30.7%) prescribed carbamazepine and 270 (20.3%) prescribed sodium valproate.

Figure 6 Antiepileptic drug discontinuation in pregnant women with epilepsy by drug

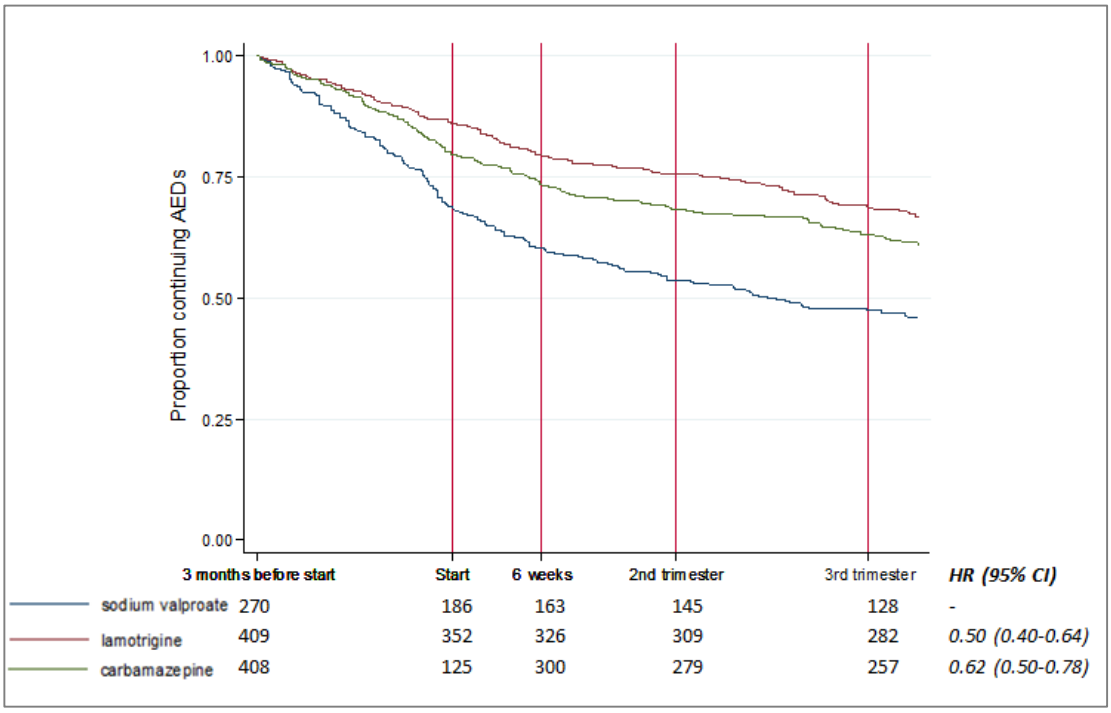


Figure 6 shows that the most marked decline in continuation of antiepileptic drugs was amongst women who were prescribed sodium valproate before pregnancy. After six weeks gestation, 59.3% (n = 163) of the sodium valproate users continued therapy, whilst 79.7% (n = 326) of the lamotrigine group and 73.5% (n = 300) of the carbamazepine group continued. By the end of the second trimester, less than half of the sodium valproate group were still receiving antiepileptic drug treatment (n = 128) compared to 68.9% (n = 282) of lamotrigine and 63.0% (n = 257) of carbamazepine users.

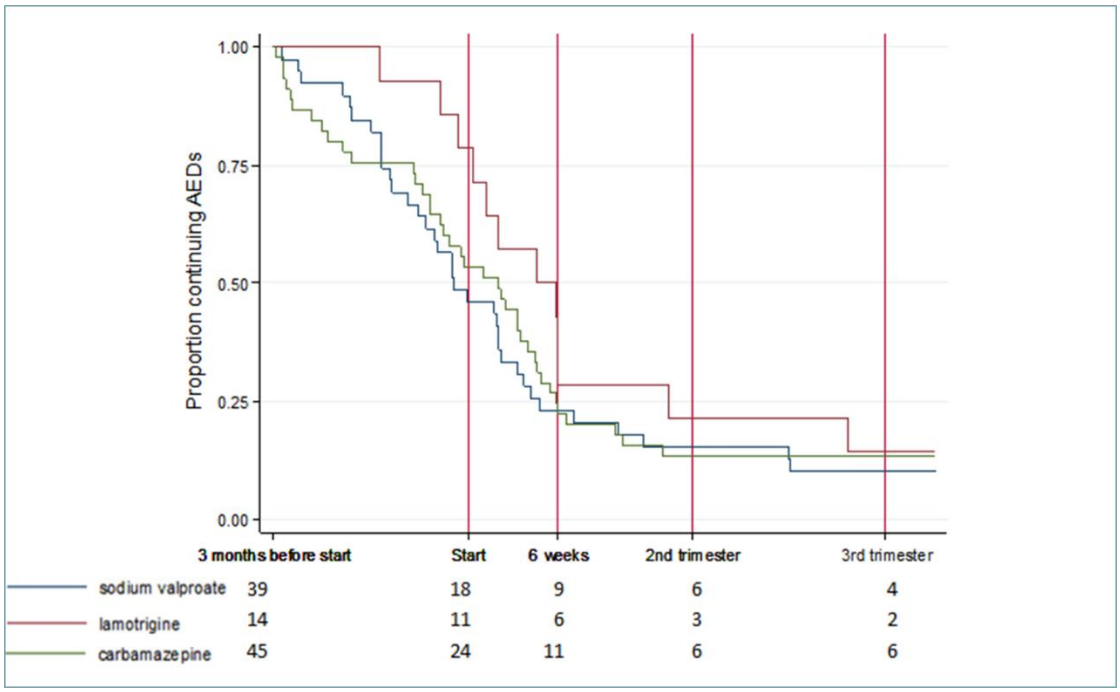
Overall, women prescribed lamotrigine before pregnancy were 50% less likely to stop antiepileptic drugs in pregnancy compared to women prescribed sodium valproate (HR 0.50, 95% CI 0.40-0.64). For women prescribed carbamazepine before pregnancy, the likelihood of stopping was 38% less than that of women prescribed sodium valproate (HR 0.62, 95% CI 0.50-0.78).

Pregnant women with bipolar disorder or depression

Of 166 pregnant women with bipolar disorder or depression prescribed antiepileptic drugs in the three months prior to pregnancy, 39 (23.5%) were receiving sodium valproate, 14 (8.4%) lamotrigine and 45 (27.1%) carbamazepine (Figure 7). At six weeks gestation, 23.1% (n = 9) of sodium

valproate users, 42.9% (n = 6) of lamotrigine users and 24.4% (n = 11) of carbamazepine users continued on therapy. By the beginning of the third trimester, 4 (10%) 2 (14%) and 6 (13%) of sodium valproate, lamotrigine and carbamazepine users, respectively, were continuing antiepileptic drugs.

Figure 7 Antiepileptic drug discontinuation in pregnant women with bipolar disorder/depression by drug



5.4.2.1. Factors predicting discontinuation of antiepileptic drugs in pregnancy

Pregnant women with epilepsy

In univariable analyses, all five examined factors were associated with the likelihood of antiepileptic drug discontinuation in pregnancy amongst women with epilepsy. A full model (maternal age, Townsend score, frequency of antiepileptic drug prescribing before pregnancy, co-medication use and, in women with epilepsy, co-morbidity with depression) was therefore analysed, and after adjusting, the variables which predicted discontinuation were age, previous prescriptions of antiepileptic drugs before pregnancy and use of co-medications. Table 7 displays the HRs for the full model.

Most pregnant women with epilepsy were aged between 25 and 34 years, thus this group were the baseline for comparison between age bands. Hazard ratios indicate that pregnant women who were younger than 25 years at the start of pregnancy were slightly more likely to discontinue (HR 1.20, 95% CI 0.99-1.47), and that women older than 35 years were less likely to discontinue (HR 0.77 95% CI 0.59-1.01). While the confidence intervals for these estimates includes 1 the overall p-value (0.012) suggests that, overall, there was a significant effect of age.

The majority of women had received two or more prescriptions of antiepileptic drugs in the three to six months prior to pregnancy and, compared to this group, those women prescribed antiepileptic drugs only once were three times more likely to stop being prescribed antiepileptic drugs in pregnancy (HR 3.46, 95% CI 2.85-4.20). Women with no antiepileptic drugs prescribed in this period were nearly six times more likely to stop being prescribed in pregnancy (HR 5.81, 95% CI 4.59-7.35).

Most women were not prescribed other drugs treating the central nervous system (CNS) (e.g. antidepressants or antipsychotics). The overall p-value (0.019) suggests there is a significant effect of co-medication with CNS drugs – those prescribed CNS drugs are more likely to discontinue (Prescribed one other CNS drug - HR 1.32 (95% CI 1.06-1.65); prescribed more than one other CNS drug – HR 1.37 (95% CI 0.98-1.91)).

Pregnant women with bipolar disorder or depression

The Townsend score of social deprivation did not affect the likelihood of discontinuation of antiepileptic drugs in pregnancy. All other factors did and were entered into a multivariable model. Adjusted HRs are displayed in Table 7.

The most common age band was 25-34 years of age forming the comparison group. Those older (35 years or more) were less likely to stop antiepileptic drugs in pregnancy (HR 0.55 95% CI 0.36-0.85), but for those younger (under 25 years) were no different (HR 0.88, 95% CI 0.54-1.42).

There was an overall significant effect of the frequency of antiepileptic drug prescribing before pregnancy on the likelihood of discontinuation in pregnancy. Those who had no prescriptions of antiepileptic drugs before pregnancy were twice as likely to discontinue in pregnancy, compared to those who had received more than one prescription before pregnancy (HR 2.02, 95% CI 1.33-3.07). Those with just one prescription were slightly more likely than those with more than one prescription to discontinue treatment in pregnancy (HR 1.31, 95% CI 0.83-2.08).

Overall, the p-value suggest that there is a difference in the likelihood of antiepileptic drug discontinuation in pregnancy depending on the number of other co-medications the woman receives. Compared to women with more than one other co-medication, those who none were twice likely to stop antiepileptic drugs in pregnancy (HR 2.20, 95% CI 1.29-3.77). Women with only one other co-medication were also more likely than those receiving more than one to cease treatment in pregnancy, however to a lesser extent (HR 1.36, 95% 0.95-1.95).

Table 7 Risk factors for discontinuation of antiepileptic drugs in pregnant women

	Pregnant women with epilepsy (N = 1329)					Pregnant women with bipolar disorder (N = 166)				
		Unadjusted		Adjusted			Unadjusted		Adjusted	
	N	HR (95% CI)	p-value	HR (95% CI)	p-value	N	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)										
<25	326	1.39 (1.15-1.69)	<0.001	1.20 (0.99-1.47)	0.012	26	1.06 (0.68-1.65)	0.004	0.88 (0.54-1.42)	0.024
25-34	809	1		1		99	1		1	
35+	194	0.84 (0.65-1.10)		0.77 (0.59-1.01)		41	0.50 (0.33-0.77)		0.55 (0.36-0.85)	
Depression/ bipolar disorder										
No	1183	1	<0.001	1	0.10					
Yes	146	1.56 (1.23-1.98)		1.24 (0.96-1.61)						
Townsend										
1	245	1		1		24	1			
2	203	1.36 (1.00-1.86)		1.31 (0.96-1.79)		24	1.14 (0.62-2.08)			
3	246	1.36 (1.01-1.82)	0.011	1.23 (0.91-1.66)	0.24	22	0.87 (0.46-1.62)	0.248		
4	294	1.46 (1.10-1.94)		1.24 (0.93-1.66)		50	1.40 (0.84-2.34)			
5	252	1.68 (1.26-2.24)		1.44 (1.07-1.94)		33	0.87 (0.49-1.54)			
Missing	92	1.19 (0.79-1.78)		1.06 (0.71-1.61)		13	1.31 (0.63-2.73)			
Previous antiepileptic drugs										
0	140	6.24 (4.95-7.88)	<0.001	5.81 (4.59-7.35)	<0.001	48	2.08 (1.43-3.04)	0.001	2.02 (1.33-3.07)	0.004
1	361	3.26 (2.70-3.95)		3.46 (2.85-4.20)		28	1.56 (1.00-2.44)		1.31 (0.83-2.08)	
2+	828	1		1		90	1		1	
Co-medications										
0	1011	1	0.008	1	0.019	18	2.09 (1.24-3.52)	0.021	2.20 (1.29-3.77)	0.011
1	235	1.32 (1.07-1.63)		1.32 (1.06-1.65)		63	1.23 (0.87-1.75)		1.36 (0.95-1.95)	
2+	83	1.41 (1.03-1.93)		1.37 (0.98-1.91)		85	1		1	

5.5. Discussion

Key findings

Approximately 1 in 200 pregnancies in primary care between 1994 and 2012 were prescribed antiepileptic drugs during pregnancy. There has been a decline in prescribing of the older antiepileptic drugs in pregnancy namely carbamazepine and sodium valproate since 1994 whereas prescribing of lamotrigine, a newer antiepileptic drug, has increased five-fold since 2000. Pregnancy was a determinant for the discontinuation of antiepileptic drugs particularly for women with bipolar disorder/depression. Furthermore, fewer prescriptions of antiepileptic drugs before pregnancy and fewer co-medications were associated with the likelihood of discontinuation in pregnant women. Finally, older women were more likely to continue treatment than younger women.

Secular trends in antiepileptic drugs prescribing in pregnancy

Secular changes in the prescribing of antiepileptic drugs in pregnancy have been analysed in other countries. The Australian Register of Antiepileptic drugs in Pregnancy found similar patterns with regards to specific antiepileptic drugs – decreases in sodium valproate and carbamazepine, and increases in the use of lamotrigine and levetiracetam.[123] The US based Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) examined trends in antiepileptic drug prescribing in pregnancy between 2001 and 2007, and although specific antiepileptic drugs were not examined, they found prescribing of older antiepileptic drugs as a group, did not vary much over the study period, whereas newer antiepileptic drugs increased by five-fold.[124] The European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) used pooled data from 38 countries to examine the utilisation of antiepileptic drugs in pregnancy, and assessed secular trends for common antiepileptic drugs which included carbamazepine, sodium valproate and lamotrigine. Again, carbamazepine use declined and lamotrigine rose, but sodium valproate fell only slightly.[125] These studies combined with the results from my study show a consistent pattern in that carbamazepine prescribing has fallen whilst lamotrigine use in pregnancy is becoming more common. There are some differences between these studies on the secular changes in sodium valproate use; however, one must bear in mind country specific differences in prescribing practices for

epilepsy and bipolar disorder, as well as for pregnant women in general, and to my knowledge, this is the first study to look at secular changes in antiepileptic drug prescribing in pregnancy in the UK.

Sodium valproate is generally not recommended for use in pregnancy because of its teratogenicity,[24;31] and the results of my study reflect this guidance being implemented. Carbamazepine has also been associated with a higher risk of major congenital malformations in some studies.[4;5;126-128] Whilst studies on lamotrigine have been few in numbers and small in scale, results have been promising in terms of risk of major congenital malformations.[5;18;129-131] The awareness of these studies may be contributory to the changes observed in the prescribing of antiepileptic drugs in pregnancy over time. In the general population, there has been a general increase in the use of newer antiepileptic drugs as observed in the study by *Nicholas et al.*[121] However, the use of carbamazepine and sodium valproate remained relatively stable over the study period, 1993-2008.[121] In my study, use of carbamazepine and sodium valproate declined in pregnancy thus it is likely that overall changes in the general population use do not fully explain the changes observed in pregnancy.

Discontinuation of antiepileptic drugs

To my knowledge, this is the first study to examine discontinuation of antiepileptic drugs in pregnancy in the UK. Women were more likely to stop antiepileptic drugs when pregnant, and when analyses were stratified by indication, those prescribed antiepileptic drugs for bipolar disorder/depression were highly likely to stop. The reasons for discontinuation may include one or all of the following:

1) Concerns over the risk of the teratogenic effects of antiepileptic drugs
2) Their condition is mild enough to allow them to be untreated in pregnancy
3) Their condition allows for alternative drugs to be prescribed

Concerns for the risk of antiepileptic drugs in pregnancy

Women should be aware of the risks that are associated with antiepileptic drugs in pregnancy when they are prescribed antiepileptic drugs for the first time, or once they reach child-bearing age.[23] This is to avoid having to make changes to treatment in pregnancy and risking the effects of inadequate management of the underlying illness. However, a recent survey of women with epilepsy found many

are still not receiving appropriate pre-pregnancy counselling and advice on the use of antiepileptic drugs in pregnancy.[118] Furthermore, a wider understanding of the risk of prescribed medications in pregnancy has been shown to be lower in certain sociodemographic groups.[9;10;132;133] This lack of communication and knowledge may lead to poorly informed decisions to discontinuation of treatment in pregnancy.

Less severe conditions allow discontinuation

Disease severity is not measured directly in THIN. However, its potential for unmeasured confounding should not be ignored. Women with different levels of severity may be more or less likely to stop medication in pregnancy. One could argue that those with a more severe form of e.g. epilepsy, may be more likely continue antiepileptic drug treatment because they were highly likely to have a relapse if untreated. Despite this, some women may still choose to stop because of the worries about the teratogenic effects of the drugs themselves.

Although one cannot directly ascertain severity from THIN, other variables can be proxies for disease severity. When the factors affecting the likelihood of discontinuation were examined, it was found that women on fewer co-medications and who were prescribed fewer times in the period prior to pregnancy were more likely to discontinue. Both of these factors may be proxies for disease severity – women on fewer medications and prescribed less often may have a less severe form of the underlying illness which may allow them to stop treatment in pregnancy.

Alternative drugs are prescribed

There are no alternatives for treating epilepsy except for non-pharmacological interventions such as surgery and a specialised (ketogenic) diet. For bipolar disorder and depression, some antipsychotics and antidepressants that have a better safety profile can be prescribed in pregnancy – this study showed just over 50% of those who stopped antiepileptic drugs continued on alternative treatments.

These are all possible explanations, and the data used in this study can support these reasons for some women – e.g. that some women stop because they can

carry on with other medicines, but the data are otherwise limited in providing a reason for antiepileptic drug cessation in pregnancy.

Strengths and weaknesses

This study has utilised routinely collected health care data from a large population representative sample in the UK. In THIN data, we see that:

- antiepileptic drug prescribing in pregnancy is well captured and comparable to one other study which estimated 1 in 250 women used antiepileptic drugs in pregnancy; [4]
- the commonly prescribed antiepileptic drugs in pregnancy are sodium valproate, carbamazepine and lamotrigine, which is consistent with reports from other UK studies;[5;17]
- there is a large proportion of women stopping antiepileptic drugs in pregnancy implying a need for more information on the risks and benefits of antiepileptic drug use in pregnancy thereby reducing the number of women who need to make changes to treatment in pregnancy.

The main limitation of THIN data in examining prescribing patterns has been mentioned in previous chapters – that is that drug adherence cannot be established from the data, only the act of prescribing the drug. However, the study of UK dispensing data showed that 98% of antiepileptic drugs prescribed are dispensed, which is step closer to being a proxy for adherence.[134]

Summary

Primary care data captures a large number of pregnant women prescribed antiepileptic drugs in pregnancy. The strengths listed above suggest it is a valuable data source for examining drug exposures in pregnancy, especially because prescribing in the UK is largely conducted through primary care. The commonly prescribed antiepileptic drugs are sodium valproate, carbamazepine and lamotrigine. Their use in pregnancy has changed over time, and newer antiepileptic drugs (lamotrigine and levetiracetam) are increasingly being prescribed despite there being fewer studies on their safety in pregnancy compared with some of the older antiepileptic drugs. Given also that pregnant women have been observed in this study to be likely to stop antiepileptic drugs in

pregnancy, this supports the need for more information to be sought on how antiepileptic drugs adversely affect the foetus in pregnancy in order to prevent unnecessary changes to treatment in pregnancy, which in itself can harm the foetus.

5.6. How this informs the next chapter

In this chapter, the exposure of interest – antiepileptic drug use in pregnancy - was examined in primary care data to establish the data's adequacy for conducting the main analysis. Next, I look at whether or not primary care data suitably records the outcomes of interest in the main research question – major congenital malformations and perinatal death.

Chapter 6

Birth prevalence of major congenital malformations and perinatal death in the general population in primary care

6.1. Aims and objectives of chapter

The main study in this thesis investigates the relationship between foetal antiepileptic drug exposure and the risk of major congenital malformations. In Chapter 5, antiepileptic drug exposure in pregnancy was examined in primary care data, and in this chapter, I examine the outcome of interest major congenital malformations, looking at the birth prevalence, secular changes and associated demographic factors. In the discussion section to this chapter, these estimates are compared against national estimates from external sources in order to judge whether or not primary care data is suitable for investigating teratogenicity.

6.2. Background

Primary care data such as that from The Health Improvement Network (THIN) should hold information on diagnoses of major congenital malformations since these are events of major importance to the GP. Major congenital malformations can have an impact on the life of a child whether it is surgical, physical or functional. However, the diagnosis is initially made in hospital at birth and its appearance in primary care data is dependent on the receipt of the hospital discharge letter and accurate entry of the details from the letter into the GP system. The diagnosis may be in either the mother or the child's records since it is pertinent to the care of both. Clearly, this is only recorded on a child's medical record if the baby was born alive. From a methodological perspective, it is important to gather as much information on pregnancy outcomes as possible – a restriction to only live born babies may introduce a bias to results and has the potential to underestimate teratogenic risks (if present) by excluding non-live births especially as some major congenital malformations may lead to the death or termination of the foetus. Therefore, both mother and child records need to be interrogated in the main study, the outcome will be a composite of major congenital malformations and perinatal death. Although perinatal death is a

possible teratogenic consequence, when such an event occurs, the recording of perinatal death may to take precedence over a diagnosis of a major congenital malformation. By capturing both events, this may reduce any selection bias induced by only including live births.

There is little research on the validation of major congenital malformations and perinatal death in primary care data. Sokal *et al* recently analysed the validity of major congenital malformations recording in THIN in children born between 1990 and 2009 by comparing prevalence rates with EUROCAT* figures for overall and system-specific major congenital malformations.[135] They found 193 per 10,000 births in THIN were diagnosed with a major congenital malformation in the first year which was slightly higher than EUROCAT estimate of 167 per 10,000. Nevertheless, THIN was regarded as a valuable resource for studying major congenital malformation by the authors. An internal validation of major congenital malformations has also been performed by Charlton *et al* who used paper records and free text data to verify diagnoses of major congenital malformations made using Read codes in the primary care database, the General Practice Research Database (GPRD, now Clinical Practice Research Datalink).[136] This study covered the time period 1990 to 2006. They found that the majority of Read code diagnoses of major congenital malformations could be confirmed – 85% were supported by paper records or free text. In another study by the same authors, estimates of major congenital malformations in children born to women with epilepsy were calculated using GPRD primary care data and compared with estimates from the UK Epilepsy and Pregnancy Register. They found similar point estimates for the overall risk of major congenital malformations associated with antiepileptic drug monotherapy but, unlike the UK Epilepsy and Pregnancy Register study, did not find statistically significant differences when compared to unexposed groups.[137]

In contrast, there are no studies to my knowledge which have validated non-live birth recording in UK primary care data. In 2012, Ban *et al* analysed non-live births in THIN data in their study of pregnancies amongst women with depression and anxiety, generating point estimates for perinatal death, miscarriages and terminations, however no validations were performed.[138]

There are some studies which indicate that major congenital malformations are well recorded in primary care. However, methods used to obtain major congenital malformation diagnoses can be varied and decisions on which congenital malformations are classed as major can be subjective. Thus a validation of methods used to determine major congenital malformations is justified if the methods will consequently be used in further studies. Given that little is known on how well perinatal death is recorded in primary care, an analysis of the prevalence will shed light on its representativeness of the general population and, furthermore, if it is sufficient to use primary care data in the main study.

6.3. Methods

6.3.1 Study design

A retrospective cohort study of pregnant women was conducted to estimate the birth prevalence of major congenital malformations and perinatal death in THIN.

6.3.2 Definitions

Birth prevalence

The birth prevalence is measured as the number of cases with the outcome amongst the birth population.

Major congenital malformations

Congenital malformations are recorded in primary care data as Read code diagnoses which may be contained in either the child's medical records or the mother's. In the child's records, a diagnosis was searched for up to one year after birth. In the mother's records, an *in utero* diagnosis was searched for during the mother's pregnancy.

The Read code system does not distinguish major and minor congenital malformations. Thus, congenital malformation records identified from the mother or child's medical records were first excluded if they were a minor malformation as classified using the EUROCAT list of minor anomalies (see Appendix 3). A specific exclusion was diagnoses of patent ductus arteriosus (PDA) recorded before 37 weeks gestation. (This is a defect of the valve connecting the

pulmonary artery and the aorta whereby the closure of the valve has failed and requires pharmacological/surgical intervention to correct. It is more likely to close without intervention in preterm babies, therefore these are not considered major malformations.) The remaining malformations records were individually reviewed by a GP to determine whether or not the congenital malformation was major. Associated free text was used to glean further information and if it remained unclear, the malformation was categorised as minor.

Perinatal death

This is defined as the death of the foetus *in utero* from 20 weeks gestation, stillbirth and early neonatal death in the first seven days of life. A Read code list based on a list of key words and synonyms of perinatal death was defined and used to identify events recorded in the medical records of pregnant women between 20 weeks gestation and one week after delivery (see Appendix 3). Pregnancies ending in stillbirth were also found in the Additional Health Data records under “Birth details”. In addition, the free text entries for pregnancies without a link to a child in THIN were interrogated for key words which identified records containing synonyms of perinatal death Table 8. Each case identified in the free text search was reviewed to confirm a diagnosis of perinatal death.

Table 8 Key words used in search of free text entries in medical records of pregnant women

Key words for perinatal death	
• stillbirth	• neonatal death
• still birth	• foetal death
• still born	• death of foetus
• stillborn	• death of fetus
• fetal death	• perinatal death
• intrauterine death	• infant death
• iud	• newborn death

Demographic factors

Maternal age

Age was calculated at the time of delivery and stratified into five-year age bands (<20, 20-24, 25-29, 30-34… ≥50 years). Where univariable analyses showed similar risks between adjacent age bands, these age bands were grouped for multivariable analyses.

Sex of baby

This was only known for pregnancies linked to a child in THIN. A separate "Unknown" category was indicated where there was no linked child.

Social deprivation

A score of social deprivation is measured in quintiles by the Townsend score. A missing category was created for those where there is no measure of social deprivation.

Calendar year

This is the year of the delivery and is defined from 1994-2012.

6.3.3 Data analysis

Major congenital malformations

The overall birth prevalence of major congenital malformations in the pregnancy cohort was calculated. Annual birth prevalence rates were calculated for each year between 1994 and 2012. Univariable analyses were conducted using Poisson regression to obtain risk ratios and 95% confidence intervals for differences in the risk of major congenital malformations across each of the demographic variables set out above. For year of delivery and age band, the group with the greatest denominator (i.e. number of pregnancies) was the reference group. For Townsend score, those with the lowest level of social deprivation (i.e. Townsend score = 1) were the reference group, and for sex of baby, males were the reference group. Adjusted risk ratios were calculated in multivariable analyses using log-likelihood ratio tests to determine the inclusion of each variable into an adjusted model. Clustering of pregnancies with the individual patient level was examined as a random effect.

The number of days from the start of pregnancy to the first record of a major congenital malformation was calculated for all pregnancies where a major congenital malformation was diagnosed. Using survival analysis techniques, the

timing of diagnosis entry into the primary care records is illustrated on a Kaplan-Meier graph.

Perinatal death

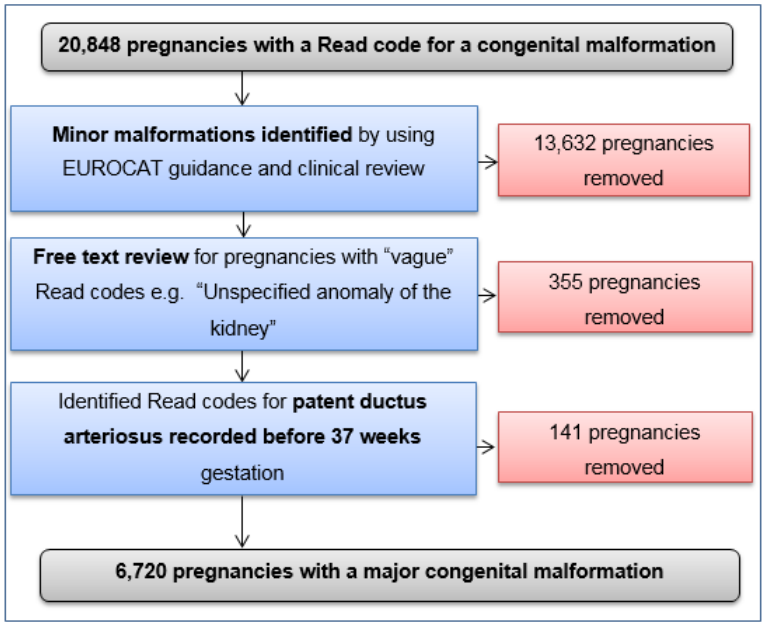
Similar to the analysis of major congenital malformations, overall prevalence was calculated and differences by socio-demographic factors examined using Poisson regression. Annual rates were calculated between 1994 and 2012 to examine time trends.

6.4. Results

6.4.1 Major congenital malformations

Of 353,171 pregnancies captured over the study period, 6,720 (1.9%) pregnancies were identified with a clinical record for a major congenital malformation recorded in either the mother's or the child's data. Figure 8 describes how 20,848 pregnancies with *any* malformation recorded were reduced to only those 6,720 with a major malformation using the methods described earlier (section 6.3.2).

Figure 8 Identification of major congenital malformations

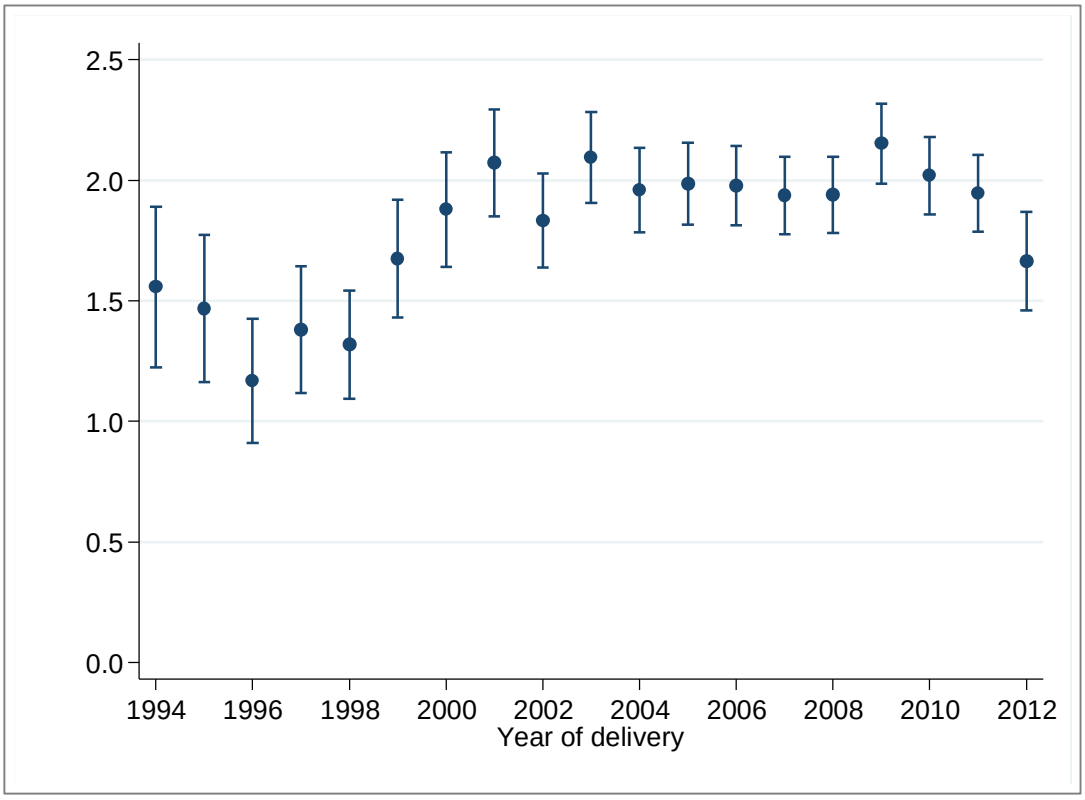


Birth prevalence rates over time

The overall birth prevalence of major congenital malformations was 1.9% (95% CI 1.9-2.0%). Figure 9 shows the prevalence rate per year for 1994-2012. A

general increase can be seen between 1996 and 2001 from 1.2% (95% CI 0.9-1.5%) to 2.1% (95% CI 1.9-2.3%) respectively. Since 2001, prevalence has remained relatively stable between 1.7% and 2.1%.

Figure 9 Birth prevalence of major congenital malformations between 1994 and 2012



Demographic characteristics

Table 9 shows the prevalence rate across year bands, maternal age, and level of social deprivation and sex of the baby.

Table 9 Prevalence of major congenital malformations (MCMs) in 353,171 pregnancies by demographic factors

	Total pregnancies (N = 353,171)	Pregnancies with MCMs, n (%)	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Year of delivery						
1994-1999	46,032	661 (1.44)	0.72 (0.66-0.78)	<0.001	0.87 (0.80-0.94)	0.006
2000-2004	92,958	1,836 (1.98)	0.99 (0.93-1.05)		0.99 (0.94-1.05)	
2005-2009	140,835	2,816 (2.00)	1		1	
2010-2012	73,346	1,407 (1.92)	0.96 (0.90-1.02)		0.95 (0.89-1.01)	
Age band (years)						
<20	24,363	488 (2.00)	1.08 (0.98-1.19)	0.017	1.08 (0.97-1.19)	0.004
20-24	58,016	1,106 (1.91)	1.03 (0.95-1.10)		1.01 (0.94-1.09)	
25-29	98,639	1,807 (1.83)	0.99 (0.93-1.05)		0.98 (0.92-1.05)	
30-34	108,699	2,020 (1.86)	1		1	
35-39	54,101	1,088 (2.01)	1.08 (1.01-1.16)		1.09 (1.01-1.17)	
40-44	8,982	200 (2.23)	1.20 (1.04-1.39)		1.21 (1.05-1.40)	
45+	371	11 (2.96)	1.60 (0.88-2.89)		1.92 (1.06-3.48)	
Townsend score						
1	81,256	1,475 (1.82)	1	0.007	1	0.007
2	66,691	1,226 (1.84)	1.01 (0.94-1.09)		1.02 (0.94-1.10)	
3	69,195	1,364 (1.97)	1.09 (1.01-1.17)		1.09 (1.02-1.18)	
4	64,902	1,327 (2.04)	1.13 (1.05-1.21)		1.14 (1.05-1.23)	
5	48,620	933 (1.92)	1.06 (0.97-1.15)		1.08 (0.99-1.18)	
Missing	22,507	395 (1.76)	0.97 (0.87-1.08)		1.00 (0.89-1.12)	
Sex of baby						
Male	147,766	4086 (2.77)	1	<0.001	1	<0.001
Female	140,515	2473 (1.76)	0.64 (0.61-0.67)		0.64 (0.61-0.67)	

Maternal age

In univariable analyses, the incidence of major congenital malformations was significantly different across age bands. Women in the higher age bands – 35-39 and 40-44 years – had a moderately increased risk of major congenital malformations (35-39: IRR 1.08 95% CI 1.01-1.16; 40-44: IRR 1.20 95% CI 1.04-1.39). Women in younger age bands were not dissimilar to the baseline group. Adjusting for year of delivery, Townsend score of deprivation and the sex of the baby did not alter the risk ratios markedly, except for in the oldest group of women. The adjusted model found these women aged 45 and over were nearly twice as likely to have a baby with a major congenital malformation than women aged 30-34 years (adjusted IRR 1.92 95% CI 1.06-3.48).

Social deprivation

The risk of having a baby with a major congenital malformation differed significantly across levels of social deprivation however the risk ratios remained close to one in both univariable and multivariable analyses. Women in the least deprived group formed the baseline category and women with Townsend scores of 3 or 4 were at a slightly higher risk of major congenital malformations (Townsend = 3; adjusted IRR 1.09 95% CI 1.02-1.18; Townsend = 4: adjusted IRR 1.14 95% CI 1.05-1.23).

Year of delivery

The year of delivery was grouped into bands and rates compared to pregnancies delivered between 2005 and 2009. In year bands 2000-2004 and 2010-2012, confidence intervals crossed one in both univariable and multivariable analyses suggesting no difference in prevalence of major congenital malformations. However, prevalence was lower in earlier years between 1994 and 1999 (adjusted IRR 0.87; 95% CI 0.80-0.94).

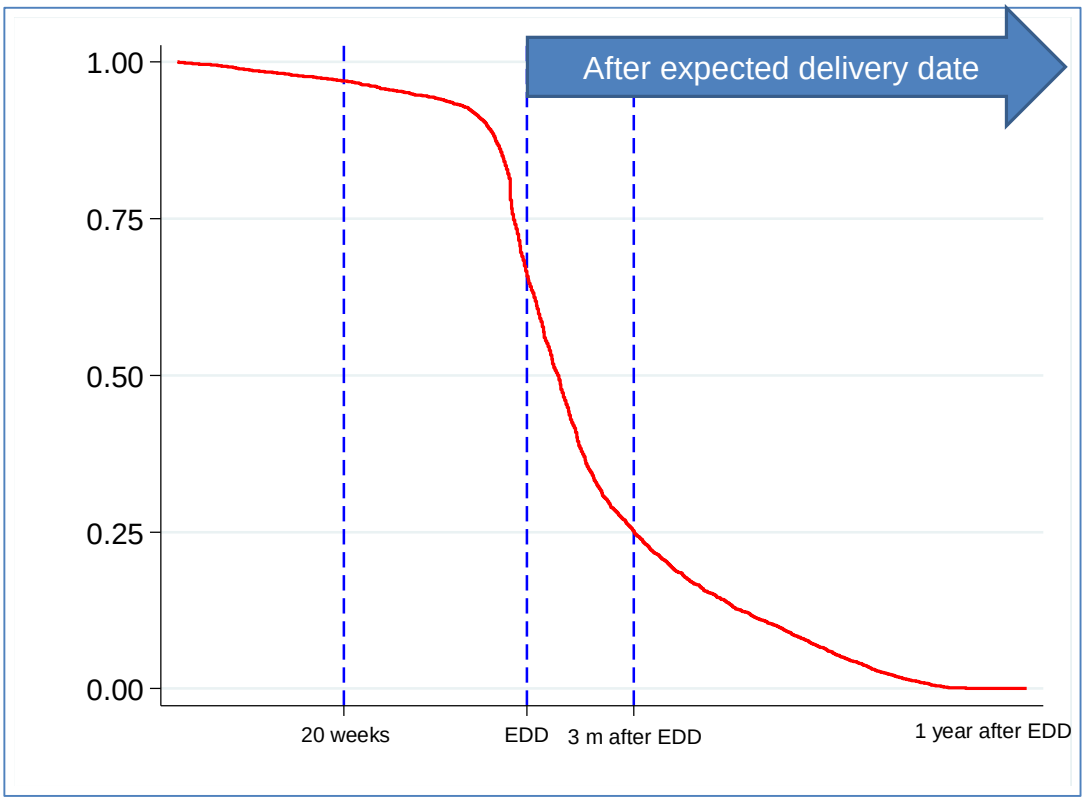
Sex of baby

Compared to males, female babies were 36% less likely to have a record of major congenital malformation (unadjusted and adjusted IRR 0.64; 95% CI 0.61-0.67).

Time of recording of major congenital malformations

Figure 10 describes the proportion of the 6,720 pregnancies with a major congenital malformation which remained undiagnosed/unrecorded according to time since the start of pregnancy. The earliest a major congenital malformation can be diagnosed is at the 20 week anomaly scan, which is reflected in this graph. There were 205 diagnoses recorded prior to 20 weeks gestation - 6,515 (96.9%) major congenital malformations remained undiagnosed/unrecorded at this point. At the expected delivery date, two-thirds (n = 4,476) were still undiagnosed. By three months after delivery, 75% of the major congenital malformations captured in the first year were diagnosed/recorded.

Figure 10 Pregnancies with a major congenital malformation diagnosis recorded up to one year after birth according to time of first diagnosis *(MCM = major congenital malformation; EDD = expected delivery date)*



6.4.2 Perinatal death

Case identification

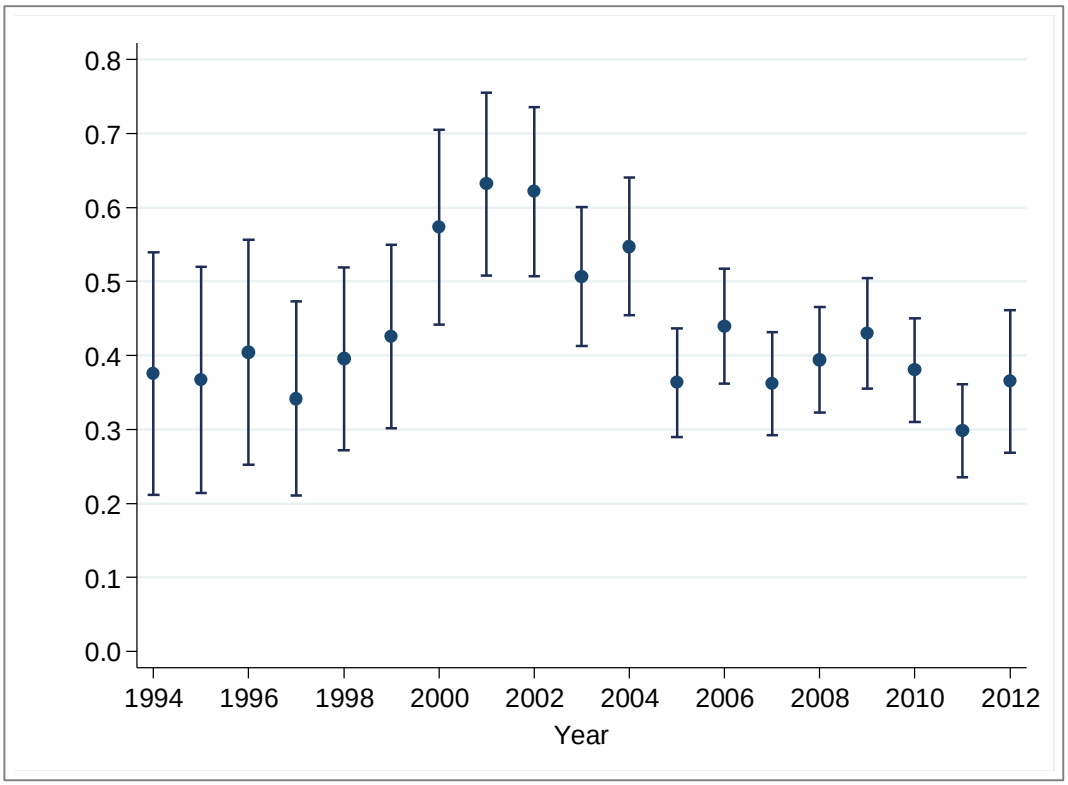
Perinatal death was defined as death in utero after 20 weeks gestation, stillbirth and early neonatal death of the newborn within seven days of life. Amongst

353,171 pregnancies recorded between 1994 and 2012, a total of 1,523 (0.4%) pregnancies ended in perinatal death. Of these, 1,401 were identified through a Read code search of the mother's medical records, whilst the remaining 122 were identified through mother's free text.

Prevalence rates over time

Annual rates of recording perinatal deaths in THIN have fluctuated over the study period (Figure 11). Prior to 2000, the prevalence of perinatal deaths was below 0.5%. Between 2000 and 2004, the prevalence fluctuated between 0.5% and 0.7% before falling back down to below 0.5%.

Figure 11 Prevalence of perinatal death between 1994 and 2012



Demographic characteristics

Table 10 describes the prevalence of perinatal deaths by the year of delivery, age band and level of social deprivation.

Table 10 Prevalence of perinatal death in 353,171 pregnancies by demographic factors

	Total pregnancies (N=353,171)	Perinatal deaths n (%)	Unadjusted IRR (95% CI)	p-value	Adjusted IRR (95% CI)	p-value
Year of delivery						
1994-1999	46,032	179 (0.39)	0.98 (0.83-1.16)	<0.001	1.01 (0.86-1.20)	<0.001
2000-2004	92,958	530 (0.57)	1.43 (1.27-1.61)		1.46 (1.30-1.65)	
2005-2009	140,835	561 (0.40)	1		1	
2010-2012	73,346	253 (0.34)	0.87 (0.75-1.00)		0.86 (0.74-1.00)	
Age band (years)						
<20	24,363	139 (0.04)	1.45 (1.20-1.75)	<0.001	1.28 (1.05-1.56)	<0.001
20-24	58,016	237 (0.07)	1.04 (0.89-1.22)		0.96 (0.82-1.13)	
25-29	98,639	374 (0.11)	0.96 (0.84-1.11)		0.94 (0.82-1.08)	
30-34	108,699	428 (0.12)	1		1	
35-39	54,101	285 (0.08)	1.34 (1.15-1.55)		1.35 (1.17-1.57)	
40-44	8,982	56 (0.02)	1.58 (1.20-2.09)		1.63 (1.23-2.15)	
45+	371	4 (0.00)	2.74 (1.02-7.33)		2.88 (1.07-7.70)	
Townsend score						
1	81,256	295 (0.08)	1	<0.001	1	<0.001
2	66,691	289 (0.08)	1.19 (1.01-1.40)		1.22 (1.04-1.43)	
3	69,195	272 (0.08)	1.08 (0.92-1.28)		1.13 (0.95-1.33)	
4	64,902	301 (0.09)	1.28 (1.09-1.50)		1.34 (1.14-1.58)	
5	48,620	270 (0.08)	1.53 (1.30-1.80)		1.61 (1.35-1.91)	
Missing	22,507	96 (0.03)	1.17 (0.93-1.48)		1.26 (1.00-1.59)	

Year of delivery

Between 1994 and 2012, the prevalence of perinatal death varied slightly from its lowest in 2011 (0.3%) to its highest in 2001 (0.6%) (Figure 11*)*. Analysis of calendar year in bands found that prevalence was slightly higher between 2000 and 2004 (0.6%) compared to that between 2005 and 2009 (0.4%), even after adjusting for age and level of social deprivation (adjusted IRR 1.46; 95% CI 1.30-1.65).

Maternal age

In univariate analyses, women aged under 20 years were more likely to suffer perinatal death compared to those aged between 30 and 34 years (IRR 1.45, 95% CI 1.20-1.75). Women in the three age bands older than 34 years were increasingly likely to suffer perinatal death – 34% more likely in those aged 35-39 years, 58% more likely in those 40-44 years and nearly three times as likely in those over 45 years though numbers were very small in this group. Although accounting for differences over time did not alter the rates dramatically, a likelihood ratio test deemed the combined model more informative.

Townsend score

There was a significant difference across the quintiles with increasingly higher likelihood of perinatal death with increasing deprivation.

A full model was tested including calendar year in bands, maternal age and Townsend score and the results of the adjusted IRRs are presented in Table 10. The most dramatic change in estimates was that for the women aged younger than 20 years compared to 30-34 years – this estimate moved towards the null and after adjusting was 1.28 (95% CI 1.05-1.56).

6.5. Discussion

Of 353,171 pregnancies recorded in THIN between 1994 and 2012, nearly 2% were found to have a diagnosis of major congenital malformations and just under half a percent (0.4%) of pregnancies ended in perinatal death. Older age and greater level of social deprivation were associated with an increase

in risk for both major congenital malformations and perinatal death. Younger women (< 20 years old) were also at increased risks of perinatal death. Additionally, major congenital malformations were less common in female babies than males. More than 75% of diagnoses of major congenital malformations diagnosed either in utero or within a year after birth were recorded by three months after delivery.

The prevalence rate of major congenital malformations identified in primary care is comparable with that estimated by other data sources. Figures for the UK from the European surveillance group, EUROCAT, showed annual rates varying between 123 per 10,000 in 1994 to 223 per 10,000 in 2006 – equivalent to 1.23% and 2.23% - and in 2012 the rate was 175 per 10,000, equivalent to 1.75% (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables).

Further UK estimates of the prevalence of major congenital malformations have, in the past, been reported by the Office for National Statistics (ONS). However, this ended in 2008 due to poor case ascertainment which is evident from their rates estimated as low as 62 per 10,000 in 2008. A more reliable estimate of major congenital malformations prevalence in the UK is provided by BINOCAR (British Isles Network of Congenital Anomaly Registers). BINOCAR collate data from six regional registers covering approximately 36% of the births in England and Wales. Their latest estimates based on data collected in 2011 was 179 per 10,000 births (equivalent to 1.79%).[139] BINOCAR also records the timing of a diagnosis of major congenital malformations and, in 2011, 68% were diagnosed at birth and the remainder within a month after birth.[139] This is faster than recording in primary care, and may reflect greater efficiency in notification of major congenital malformations to congenital anomaly registers compared to primary care.

The prevalence of perinatal deaths estimated in THIN (0.4%) was slightly lower than national figures reported by the ONS. In 2012, 4.9 per 10,000 equivalent to 0.49% pregnancies ended in perinatal death; in previous years back to 1992, the rate was just above 5 per 10,000

(http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-320855).

Both maternal age and social deprivation were associated with the likelihood of a major congenital malformation or perinatal death. Older maternal age has long been associated with higher risks in pregnancy, particularly with chromosomal defects such as Down's syndrome.[140;141] However, the association with structural malformations such as those captured in this study, has been debated. Despite positive associations in several studies between older age and a specific malformation, cleft lip, some reviews have concluded that the overall risk of malformations is not substantially greater than in women of younger age. [142-145] My study found a higher risk of perinatal death was also increased in women younger than 20 years old. Adolescents are more likely to suffer certain complications such as anaemia and preterm birth,[146-148] which may be contribute to the increased proportion of perinatal deaths observed in this age group. Other studies have conflicted, but the one of the largest studies conducted on data from the Center for Disease Control and Prevention's Linked Birth-Infant Death and Fetal Death database supported my finding when they compared women <15 years old to those ≥ 15 years and identified a higher prevalence of stillbirths in the younger population.[149] Similar findings have been apparent amongst women of older maternal age – a greater likelihood of pregnancy complications and higher rates of foetal death in older women.[150;151] The link between greater deprivation and poor pregnancy outcomes has also been observed in other studies.[142;152;153] Women living in areas of higher deprivation are more likely to be smokers and consume alcohol in excess – behaviours which can affect the foetus if continued in pregnancy.[154-156] A recent study recently found a disparity in the use of preconceptional folic acid between women from different levels of social deprivation.[157] This may indicate a lower level of education on health in pregnancy in women from poorer areas.

The results of this study have both research and clinical implications. Clinically, these results once again highlight certain groups which have a higher risk of serious adverse outcomes in pregnancy – older women and those in areas of greater deprivation – further reinforcing the need to continue efforts in

identifying and managing women who may need more support ante- and postnatally. In terms of research, this study shows that UK primary care data from THIN adequately captures cases of major congenital malformations and would therefore be ideal for research into drug teratogenicity, however perinatal deaths are slightly underestimated.

The main strength of this study is that a large number of pregnancies in UK primary care were included, nearly 80% of which could be linked to a child. Thus the prevalence rate is likely to be representative of the UK population – this is evident from the comparison with EUROCAT and BINOCAR. However, there is a limited data on the outcome of pregnancies which could not be linked to a child. Despite a search of free text information for these pregnancies, there are still unknown outcomes which may have not been recorded in primary care such as terminations due to *in utero* diagnosis of a major congenital malformation. In this study, I used Read code diagnoses to identify which malformations were major, not minor. Given the complexity of diagnosing major congenital malformations, an ideal approach would be to gather information at the point of diagnosis with an examination of the foetus/newborn. This would reduce the likelihood of misclassification bias that may be prevalent without the option of examining each foetus/newborn.

6.6. The next chapter

Major congenital malformations and perinatal death are well recorded in primary care. The study confirms that THIN is a valid data source for examining major congenital malformations, and informs how THIN data can be used in the main study which is presented in the next chapter.

Chapter 7

Antiepileptic drugs in pregnancy and the risk of major congenital malformations or perinatal death

7.1. Aims and objectives of the chapter

The aim of this chapter is to examine the drug specific associations between antiepileptic drug use in pregnancy and the risk of major congenital malformations and perinatal death.

The objectives are as follows:

1) In women who were prescribed antiepileptic drugs before pregnancy, determine the absolute risk of major congenital malformations or perinatal death for:
    a. each group of pregnancies prescribed individual antiepileptic drug monotherapy in the first trimester of pregnancy.
    b. pregnancies prescribed sodium valproate polytherapy in the first trimester of pregnancy.
    c. pregnancies where no antiepileptic drug therapy was prescribed in the first trimester of pregnancy.

2) In women who were prescribed antiepileptic drugs before pregnancy, conduct head to head pairwise comparisons of the risk of the major congenital malformations or perinatal death between each of the following first trimester regimens, adjusting for differences in demographic and clinical characteristics:
    a. Lamotrigine monotherapy
    b. Carbamazepine monotherapy
    c. Sodium valproate monotherapy
    d. Sodium valproate polytherapy
    e. No therapy

7.2. Background

Antiepileptic drugs are used by approximately two-thirds of people with epilepsy, and in recent years, are increasingly prescribed for mental health conditions, particularly bipolar disorder.[30;34]

There are a wide variety of antiepileptic drugs available and drug regimens are tailored to individual needs and lifestyle preferences with respect to symptom control and side effects. For women, additional considerations are made because some antiepileptic drugs may be teratogenic – thus treatment choices should address how women wish to proceed with treatment in pregnancy.

This can be a difficult decision because, as the literature review in Chapter 1 revealed, there is lack of consistent findings from good quality research on some commonly used antiepileptic drugs in pregnancy and whether or not there are differential risks for the foetus between these drugs.

In the UK, primary care is the first point of contact for over three-quarters of women when they become pregnant.[109] It is also the main source of prescribing once a treatment regimen is established. Prescribing by general practitioner continues if a woman becomes pregnant, and thus primary care data provides crucial information on the type and timing of use of antiepileptic drugs in pregnancy. This information is crucial in attributing major congenital malformations to drug exposures.

In Chapter 5, I showed that 1 in 200 pregnant women in the UK were prescribed antiepileptic drugs during pregnancy, and furthermore that they were most commonly prescribed lamotrigine, carbamazepine and sodium valproate. Chapter 6 showed that, in UK primary care data, the prevalence of major congenital malformations and perinatal death were well captured in the patient records.

This study therefore uses UK primary care data from The Health Improvement Network to examine whether there are specific associations between antiepileptic drug used in the first trimester and major congenital malformations and perinatal death. Furthermore, to compare risk estimates

amongst commonly used antiepileptic drugs in pregnancy and no therapy in pregnancy.

7.3. Methods

7.3.1. Study design

This was a retrospective cohort study using primary care data from The Health Improvement Network.

7.3.2. Definitions

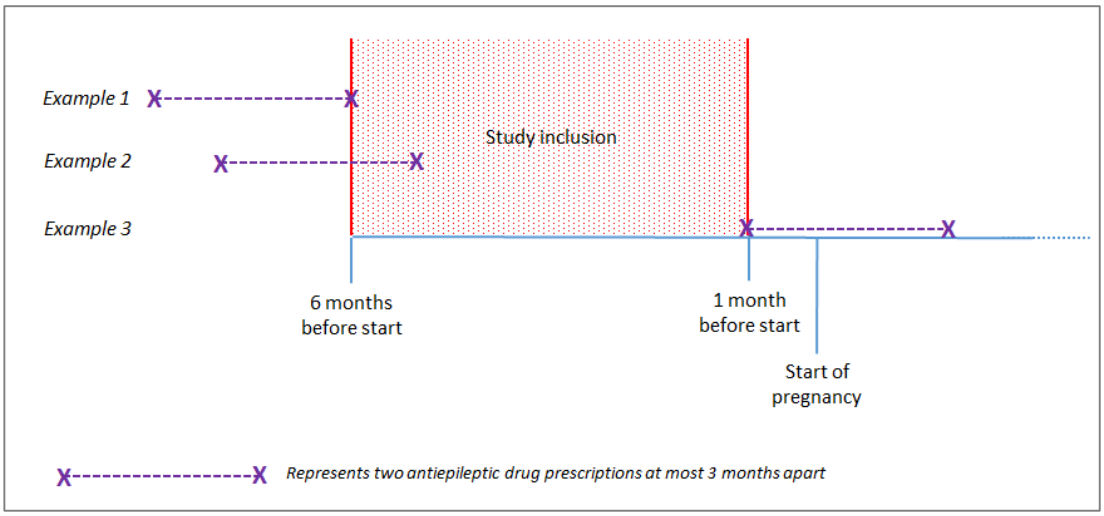
Study population

The pregnancy cohort described in Chapter 3 was used. To recap, this included women if they met the following criteria:

- Pregnant in the study period from 1994 to 2012, with the delivery date ending in the study period;
- Aged 13-55 years at the time of delivery;
- At least nine months of data prior to pregnancy start date;
- At least six months of data after the delivery date;

From this cohort, women were required to have at least two prescriptions of any antiepileptic drug within a three month period, of which at least one prescription was prior to pregnancy (six months to one month before pregnancy) in order to be included in the study population. This inclusion criterion was used to identify those women who were regularly receiving antiepileptic drugs rather than those who may be one-off users. Figure 12 below illustrates this criterion. Where a woman had more than one pregnancy, one pregnancy was selected at random.

Figure 12 Women were required to have two prescriptions within 3 months, and at least one prescription inside the inclusion period



Exposure

Exposure was defined as having received a prescription of an antiepileptic drug in the first trimester.

Monotherapy exposure was defined as having received a prescription of only one type of antiepileptic drug.

Polytherapy exposure was defined as having received prescriptions for more than one type of antiepileptic drug.

First trimester was the period from one month before pregnancy to 105 days after the start of pregnancy (date of last menstrual period). The month before pregnancy has been included in the definition to capture accidental foetal exposure to antiepileptic drugs in the early weeks of pregnancy, before the pregnancy is known.

Outcome

The outcome was a composite of major congenital malformations and perinatal death i.e. babies with *either* a major congenital malformation or pregnancies ending in perinatal death being the outcome of interest. They were defined using the same methods as in Chapter 6. Perinatal death was

included to increase the sensitivity of the measure capturing those major congenital malformations which resulted in foetal death.

Demographic and clinical characteristics

To describe the characteristics of the women in each group, several demographic and clinical variables were extracted. Any differences in characteristics were then accounted for in the analysis.

Year of delivery

This was categorised as 1994-2000, 2001-2004, 2005-2009, 2009-2012 based on the year in which the pregnancy ended.

Maternal age

This was the age of the mother at the time of delivery, stratified into five year age bands (<20, 20-24, 25- 29, 30-34, 35-39, 40-44, 45+).

Social deprivation

Social deprivation was measured by the quintiles of Townsend score, as has been used in the previous studies.

Indication for antiepileptic drugs

This was categorised into epilepsy, bipolar disorder/depression and other. Read code lists created for the prescribing patterns study in Chapter 5 were used to identify clinical records of epilepsy and bipolar disorder/depression made prior to the start of pregnancy. If a woman had more than one condition which could be treated with antiepileptic drugs, the hierarchy epilepsy > bipolar disorder/depression > other was used to categorise indication.

Previous history of very heavy drinking

Women who were heavy drinkers were identified through:

- Alcohol consumption of greater than 35 units a week recorded in additional health data made either in pregnancy or in the preceding three years;

- A Read code diagnosis for a very heavy drinker recorded either in pregnancy or in the preceding three years;
- A prescription for alcohol cessation drugs received either in pregnancy or in the year before.

Smoking status

Women who were last recorded as a current smoker in the period from three years before pregnancy to delivery date were identified in three ways:

- One or more cigarettes smoked per week recorded in additional health data;
- Read codes indicating current smoker;
- A prescription for smoking cessation drugs.

Previous history of substance misuse

Women who had a record of substance misuse in the three years before pregnancy or during pregnancy were identified through:

- A Read code diagnosis indicating substance misuse;
- A prescription for drugs to treat opioid dependence.

Obesity

Woman who were obese any time before pregnancy, excluding periods of previous pregnancies, were identified through

- A recorded or calculated BMI ≥ 30 in additional health data before the start of pregnancy;
- A Read code diagnosis of obesity before the start of pregnancy.

Diabetes (uncontrolled glucose levels in pregnancy)

Women with gestational diabetes, newly diagnosed diabetes in pregnancy or those with poorly controlled glucose levels in pregnancy. These were identified in three ways:

- A Read code diagnosis for gestational or incident diabetes in pregnancy.
- Abnormal (high, or greater than 6mmol/L) results from fasting glucose tests and glucose tolerance tests in additional health data;

- A Read code for abnormal glucose tolerance tests in pregnancy.

Co-medications

Other drugs taken in pregnancy have been associated with an increased malformation risk. A binary variable was created indicating two or more prescriptions of each of the following drugs in the first trimester of pregnancy:

- Antidepressants;
- Antipsychotics;
- Hypnotics and anxiolytics;
- Non-steroidal anti-inflammatory drugs.

7.3.3. Data analysis

Absolute risks

The absolute risk (AR) of major congenital malformations or perinatal death was calculated, with 95% confidence intervals (CIs), for each antiepileptic drug prescribed as monotherapy, for polytherapy regimens including sodium valproate and amongst pregnancies where no antiepileptic drugs were prescribed in the first trimester.

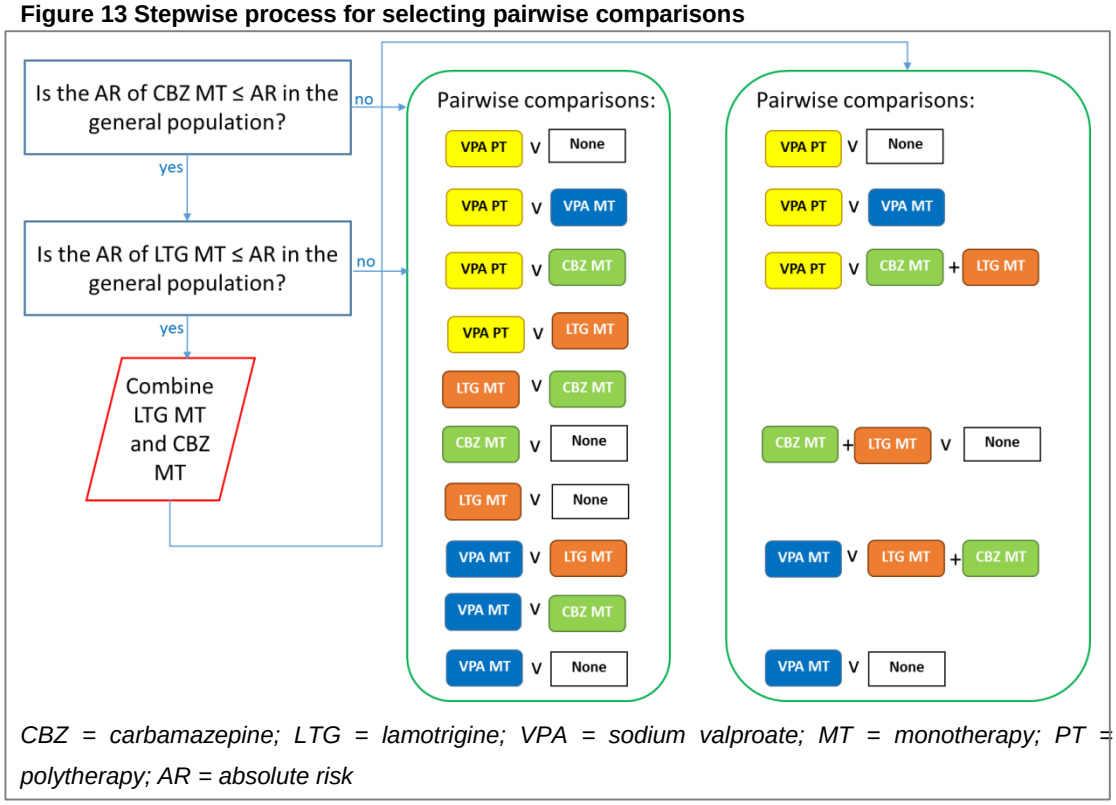
Baseline characteristics

Baseline demographic and clinical characteristics of women included in the study and in each of the sub groups of interest (lamotrigine monotherapy, carbamazepine monotherapy, sodium valproate monotherapy, sodium valproate polytherapy and no therapy) were described.

Pairwise comparisons

Unadjusted and adjusted analyses were conducted using Poisson regression to estimate incidence risk ratios (IRRs) and associated 95% CIs. A manual stepwise procedure to selecting pairwise comparisons was taken to reduce the likelihood of finding a falsely significant association due to multiple comparisons. This is described in Figure 13. Significant associations were determined at the 5% level.

Figure 13 Stepwise process for selecting pairwise comparisons



CBZ = carbamazepine; LTG = lamotrigine; VPA = sodium valproate; MT = monotherapy; PT = polytherapy; AR = absolute risk

Confounders

All variables listed above were considered for inclusion in multivariable analyses of each pairwise comparison. Inclusion in the model was based examining the distribution of each variable amongst the exposure groups and clinical input.

Sensitivity analysis

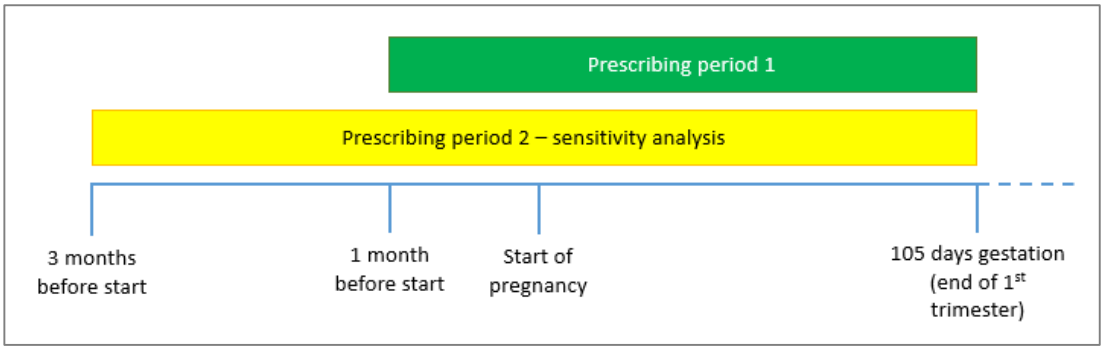
Extending the first trimester period for pregnancies receiving no therapy

The first trimester is the crucial period of foetal development during which major congenital malformations are likely to occur. In this study, the definition of first trimester has included the month before pregnancy – this is to capture foetal exposure to antiepileptic drugs from prescriptions made before conception and this is represented in Figure 14 as “Prescribing period 1”. Women with no antiepileptic drug prescriptions in prescribing period 1 are classed as the “no therapy” group in the analysis.

Given it is possible for prescriptions to be issued by a general practitioner for periods as long as three months, there may be some women in this group who have exposed their baby to antiepileptic drugs *in utero* if the prescription was made any time after two months before the start of pregnancy.

A sensitivity analysis was conducted extending the prescribing period to three months before the start of pregnancy to the end of the first trimester, as per "Prescribing period 2" in Figure 14. This absolute risk was recalculated in this newly defined "no therapy" group and if different to the absolute risk obtained in the previous definition, pairwise comparisons were reanalysed using the new "no therapy" group.

Figure 14 Sensitivity analysis - changing the length of the prescribing period



7.4. Results

Of 353,171 pregnancies, 1,933 had received more than one prescription of an antiepileptic drug in three months, with at least one prescription in the six months before pregnancy, and these were thus eligible for inclusion in the study. Selection of one pregnancy per woman reduced this to 1,633 pregnancies.

Table 11 sets out the different therapeutic regimens prescribed in the first trimester of the 1,633 pregnancies, including those not prescribed as a separate group.

Most women in the study were prescribed carbamazepine monotherapy (22.1%; n = 361) followed by lamotrigine monotherapy (20.5%; n = 334) and sodium valproate monotherapy (13.9%; n = 227) in the first trimester. Other

monotherapy regimens were prescribed in 14.6% (n = 240) of pregnancies. Polytherapy including sodium valproate was prescribed in 5.1% of pregnancies (n = 83). Other polytherapy regimens were prescribed in 9.4% (n = 154) of pregnancies. No therapy was given in 14.3% (n = 234) pregnancies.

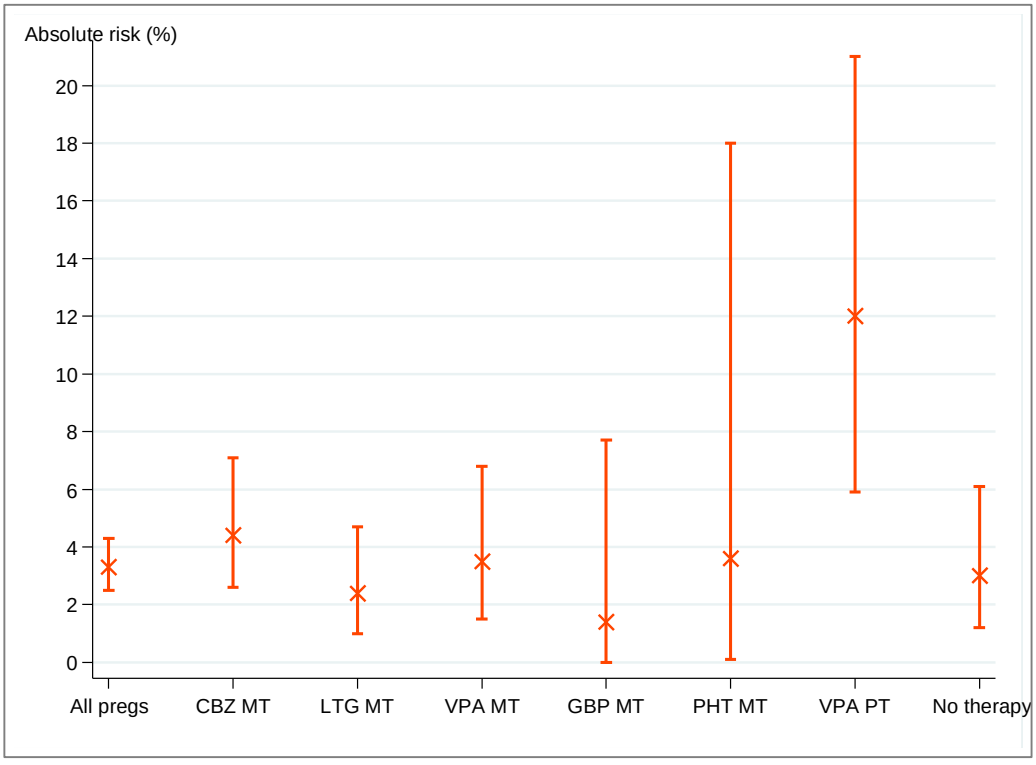
Absolute risks

Table 11 further describes the number of pregnancies with a major congenital malformation, or that ended in perinatal death by the different antiepileptic drug regimens. Overall, there were 54 cases of major congenital malformations or pregnancies ending in perinatal death, thus the overall absolute risk was 3.3% (95% CI 2.5-4.3%). Amongst the different regimens, the absolute risk of the composite outcome was highest in the sodium valproate polytherapy group where 10 out of the 83 pregnancies were cases (AR 12.0%; 95% CI 5.9-21.0%). Among those prescribed monotherapy regimens, the absolute risk of major congenital malformations or perinatal death was highest in the carbamazepine group (AR 4.4%; 95% CI 2.6-7.1%), followed by sodium valproate (AR 3.5%; 95% CI 1.5-6.8%) and lamotrigine (AR 2.4%; 95% CI 1.0-4.7%). Of those women who were prescribed antiepileptic drugs before, but not in the first trimester of pregnancy, the absolute risk was 3.0% (95% CI 1.2-6.1%). There were 3 cases amongst 154 pregnancies prescribed polytherapy without sodium valproate, 1 case in the gabapentin monotherapy group and another case in the phenytoin monotherapy group. Figure 15 illustrates the absolute risks graphically.

Table 11 Absolute risks of major congenital malformations or perinatal death by drug regimen

	Number of pregnancies, n (%)	Number of cases, n (%)	AR (95% CI)
All pregnancies	1633 (100.0)	54 (100.0)	3.3 (2.5-4.3)
Monotherapy regimens			
carbamazepine	361 (22.1)	16 (29.6)	4.4 (2.6-7.1)
lamotrigine	334 (20.5)	8 (14.8)	2.4 (1.0-4.7)
sodium valproate	227 (13.9)	8 (14.8)	3.5 (1.5-6.8)
gabapentin	70 (4.3)	1 (1.9)	1.4 (0.0-7.7)
pregabalin	51 (3.1)	0 (0.0)	-
phenytoin	28 (1.7)	1 (1.9)	3.6 (0.1-18.3)
topiramate	28 (1.7)	0 (0.0)	-
levetiracetam	25 (1.5)	0 (0.0)	-
clonazepam	15 (0.9)	0 (0.0)	-
acetazolamide	12 (0.7)	0 (0.0)	-
phenobarbital	4 (0.2)	0 (0.0)	-
ethosuximide	2 (0.1)	0 (0.0)	-
oxcarbazepine	2 (0.1)	0 (0.0)	-
zonisamide	2 (0.1)	0 (0.0)	-
primidone	1 (0.1)	0 (0.0)	-
Sodium valproate polytherapy	83 (5.1)	10 (18.5)	12.0 (5.9-21.0)
No therapy in pregnancy	234 (14.3)	7 (13.0)	3.0 (1.2-6.1)

Figure 15 Absolute risks of major congenital malformations or perinatal death by drug regimen



CBZ = carbamazepine; LTG = lamotrigine; VPA = sodium valproate; GBP = gabapentin; PHT = phenytoin; MT = monotherapy; PT = polytherapy

Baseline characteristics

Table 12 describes the characteristics of all 1,633 pregnancies included in the study and in the sub groups which were analysed in pairwise comparisons – (i.e. no therapy, carbamazepine monotherapy, lamotrigine monotherapy, sodium valproate monotherapy and sodium valproate polytherapy).

Overall, the median age of the cohort was 30 years old [IQR 26-34]. Within each group, the median age did not differ from the overall median. The level of social deprivation varied slightly between groups. Amongst those prescribed no therapy in pregnancy, sodium valproate monotherapy and sodium valproate polytherapy in the first trimester, there were a higher proportion of women living in more deprived areas.

The indication for antiepileptic drug prescribing was mainly epilepsy for each of the sub groups, with the exception of the no therapy group. Here, 50% of women were prescribed antiepileptic drugs for reasons other than epilepsy and bipolar disorder, approximately 30% for epilepsy, and around 20% for bipolar disorder. In each of the other groups, epilepsy was the indication for over 80% of women. However, in women prescribed lamotrigine monotherapy and women prescribed sodium valproate polytherapy, the proportion was closer to 95%. There were only 8 women (2%) and just 1 woman (1%) with bipolar disorder, and 7 women (2%) and 2 women with other reasons for antiepileptic drugs in the lamotrigine monotherapy group and sodium valproate polytherapy group respectively.

Only 1% (n=16) of all women in the study population were found to have a record indicating they had been a very heavy drinker i.e. consuming more than 35 units a week. There were less than 5 women in each subgroup. Similarly, few women were found to have incident or gestational diabetes in pregnancy affecting less than 2% of the study population.

Around a quarter of women were most recently current smokers at the time of pregnancy – this was closer to 30% amongst women in those who received

no therapy in the first trimester and 20% in the carbamazepine monotherapy and sodium valproate polytherapy prescribed groups. A history of obesity was found in 20% of all pregnancies, as well as within each sub group - the exception was the carbamazepine monotherapy group where approximately 15% of women had history of obesity. A history of substance misuse was low, around 2-3% in each group.

Co-medication use varied across the subgroups - notably few women in the sodium valproate polytherapy group received other co-medications, possibly explained by the lower number with indications other than epilepsy. Antidepressant use was common in the first trimester, prescribed to 16% (n = 266) overall, but only 6% (n = 5) in the sodium valproate polytherapy group. Overall antipsychotics use in the first trimester was low, approximately 4%. Very few were prescribed these in the lamotrigine monotherapy group and sodium valproate polytherapy group (n = 8 and 3, respectively). The use of hypnotics or anxiolytics was greater in those who received no therapy in the first trimester and in the sodium valproate group (~10%) compared to the carbamazepine and lamotrigine prescribed women (~5%).The use of NSAIDs was low (<5%) across all groups.

Table 12 Baseline characteristics of women in the study population

		First trimester antiepileptic drug treatment				
	All N = 1633 n (%)	No therapy N = 234 n (%)	Carbamazepine monotherapy N = 361 n (%)	Sodium valproate monotherapy N = 227 n (%)	Lamotrigine monotherapy N = 334 n (%)	Sodium valproate polytherapy N = 83 n (%)
Maternal age (years) median [IQR]	30 [26-34]	30 [26-34]	27 [31-34]	30 [25-33]	29 [26-32.25]	30 [27-33]
Maternal age (5 year age band)						
13-19	62 (3.8)	11 (4.7)	12 (3.3)	11 (4.8)	14 (4.2)	2 (2.4)
20-24	230 (14.1)	31 (13.2)	41 (11.4)	37 (16.3)	51(15.3)	14 (16.9)
25-29	451 (27.6)	66 (28.2)	97 (26.9)	59 (26.0)	104 (31.1)	20 (24.1)
30-34	534 (32.7)	74 (31.6)	122 (33.8)	79 (34.8)	113 (33.8)	31 (37.3)
35-39	286 (17.5)	43 (18.4)	74 (20.5)	36 (15.9)	44 (13.2)	11 (13.3)
40-44	67 (4.1)	9 (3.8)	15 (4.2)	4 (1.8)	7 (2.1)	5 (6.0)
44-55	3 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)
Social deprivation Townsend score						
1	288 (17.6)	41 (17.5)	77 (21.3)	34 (15.0)	60 (18.0)	13 (15.7)
2	251 (15.4)	35 (15.0)	58 (16.1)	32 (14.1)	53 (15.9)	8 (9.6)
3	300 (18.4)	36 (15.4)	76 (21.1)	34 (15.0)	77 (23.1)	7 (8.4)
4	367 (22.5)	56 (23.9)	58 (16.1)	75 (33.0)	61 (18.3)	24 (28.9)
5	317 (19.4)	49 (20.9)	70 (19.4)	37 (16.3)	54 (16.2)	22 (26.5)
Missing	110 (6.7)	17 (7.3)	22 (6.1)	15 (6.6)	29 (8.7)	9 (10.8)
Year of delivery						
1994-1999	191 (11.7)	15 (6.4)	76 (21.1)	45 (19.8)	5 (1.5)	22 (26.5)
2000-2004	361 (22.1)	46 (19.7)	115 (31.9)	71 (31.3)	47 (14.1)	21 (25.3)
2005-2009	611 (37.4)	84 (35.9)	115 (31.9)	69 (30.4)	164 (49.1)	29 (34.9)
2010-2012	470 (28.8)	89 (38.0)	55 (15.2)	42 (18.5)	118 (35.3)	11 (13.3)

	All N = 1633 n (%)	First trimester antiepileptic drug treatment				
		No therapy N = 234 n (%)	Carbamazepine monotherapy N = 361 n (%)	Sodium valproate monotherapy N = 227 n (%)	Lamotrigine monotherapy N = 334 n (%)	Sodium valproate polytherapy N = 83 n (%)
Indication for AEDs						
Epilepsy	1177 (72.1)	69 (29.5)	295 (81.7)	185 (81.5)	319 (95.5)	80 (96.4)
Bipolar disorder/depression	137 (8.4)	46 (19.7)	26 (7.2)	23 (10.1)	8 (2.4)	1 (1.2)
None/other	319(19.5)	119 (50.9)	40 (11.1)	19 (8.4)	7 (2.1)	2 (2.4)
History of very heavy drinking[**]	16 (1.0)	2 (0.9)	3 (0.8)	1 (0.4)	4 (1.2)	0 (0.0)
Smoker[††]	400 (24.5)	66 (28.2)	79 (21.9)	59 (26.0)	79 (23.7)	18 (21.7)
Diabetes in pregnancy	24 (1.5)	4 (1.7)	6 (1.7)	6 (2.6)	3 (0.9)	0 (0.0)
History of obesity[‡‡]	334 (20.5)	49 (20.9)	53 (14.7)	41 (18.1)	66 (19.8)	17 (20.5)
Substance misuse[§§]	47 (2.9)	9 (3.8)	7 (1.9)	9 (4.0)	6 (1.8)	1 (1.2)
Antidepressants[***]	266 (16.3)	32 (13.7)	59 (16.3)	27 (11.9)	31 (9.3)	5 (6.0)
Antipsychotics[***]	60 (3.7)	10 (4.3)	17 (4.7)	11 (4.8)	8 (2.4)	3 (3.6)
Hypnotics/Anxiolytics[***]	110 (6.7)	22 (9.4)	16 (4.4)	15 (6.6)	16 (4.8)	8 (9.6)
NSAIDs[***]	92 (5.6)	6 (2.6)	15 (4.2)	7 (3.1)	11 (3.3)	2 (2.4)

[**] > 35 units alcohol per week recorded in the period from three years prior to pregnancy to delivery date
[††] Last recorded as a current smoker in the period from three years prior to pregnancy to delivery date
[‡‡] Record of obesity or body mass index > 30 recorded ever before pregnancy (excluding periods of previous pregnancies)
[§§] Recorded in the period from three years prior to pregnancy to delivery date
[***] Two or more prescriptions in the first trimester

Pairwise comparisons

Carbamazepine and lamotrigine monotherapy prescribed groups

In Chapter 6, I described that 1.9% (95% CI 1.9-2.0%) of pregnancies in the general population were diagnosed with a major congenital malformation. The absolute risk for major congenital malformations or perinatal death in carbamazepine and lamotrigine monotherapy prescribed pregnancies was greater than this (AR 4.4%; 95% CI 2.6-7.1% and AR 2.4%; 95% CI 1.0-4.7% respectively), therefore for the purposes of pairwise comparisons, these two groups were not combined.

Unadjusted analyses

Table 13 shows the unadjusted incident rate ratio (IRR) and associated 95% CIs of each pairwise comparison. The risk of major congenital malformations or perinatal death was significantly higher in sodium valproate polytherapy prescribed pregnancies compared to no therapy in pregnancy (IRR 4.03; 95% CI 1.53-10.58), carbamazepine monotherapy (IRR 2.72; 95% CI 1.23-5.99), lamotrigine monotherapy (IRR 5.03; 95% CI 1.99-12.74) and sodium valproate monotherapy (IRR 3.42; 95% CI 1.35-8.66) in the first trimester. For each of the other comparisons, there was no evidence of a difference in risk.

Adjusted analyses

History of very heavy drinking, diabetes in pregnancy and history of substance misuse were excluded from every model due to low numbers. Further exclusions were made in the below pairwise comparisons where frequencies were below 5. These are also set out in Table 13.

- First trimester antipsychotic and NSAIDs use between sodium valproate polytherapy and carbamazepine monotherapy and also between sodium valproate polytherapy and monotherapy
- First trimester NSAIDs use between sodium valproate polytherapy and lamotrigine monotherapy
- First trimester use of antidepressants, antipsychotics and NSAIDs between sodium valproate polytherapy and no therapy

Adjusted results are shown in Table 13. The impact was minimal on the previously significant findings from unadjusted comparisons between sodium valproate polytherapy and each of the other drugs – effect estimates changed slightly. However, the adjusted model comparing the risk in the lamotrigine monotherapy group with the no therapy groups finds a lower likelihood in the lamotrigine prescribed group, (adjusted IRR 0.27; 95% CI 0.08-0.82 and unadjusted IRR 0.80; 95% CI 0.29- 2.21).

I conducted a further adjusted analysis on each of the four comparisons with sodium valproate polytherapy, restricting to only women with epilepsy. This is because there were few women given sodium valproate polytherapy for other indications - one woman had bipolar disorder and two had other indications Table 12). After restricting the analysis to women with epilepsy, and adjusting for other variables, the association between sodium valproate polytherapy and those who received no therapy was no longer significant (adjusted IRR 1.67; 95% CI 0.63-4.45). There was little change in the IRRs for the other comparisons with sodium valproate polytherapy (Table 13).

Table 13 Drug specific pairwise comparisons of incidence of major congenital malformations or perinatal death

Drug 1	Drug 2 (Reference group)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)	Adjusted IRR* (95% CI) (WWE only)	Variable exclusions
Sodium valproate polytherapy (PT)	No therapy	4.03 (1.53-10.58)	4.07 (1.77-9.38)	1.67 (0.63-4.45)	*Antidepressants; antipsychotics; NSAIDs*
Sodium valproate PT	Carbamazepine monotherapy (MT)	2.72 (1.23-5.99)	2.45 (1.19-5.04)	2.24 (1.07- 4.67)	*Antipsychotics; NSAIDs*
Sodium valproate PT	Lamotrigine MT	5.03 (1.99-12.74)	4.46 (1.62-12.27)	4.53 (1.61-12.69)	*NSAIDs*
Sodium valproate PT	Sodium valproate MT	3.42 (1.35- 8.66)	3.40 (1.38-8.34)	3.51 (1.37-8.99)	*Antipsychotics; NSAIDs*
Sodium valproate MT	No therapy	1.18 (0.43-3.24)	0.89 (0.27-2.98)		
Sodium valproate MT	Carbamazepine MT	0.80 (0.34-1.86)	0.82 (0.32-2.10)		
Sodium valproate MT	Lamotrigine MT	1.47 (0.55-3.92)	1.77 (0.57-5.48)		
Lamotrigine MT	Carbamazepine MT	0.54 (0.23-1.26)	0.49 (0.20-1.23)		
Lamotrigine MT	No therapy	0.80 (0.29-2.21)	0.27 (0.08-0.82)		
Carbamazepine MT	No therapy	1.48 (0.61-3.60)	0.92 (0.32-2.67)		

**Full model comprised maternal age band, Townsend, year of delivery, indication for AEDs, smoker, history of obesity, antidepressants, antipsychotics, hypnotics/anxiolytics, NSAIDs use in the first trimester. Some of these variables were excluded, as stated in the table, due to few numbers (less than 5 events). WWE = women with epilepsy*

Sensitivity analyses

Extension of prescribing period

To recap, the definition of the first trimester was altered for identifying women who received no therapy in the first trimester as follows:

- Previous definition: women who were not prescribed antiepileptic drugs from one month before pregnancy to the end of the first trimester
- New definition: women who were not prescribed antiepileptic drugs from three months before pregnancy to the end of the first trimester

Using the new definition, the number of women receiving no therapy in the first trimester was reduced from 234 to 120 pregnancies. Of these, four cases of major congenital malformations or perinatal death were identified resulting in an absolute risk of 3.3% (95% CI 0.9-8.3%). This was similar to the risk obtained using the previous definition (AR 3.0%; 95% CI 1.2 -6.1%).

Additional analysis of polytherapy regimens

Table 14 below provides a breakdown of the antiepileptic drugs which were prescribed with sodium valproate, and the number of cases found according to each regimen. Nearly a third were prescribed lamotrigine, and nearly 20% prescribed carbamazepine with sodium valproate. The 10 cases were spread out amongst different treatment regimens showing no clear pattern due to the small numbers found in each regimen.

Table 14 Polytherapy regimens in women prescribed sodium valproate in the first trimester of pregnancy

Polytherapy regimen with sodium valproate (N = 83)	n (%)	Number of cases (N = 10)
lamotrigine	27 (32.5)	2
carbamazepine	16 (19.3)	2
phenytoin	8 (9.6)	2
levetiracetam	5 (6.0)	1
clonazepam	5 (6.0)	0
topiramate	5 (6.0)	1
lamotrigine, carbamazepine	4 (4.8)	0
ethosuximide	2 (2.4)	0
lamotrigine, levetiracetam	2 (2.4)	0
vigabatrin	1 (1.2)	0
clobazam	1 (1.2)	0
carbamazepine, acetazolamide	1 (1.2)	0
carbamazepine, ethosuximide	1 (1.2)	0
carbamazepine, clonazepam	1 (1.2)	1
carbamazepine, phenytoin	1 (1.2)	0
lamotrigine, clobazam	1 (1.2)	0
lamotrigine, topiramate	1 (1.2)	1
lamotrigine, carbamazepine, topiramate	1 (1.2)	0

7.5. Summary

This was a retrospective cohort study of women who were prescribed antiepileptic drugs, examining their pregnancies between 1994 and 2012 for first trimester use of antiepileptic drugs and the associated drug specific risks of major congenital malformations or perinatal death using UK primary care data.

Approximately 3% (AR 3.3%; 95% CI 2.5-4.3%) of pregnancies in primary care between 1994 and 2012 resulted in a major congenital malformation or ended in perinatal death. Of pregnancies where carbamazepine monotherapy was prescribed in the first trimester, 4% (AR 4.4%; 95% CI 2.6-7.1%) had a major congenital malformation or ended with perinatal death. A similar risk was observed for first trimester sodium valproate monotherapy prescribed pregnancies (AR 3.5%; 95% CI 1.5-6.8%). Around 2% (AR 2.4%; 95% CI 1.0-4.7%) of first trimester lamotrigine monotherapy prescribed pregnancies were affected. The highest risk was found amongst women prescribed sodium valproate as polytherapy in the first trimester where 12% (AR 12.0%; 95% CI 5.9-21.0%) of pregnancies led to major congenital malformations or ended in perinatal death. Women who were prescribed antiepileptic drugs before pregnancy but not during the first trimester, had a similar risk to the overall study population (AR 3.0%; 95% CI 1.2-6.1%)

There is a significantly greater risk of the major congenital malformations or perinatal death associated with sodium valproate polytherapy compared to other antiepileptic drug monotherapy regimens. Specifically, a three-fold greater risk compared to women taking first trimester carbamazepine monotherapy (IRR 2.72; 95% CI 1.23-5.99), three-fold compared to women taking first trimester sodium valproate monotherapy (IRR 3.42; 95% CI 1.35-8.66) and five-fold compared to women taking lamotrigine monotherapy (IRR 5.03; 95% CI 1.99-12.74). The risk of major congenital malformations or perinatal death was comparable between pregnancies prescribed first trimester lamotrigine monotherapy, carbamazepine monotherapy, sodium valproate monotherapy and no therapy.

In this study there was a risk of 3.0% (95% CI 1.2-6.1%) among those who were receiving antiepileptic drugs prior to pregnancy but were not prescribed

antiepileptic drugs in the first trimester. This was similar to the Australian Register of Antiepileptic Drugs in Pregnancy (3.3%),[158] the UK Epilepsy and Pregnancy Register[17] (3.5%) and in Finland (2.8%)[11] but higher than the North American AED Pregnancy Registry (1.1%).[129]

Many studies have found a low risk of major congenital malformations amongst lamotrigine exposed pregnancies, which is consistent with the findings in this study where 2.4% (95% CI 1.0-4.7%) of pregnancies were affected. The UK, North America, and several international collaborative studies including the International Lamotrigine Pregnancy Registry,[15;81;129;159;159-161] have found estimates of risk to be between 1 and 3%.

However, estimates of risk in carbamazepine monotherapy pregnancies vary - in this study, the risk was 4.4% (95% CI 2.6-7.1%) whereas other studies produced a wide range of estimates from the 2.6% (95% CI 1.9-3.5%) in the UK Epilepsy and Pregnancy Register to 8.2% (95% CI 3.8-15.0%) in the US/UK Neurodevelopmental Effects of Antiepileptic Drugs study.[15;81;131;160]

Similarly, estimates of risk in sodium valproate monotherapy exposed pregnancies has been varied in previous research from 6.3% to 20.3%.[15;81;131;158] The absolute risk amongst sodium valproate monotherapy users was lower in this study (3.5%; 95% CI 1.5-6.8%) compared to previous findings.

Few studies have examined the risk of foetal outcomes associated with polytherapy regimens. In Norway, Veiby *et al* studied foetal growth restriction and major congenital malformations in antiepileptic drug prescribed pregnancies.[131] There were 77 pregnancies with exposure to sodium valproate polytherapy, of which only four children had a major congenital malformation (5.2%). A larger study in the UK by Morrow *et al* used data from the UK Epilepsy and Pregnancy Register which included 304 pregnancies with sodium valproate polytherapy exposure, of which 9% had a major congenital malformation.[17] In the Australian Pregnancy Registry, Vadja *et al* identified a risk of 10.2% in sodium valproate polytherapy exposed pregnancies.[158]

Due to the few studies which have examined women on sodium valproate polytherapy, there is little research to corroborate the associations found between sodium valproate polytherapy prescribed pregnancies and the other monotherapy regimens in this study. The Australian Pregnancy Registry found a higher rate of malformation in the sodium valproate polytherapy group compared to lamotrigine monotherapy, carbamazepine monotherapy and no therapy (10.2% vs. 4.6%, 5.5% and 3.3% respectively), however it was lower than that in women who took sodium valproate monotherapy (13.8%).[158] Similarly, Veiby *et al* found rates in sodium valproate polytherapy exposed pregnancies higher than that in lamotrigine monotherapy, carbamazepine monotherapy but not compared to sodium valproate monotherapy (5.2% vs. 3.4%, 2.9% and 6.3% respectively).[131]

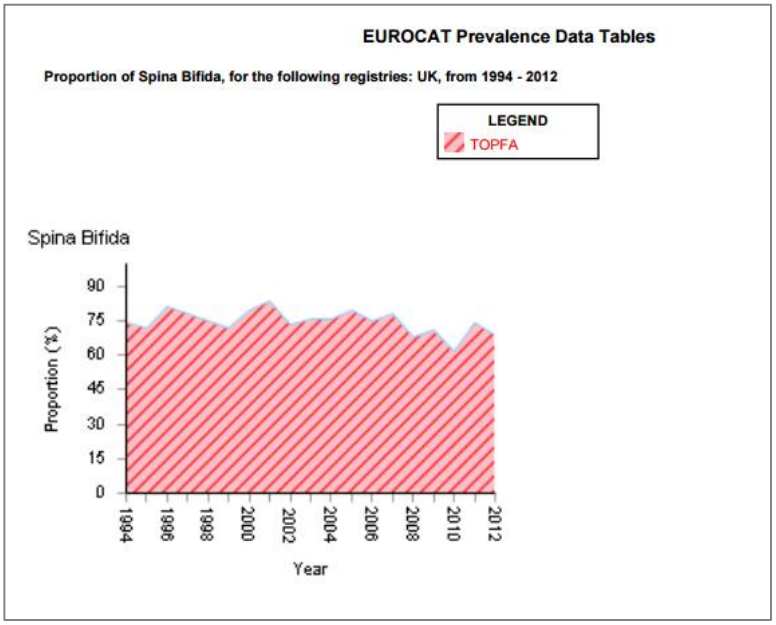
There was evidence from the UK Epilepsy and Pregnancy Register that there is a greater risk amongst women who take sodium valproate polytherapy compared to lamotrigine monotherapy, carbamazepine monotherapy and sodium valproate monotherapy (9.0% vs. 3.2%, 2.2%, 6.2% respectively).[17] Another study from the North American AED Pregnancy Registry in 2011 also identified a negative effect of sodium valproate in polytherapy.[161] They examined specific polytherapy regimens involving only two drugs, one drug being sodium valproate, and compared the rate of malformations with pregnancies exposed to the other drug in monotherapy. The difference was stark – carbamazepine monotherapy had a risk of 2.9% whilst carbamazepine plus sodium valproate carried a risk of 15.4% (OR 6.2; 95% CI 2.0-16.5). For lamotrigine monotherapy, the risk was 1.9%; lamotrigine plus sodium valproate 9.1% (OR 5.0; 95% CI 1.5-14.0).

The significantly higher risk pregnancies with sodium valproate polytherapy could be due to the teratogenic properties of sodium valproate, however, there is a differential in risk between sodium valproate polytherapy and sodium valproate monotherapy regimens indicating that there is an alternative, or additional, reason. Polytherapy itself may play a role - this is an understudied area due to the low numbers that are generally observed to be prescribed polytherapy in pregnancy, which is a further compounded when studying specific regimens. This study did not investigate all polytherapy regimens, and Table 14 shows that there were too few women in specific polytherapy regimen groups to study separately.

Another explanation is that women who are prescribed polytherapy in pregnancy have a greater disease severity than those who were prescribed monotherapy regimens. If the severity of an underlying condition for which antiepileptic drugs are prescribed is associated with a higher risk of malformations independent of the specific drug treatment then this may explain the findings. Unfortunately, disease severity is one measure that cannot be directly measured in THIN data.

In contrast to other studies, the risk amongst sodium valproate monotherapy exposed pregnancies, in this study, was not significantly higher than in the other regimens. In Chapter 1, the literature search found consistent evidence of elevated teratogenic risks in sodium valproate exposed pregnancies which has been key in changing practice guidelines for women with epilepsy.[31;63] Therefore one questions whether or not the observed relatively low risk of 3.5% is representative. A possible explanation is the under recording of termination data. Sodium valproate is associated, specifically, with *spina bifida* – a malformation which can be detected in the 20 week anomaly scan conducted on all pregnancies.[14;81;162] According to EUROCAT, approximately 75% of prenatally diagnosed cases of *spina bifida* are terminated (Figure 16). Without knowledge of terminations, prenatal diagnoses may be missed and therefore risks underestimated.

Figure 16 Proportion of cases of *spina bifida* terminated following prenatal diagnosis (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables)



A second explanation for the observed lower risk in women prescribed sodium valproate monotherapy may be due to misclassification. Women may be prescribed the treatment, but do not take the drugs in the first trimester thus incorrectly defined as exposed leading to a dilution of the true effect in this group.

This study used real-world data to explore the comparative teratogenicity of antiepileptic drugs. In the UK, the use of real-world data for this study has several advantages:

- A medical history including diagnoses, medications prescribed, and test data is collected for the purposes of patient management, therefore UK primary care data should be accurate and complete;
- Prospective collection of data reduces bias in the recalling of risk factors;
- The UK operates a "gatekeeper" health care system whereby the general practitioner must be the first point of contact for onward referral to specialist care;
- Unlike pregnancy registry studies, selection bias is minimised since over 95% of pregnant women consult their GP in pregnancy in the UK;[109]
- Medical record based information on prescriptions provides a more reliable method for ascertainment of the timing an type of exposure than a retrospective interview;
- An internal comparison group who had previously been prescribed antiepileptic drugs but were not given further antiepileptic drug treatment in their first trimester was available.

However, there are limitations which must be borne in mind:

- The use of prescriptions to examine teratogenicity assume that the woman has consumed the drugs as prescribed;
- The pregnancy cohort was large, however when examining specific drugs, the sample size was reduced and may not have been adequate to detect moderate differences in risk;
- Despite a reasonable estimate of birth prevalence of major congenital malformations in the general population, there may be cases of non-live birth not captured, particularly from terminations;

- As described earlier, a measure of disease severity is difficult to find in the given data, which may be an issue if it is associated with the outcome.

7.6. How this informs the next chapter

The results of this study help to inform women and health care professionals on their choice of antiepileptic drug treatment in pregnancy, and furthermore, it provides direction for future research in this area. The next chapter summarises the three studies covered in this thesis and returns to the literature bringing together the findings from this PhD with the current understanding of the teratogenic effects of antiepileptic drugs. This overview informs overall recommendations for clinical practice and how research should be conducted in this area in the future.

Chapter 8

Thesis discussion

8.1. Summary of key points in the thesis

The broad aim of this PhD was to develop an understanding of the pharmacoepidemiology behind antiepileptic drugs in pregnancy. This is demonstrated by this thesis. The main research contained in this thesis aimed to provide quantitative estimates of comparative risks of major congenital malformations and perinatal death between common antiepileptic drugs regimens, thus increasing the information available to treating physicians and women taking antiepileptic drugs.

At the beginning of the thesis, I provided a broad background to assist the reader in understanding the content of the thesis, along with a current review of the literature around the comparative risk of major congenital malformations between common antiepileptic drugs taken in the first trimester of pregnancy. Here, I highlighted that although research into these adverse effects has been conducted for decades, the overall understanding of the effects of individual drug regimens, and the effect relative to other regimens, is unclear. Studies find conflicting evidence of a difference in risk when comparing carbamazepine, lamotrigine and no therapy. However, the exception to this was the one drug, sodium valproate which according to national guidelines one needs to avoid in pregnancy, if possible. Research consistently found an increased risk of major congenital malformations amongst women who took sodium valproate in pregnancy – risk increases as high as fivefold.[17;18;20] With respect to study design, the literature review also highlighted a series of biases in previous studies including selection, information and recall bias.

For the three studies in this thesis, I have used data from The Health Improvement Network (THIN). This holds routinely collected data from UK primary care GP consultations for over 11 million patients since 1994. The main advantage of using such data was that it would provide a large sample size without selection bias which accompanies the use of pregnancy registries for

these types of studies. Furthermore, it holds prospectively collected data based on information which, by nature, should be accurate as the primary purpose of the database is for patient care and management.

Between 1994 and 2012, a cohort of over 350,000 pregnancies was identified in THIN, of which 80% of the mother's medical records could be matched to a set of child's records. This cohort of pregnancies formed the basis of each study in this thesis. Specifically, these three studies were:

1. Antiepileptic drug prescribing in pregnancy in primary care
2. Prevalence of major congenital malformations and perinatal death in primary care
3. Antiepileptic drugs in pregnancy and the risk of major congenital malformations or perinatal death

The first study revealed around 1 in 200 pregnant women in UK primary care were prescribed antiepileptic drugs during their pregnancy. Amongst these women, the most commonly used drugs were carbamazepine, sodium valproate and lamotrigine. However, the order of preference over these three drugs varied over the study period 1994-2012 with carbamazepine and sodium valproate declining in use whilst lamotrigine became increasingly prescribed. Many women with epilepsy, approximately 60%, prescribed antiepileptic drugs before pregnancy, continued to do so throughout pregnancy however there was a different picture for the smaller group of women prescribed antiepileptic drugs for mental health conditions. Here, the discontinuation rate was steep at the beginning of pregnancy with only 25% continuing therapy past the first six weeks of pregnancy.

In the second study, the focus was on the outcome of interest for the main study – major congenital malformations and perinatal death. It was necessary to examine overall recording of these outcomes in the data since these are usually diagnosed in hospital – thus, the reliance is on effective communication of such diagnoses from hospital to primary care. Of the 350,000 pregnancies in the cohort, nearly 2% were identified to have a diagnosis of a major congenital malformation. Compared to a number of external sources, this was a reasonable

estimate and this suggested that these data were well recorded. The recording of perinatal death was 0.4%, slightly lower than figures from the Office for National Statistics (0.49%).

The third and final study was the main feature of this thesis. The aim was to be able to provide quantified differences in risk between antiepileptic drug regimens in order that women and health care professionals can balance their individual risks and benefits of continued drug therapy in pregnancy. Of women who were taking antiepileptic drugs prior to pregnancy, the overall risk of major congenital malformations or perinatal death was higher than that estimated in the general population – 3.3% (95% CI 2.5-4.3%) vs. 1.9% (95% CI 1.9-2.0%). When dividing this cohort into sub groups according to their treatment in the first trimester, risks varied between common monotherapies – carbamazepine (AR 4.4%; 95% CI 2.6-7.1%), lamotrigine (AR 2.4%; 95% CI 1.0-4.7%) and sodium valproate (AR 3.5%; 95% CI 1.5-6.8%) Women who were not prescribed antiepileptic drug treatments in the first trimester, had a risk similar to the overall cohort, around 3% (95% CI 1.2-6.1%). The greatest concern is for women taking sodium valproate polytherapy. Of those prescribed this in their first trimester, there was an absolute risk of 12% (95% CI 5.9-21.0%) and a threefold increase in risk compared to carbamazepine monotherapy, and sodium valproate monotherapy and fivefold compared to lamotrigine monotherapy.

8.2. Discussion of findings

8.2.1. Background

It is important to recall the fundamental reasons for studying adverse effects of drugs in pregnancy. It is known that a foetus undergoes significant development in the first trimester of pregnancy. It is known that some drugs ingested by the mother can cross the placental barrier. It is known that some drugs that cross this barrier have the potential to interfere with foetal development causing structural deformities. Yet, what is not known is the extent to which certain drugs have these effects prior to new drugs being marketed for general use. Therefore the only way of assessing adverse effects of drugs in pregnancy is to study this in post marketing observational studies.

Major congenital malformations can occur in any pregnancy – the risk being between 1 and 3%.[3] Major malformations are distinguished from minor ones by the extent of the malformation and the need for intervention such as surgery or long term care, as well the associated risk of death as a result. The historic scandal of thalidomide and its devastating malformations of the foetus marked the initiation of a wave of regulation, monitoring and research. Since then research into drug safety in pregnancy has developed in all forms from observational cohort studies to the establishment of pregnancy registries.

Research on antiepileptic drugs has spanned decades – one of the earliest by Spediel and Meadow in 1972 found pregnant women with epilepsy were twice as likely to result in a congenital abnormality or foetal death.[163] There have since been a large number of studies into these older antiepileptic drugs. However, research on many of these older drugs is no longer necessary, with the exception of sodium valproate and carbamazepine which are still commonly used in the general population as well as in pregnancy.[121;164;165] This past research is likely to have led to the generally used statistic that, on average, antiepileptic drugs increase the risk of major congenital malformations by two to three times. However, many studies used women in the general population as a comparator and were possibly subject to confounding by indication should the disease indication be a risk factor itself. Despite this and other limitations to the studies on these older drugs, the common finding was that sodium valproate bore a high risk of teratogenic effects.[17;18;20;73;166;167] As for the newer antiepileptic drugs which have been increasingly used in the general population,[121;164;165] examining the effect of the drug in pregnancy has been limited since it requires observation of a large numbers. Previous studies have mostly been based on small sample sizes because research was carried out in years soon after the drug was marketed. More recent studies have been larger in size (these are discussed in a later section), reflecting the increased use of lamotrigine in pregnancy, however at the time of the starting this PhD, little could be inferred from the limited evidence available on lamotrigine. Of studies that had been reviewed in Chapter 1, all but one found no evidence of a difference in risk of major congenital malformations for lamotrigine.

8.2.2. Discussion of results in relation to current literature

8.2.2.1. Key points of the thesis

The primary question of this thesis was, what are the risks of major congenital malformations associated with first trimester antiepileptic drug use? Further, it was to examine how the risks were relative to other regimens. Using UK primary care electronic health records from THIN to study this research question, the first two studies were conducted to gain an understanding of THIN data so as to allow the exploration of antiepileptic drugs and the recording of adverse foetal outcomes which are not generally diagnosed in the primary care setting.

The drug utilisation study described in Chapter 5 confirmed well-recorded data on antiepileptic drug prescribing. The findings were similar to several other studies, specifically, the most commonly used drugs in pregnancy and the secular trends in prescribing. As expected, sodium valproate, carbamazepine and lamotrigine were preferred treatments in pregnancy. Over time, an increasing number of pregnant women were prescribed lamotrigine, and fewer getting sodium valproate and carbamazepine, the two older drugs associated with negative foetal effects in previous studies. This study also examined whether or not pregnancy was a determinant for discontinuation. There has to my knowledge, been little research on this despite the need to be aware of the risks of abrupt discontinuation of medication in pregnancy. There was a disparity in discontinuation rates between pregnant and non-pregnant women. Pregnant women were more likely to discontinue treatment and this differed depending on whether the woman had epilepsy or bipolar disorder. Women with bipolar disorder were highly likely to cease medication in the first trimester. Bipolar disorder is a severe mental illness with characteristic illness peaks and troughs and hence, must be managed to prevent mood relapses. Of the small number of women treated for bipolar disorder, only half continued on alternative antidepressant or antipsychotic drugs. An interesting finding that emerged from this work is that discontinuation amongst women with epilepsy was more likely to occur in women prescribed sodium valproate rather than carbamazepine and lamotrigine. This indicates that there is an awareness of the greater negative effects of the use of sodium valproate in pregnancy.

Having examined the recording of antiepileptic drug prescribing in pregnancy, the next step was to validate the outcomes of interest in the main study. Although, antiepileptic drug prescribing occurs predominantly in primary care, major congenital malformations and perinatal death are generally diagnosed elsewhere and communicated back to the general practitioner after the event. Thus the purpose of the second study (Chapter 6), was to estimate the incidence in the general population in THIN and assess whether this compared favourably with other external sources. The incidence of major congenital malformations was estimated to be 1.9%, which was within the background risk of 1-3%. Comparison with external sources such as EUROCAT (an international congenital malformation registry) and BINOCAR (a UK congenital malformation registry) suggested that this compared favourably with their figures suggesting that most major congenital malformations were captured in THIN. The estimate of incidence of perinatal death was very slightly lower when compared to ONS figures – 0.4% compared to 0.5%.

These two studies supported the decision to use data from THIN for the main study looking into the relative risks of major congenital malformations or perinatal death associated with first trimester antiepileptic drug use. In unadjusted comparisons between the three most commonly prescribed monotherapy regimens (lamotrigine, carbamazepine, sodium valproate), I found the risks of major congenital malformations or perinatal death were similar (lamotrigine monotherapy vs. carbamazepine monotherapy, IRR 0.54, 95% CI 0.23-1.26; sodium valproate monotherapy vs. carbamazepine monotherapy, IRR 0.80, 95% CI 0.34- 1.86; sodium valproate monotherapy vs. lamotrigine monotherapy, IRR 1.47, 95% CI 0.55-3.92). Furthermore, there was no evidence of a difference in each of these groups compared to the risk amongst women who were not treated in the first trimester. The major concern drawn from this study was the risk associated with sodium valproate polytherapy – an absolute risk of 12%, increases the risk fivefold compared to lamotrigine monotherapy (IRR 5.03; 95% CI 1.99-12.74), threefold compared to sodium valproate monotherapy (IRR 3.42; 95% CI 1.35-8.66), threefold compared to carbamazepine monotherapy (IRR 2.72; 95% CI 1.23-5.99) and fourfold in comparison with women who were untreated in the first trimester (IRR 4.03; 95% CI 1.53-10.58).

8.2.2.2. Updated literature review

These findings need to be considered in light of current research conducted after I had started working on these data. In Chapter 1, it was clear that there was a high level of heterogeneity between research studies which had investigated the teratogenicity of antiepileptics. I described relevant studies detail rather than combined into a meta-analysis. Since this review was conducted in 2010, there have been several key papers published in this area thus in order to discuss my results relative to current understanding, I have conducted a second review identifying relevant literature available since 2010.

I used the same search strategy as used in the original review (Appendix 1), covering a new time period from 1 October 2010 to 31 June 2015. The studies are, once again, described rather than meta-analysed. Most studies provided only absolute risk estimates. I used these figures, I to calculate odds ratios in order to provide a crude estimate of the relative risk.

Selection of articles for review

A total of 1187 articles were identified, of which 54 were selected for a review of their abstracts based on the titles. Full text reviews were then performed on 40 studies. Several articles were excluded:

- One duplicate study
- Eight were comments on a study
- Two reviews
- Nine had no estimates of risk for any of the interest groups
- Six no comparison group of interest
- Two did not examine major congenital malformations as an outcome
- Two were unavailable

Of the remaining 10 papers, in view of duplicate publications, there were seven studies included in the review.

Description of selected articles

Three studies were published from Australian Pregnancy Register[158;168;169] between 2010 and 2015, each an update on the last. Therefore, only the latest study published in 2014 was included in the review. With data up to November 2013, this study examined 1,725 pregnancies where antiepileptic drugs were taken at some stage in pregnancy. It was not limited to women with epilepsy, and contained some pregnancies with no first trimester use of antiepileptic drugs (these women had to have been exposed later in pregnancy in order to be included in the register). Information was ascertained through interviews antenatally and postnatally and through liaison with the woman's medical practitioners. Derived unadjusted odds ratio and associated 95% confidence intervals are below (Table 15).

Table 15 The teratogenicity of the newer antiepileptic drugs - an update; Vadja (2014)

Reference group	Malformations n/N (%)	Comparator group, OR (95% CI) †††			
		Sodium valproate polytherapy	Sodium valproate monotherapy	Lamotrigine monotherapy	Carbamazepine monotherapy
Untreated	5/153 (3.3)	3.35 (1.21-9.25)	4.75 (1.82-12.41)	1.41 (0.50-4.00)	1.72 (0.63-4.69)
Lamotrigine monotherapy	14/307 (4.6)	2.37 (1.15-4.89)	3.36 (1.76-6.40)	-	1.22 (0.60-2.47)
Carbamazepine monotherapy	19/346 (5.5)	1.95 (1.00-3.82)	2.76 (1.54-4.96)	-	-
Sodium valproate monotherapy	35/253 (13.8)	0.71 (0.39-1.29)	-	-	-
Sodium valproate polytherapy	18/177 (10.2)	-	-	-	-

††† Derived unadjusted odds ratio and 95% confidence intervals

The significant findings were a threefold increase in risk in women exposed to sodium valproate polytherapy compared to women untreated in the first trimester, (unadjusted OR 3.35; 95% CI 1.21-9.25), a twofold increase compared to lamotrigine monotherapy (unadjusted OR 2.37; 95% CI 1.15-4.89) and similarly compared to carbamazepine monotherapy (unadjusted OR 1.95; 95% CI 1.00-3.82) (Table 15). Women treated with sodium valproate monotherapy were nearly five times more likely to have a major congenital malformation compared to untreated women (unadjusted OR 4.75; 95% CI 1.82-12.41), three times as likely as women treated with lamotrigine monotherapy (unadjusted OR 3.36; 95% CI 1.76-6.40) and carbamazepine monotherapy (unadjusted OR 2.76; 95% CI 1.54-4.96). Risks were comparable between carbamazepine monotherapy, lamotrigine monotherapy and women untreated in the first trimester. Furthermore, they found no evidence of a difference in risk between sodium valproate users on monotherapy and polytherapy. No adjustment for confounding was performed.

Two studies from the North American Antiepileptic Drug Pregnancy Registry have been published since 2010, and therefore the latest was included.[129;161] Pregnancies enrolled in the registry up to 2011 were examined for first trimester antiepileptic drug exposure which was ascertained through interviews and medical records. The authors compared the risk of major congenital malformations between different exposure groups, adjusting for confounding factors, and found no difference in risk between carbamazepine and lamotrigine, but a five times greater risk in sodium valproate monotherapy compared to lamotrigine monotherapy (adjusted RR 5.1; 95% CI 3.0-8.5) and a threefold increase compared to carbamazepine (unadjusted OR 3.3; 95% CI 2.0-5.6) (Table 16).

Table 16 Comparative safety of antiepileptic drugs during pregnancy, Hernandez-Diaz (2012)

Reference group	Malformations n/N (%)	Comparator group RR (95% CI)	
		Carbamazepine monotherapy	Sodium valproate monotherapy
Lamotrigine monotherapy	31/1862 (2.0)	1.5 (0.9-2.5)	5.1 (3.0-8.5)
Carbamazepine monotherapy	31/1033 (3.0)	-	3.3 (2.0-5.6)†††
Sodium valproate monotherapy	30/323 (9.3)	-	-

An update from the UK and Ireland Epilepsy and Pregnancy Registers was recently published with pregnancies enrolled up to 2012.[81] Similar to the Australian Pregnancy Register and the North American AED and Pregnancy Registry, no evidence of a difference was found between lamotrigine and carbamazepine monotherapy groups. However, sodium valproate monotherapy, once again, was associated with a three times greater likelihood of major congenital malformations compared to both carbamazepine monotherapy and lamotrigine monotherapy (Table 17).

Table 17 Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers, Campbell (2014)

Reference group	Malformations n/N (%)	Comparator group OR (95% CI)	
		Carbamazepine monotherapy	Sodium valproate monotherapy
Lamotrigine monotherapy	49/2198 (2.3)	1.1 (0.7-1.7)	3.0 (2.1-4.3)
Carbamazepine monotherapy	43/1718 (2.6)	-	2.7 (1.9-3.9)
Sodium valproate monotherapy	82/1290 (6.7)	-	-

The International Registry of Antiepileptic Drugs and Pregnancy (EURAP), which collects data from 42 countries, examined dose dependent risks of major congenital malformations across different first trimester regimens.[170] EURAP collects data prospectively from participating physicians on pregnancies prior to foetal outcome being known. Exposure to antiepileptic drugs was examined in

the first trimester and major congenital malformations were identified within 12 months of birth.

Table 18 Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry, Tomson (2011)

Reference group	Malformations n/N (%)	Comparator group OR (95% CI)†††	
		Carbamazepine monotherapy	Sodium valproate monotherapy
Lamotrigine monotherapy	37/1280 (2.9)	**2.0 (1.4-3.0)**	3.6 (2.5-5.3)
Carbamazepine monotherapy	79/1402 (5.6)	**-**	1.8 (1.3-2.5)
Sodium valproate monotherapy	98/1010 (9.7)	-	-

Contrary to the previously mentioned studies, there was evidence of a difference in risk between lamotrigine and carbamazepine (unadjusted OR 2.0 95% CI 1.4-3.0). Furthermore, a fourfold increase in risk between sodium valproate and lamotrigine monotherapy (unadjusted OR 3.6 95% CI 2.5-5.3) and nearly twofold increase in sodium valproate exposed pregnancies compared to carbamazepine exposed pregnancies (unadjusted OR 1.8 95% CI 1.3-2.5) (Table 18). However, these are not adjusted results and, importantly, do not account for cross country differences.

Using EUROCAT data, Jentink *et al* studied specific malformations associated with first trimester carbamazepine monotherapy use in pregnancy.[127] In adjusted analyses, compared to untreated women, the risk of *spina bifida* was twice as likely (OR 2.6 95% CI 1.2-5.3) but was lower compared to women exposed to sodium valproate (OR 0.2 95% CI 0.1-0.6). However, there was no evidence of an association between carbamazepine and other malformations compared to untreated women.

The Medical Birth Registry of Norway was used by Veiby *et al* to study foetal outcomes of antiepileptic drug use in pregnancy.[131] The registry is a population wide database of all deliveries from 12 weeks gestation containing information pertinent to maternal health, pregnancy and perinatal outcomes. Data is supplied to the registry through the attending physicians and midwife at delivery. The study

also included linked data from the Register of Pregnancy Terminations on induced abortions. Use of antiepileptic drugs in pregnancy (not limited to the first trimester) was stratified according to selected regimens. Women with epilepsy untreated in pregnancy formed an internal comparison group.

Table 19 Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy, Veiby (2014)

Reference group	Malformations n/N (%)	Comparator group, OR (95% CI)†††			
		Sodium valproate polytherapy	Sodium valproate monotherapy	Lamotrigine monotherapy	Carbamazepine monotherapy
Untreated	106/3773 (2.8)	1.9 (0.7-5.3)	2.3 (1.4-3.8)	1.2 (0.8-1.8)	1.0 (0.6-1.7)
Lamotrigine monotherapy	28/833 (3.4)	1.6 (0.5-4.6)	1.9 (1.1-3.5)	-	0.9 (0.5-1.6)
Carbamazepine monotherapy	20/685 (2.9)	1.8 (0.6-5.5)	2.2 (1.2-4.2)	-	
Sodium valproate monotherapy	21/333 (6.3)	0.8 (0.3-2.4)	-	-	-
Sodium valproate polytherapy	4/77 (5.2)	-	-	-	-

Unadjusted odds ratios show evidence of a difference in risk between sodium valproate monotherapy and the women with untreated epilepsy (OR 2.3; 95% CI 1.4-3.8), lamotrigine monotherapy (OR 1.9; 95% CI 1.1-3.5) and carbamazepine monotherapy (OR 2.2; 95% CI 1.2-4.2). There was no evidence to suggest sodium valproate polytherapy was higher risk than the other regimens of interest, or between carbamazepine and lamotrigine monotherapy exposed pregnancies (Table 19).

Kulaga *et al* studied data from the Quebec Pregnancy Registry.[171] This registry combines data from three administrative databases – the *Régie de l'Assurance Maladie du Québec* (a database of medical services used by all residents of Quebec, and prescription fills for Quebec residents under the Quebec Public Prescription Drug Insurance Plan), Med-Echo (acute hospitalisations for all residents including planned and spontaneous abortions and deliveries), and the *Institut de la Statistique du Québec* (database on all births and deaths in Quebec). Data was collected routinely and prospectively. Women with a diagnosis of

epilepsy and having had received antiepileptic drugs prior to pregnancy were identified and stratified into three groups based on treatment in pregnancy – no treatment, monotherapy or polytherapy – however, this was also not restricted to the first trimester but the whole of pregnancy.

Table 20 Antiepileptic drug use during pregnancy: perinatal outcomes, Kulaga (2011)

Reference group	Malformations n/N (%)	Comparator group OR (95% CI)†††	
		Any monotherapy	Any polytherapy
Untreated	4/20 (20.0)	0.4 (0.1-1.6)	0.9 (0.3-3.6)
Any monotherapy	11/111 (9.9)	-	2.1 (0.8-5.8)
Any polytherapy	8/42 (19.0)	-	-

This study found each of the groups were comparable in their risk of major congenital malformations, however, this is likely to be affected by the small sample sizes observed.

Summary of findings from original and updated reviews and the main study

1. Carbamazepine monotherapy vs. untreated

Carbamazepine monotherapy and women untreated with antiepileptic drugs in pregnancy were compared in three studies in the original literature review from Chapter 1. Two studies were from the same cohort, the Australian Pregnancy Register. Using only the latest set of results from this cohort and the third study which was a hospitals based study in Boston, the studies concluded that there was no evidence of a difference in the teratogenic risk between women given carbamazepine monotherapy and women given no antiepileptic drugs in the first trimester.[4;18] In updating the literature review, two more studies were identified. One was a further update on the Australian Pregnancy Registry. Here, Vadja *et al* continued to find similar estimates of risk to their previous study in women untreated and women with carbamazepine monotherapy use in pregnancy (3.3% and 5.5% respectively; Table 15).[158] A crude estimate of the odds ratio could be calculated, which indicated no evidence of difference in risk of malformations (unadjusted OR 1.72 95% CI 0.63-4.69). Veiby *et al* came to a similar conclusion in their study in the Norwegian Birth Registry.[131] They found 2.8% and 2.9% of

pregnancies resulting in major congenital malformations in women untreated and women given carbamazepine monotherapy in pregnancy (though not limited to the first trimester) (unadjusted OR 1.0 95% CI 0.6-1.7; Table 19). These studies provide support to my findings, which also did not find evidence of a difference in teratogenic risk between carbamazepine exposed and untreated pregnancies.

2. Sodium valproate monotherapy vs. untreated

The two studies in the original review found highly elevated risks of major congenital malformations in sodium valproate exposed pregnancies compared to untreated women.[11;18] However, one of these, by Artama *et al,* pooled minor and major malformations, potentially leading to overestimation of risk.[11] Bearing this in mind, their study found 10.6% of sodium valproate exposed and 2.8% unexposed pregnancies were affected, which after adjusting was a fourfold increase in risk (OR 4.01, 95% CI 2.32-7.01)[11]. Vadja *et al* found 15.1% and 3.4% of sodium valproate and untreated women affected, which equated to a fivefold increase (OR 4.99, 1.73-14.44).[18] The 2014 study from the same authors updated these estimates to 13.8% and 3.3% of pregnancies with sodium valproate monotherapy use and no therapy used, respectively, giving an unadjusted odds ratio of 4.75 (95% CI 1.82-12.41) (Table 15).[158] Veiby *et al* found 6.3% of pregnancies with sodium valproate monotherapy exposure had a major congenital malformation, while this was only 2.8% in untreated women.[131] This was a twofold increase in risk (OR 2.33, 95% CI 1.44-3.77) (Table 19). In my study, the absolute risk amongst women with sodium valproate monotherapy prescribed in the first trimester was much lower than these studies (3.5%), and thus pair wise comparisons with the untreated group where 3.0% of pregnancies were affected found no evidence of a difference in risk (adjusted OR 0.89; 95% CI 0.27-2.98). As discussed in Chapter 7, this suggests that there is either an under recording of cases particular to women who took sodium valproate monotherapy in pregnancy, or that there may be a misclassification of women in this group as exposed when possibly they did not take the prescribed drugs in the first trimester.

3. *Lamotrigine monotherapy vs. untreated*

The UK and Ireland Epilepsy and Pregnancy Registers and the Australian Pregnancy Register were reviewed in Chapter 1 where women on lamotrigine monotherapy were compared with women not treated with antiepileptic drugs in pregnancy. Recall, that women in these studies are not necessary limited to those with epilepsy – in both registers, the untreated group are women who had been prescribed antiepileptic drugs either before or after the first trimester. Both studies found no evidence of a difference in risk of major congenital malformations.[17;19] Women with first trimester use of lamotrigine monotherapy experienced a risk of 3.2% (21/647) and 4.9% (12/243) in the UK and Australia respectively.[17;19] Whilst these risks are quite different from each other, and different from that estimated in my study, they were relatively similar to risks in women who were untreated (8/227 = 3.5% in the UK and Ireland Epilepsy and Pregnancy Register; 4/118 = 3.4% in the Australian Registry).[17;19] Vadja *et al* have since published more recent figures from the Registry which continue to find no difference in risk when lamotrigine monotherapy is prescribed in the first trimester (4.6% vs. 3.3%; OR 1.41; 95% CI 0.50-4.00 (Table 15)).[158] Similarly, the Norwegian study by Veiby *et a*l also found no difference (3.4% vs. 2.8%; lamotrigine monotherapy vs. untreated respectively; OR 1.20; 95% CI 0.79-1.84).[131] My study found lamotrigine monotherapy was associated with a risk of 2.4% while women with no antiepileptic drugs in the first trimester were slightly higher, 3.0%. The unadjusted comparison finds no evidence of a difference.

4. *Carbamazepine monotherapy vs. lamotrigine monotherapy*

In the original literature review, just one study compared risks between these two groups. This was the UK Epilepsy and Pregnancy study which found 3.2% of women on lamotrigine monotherapy were affected. In comparison, only 2.2% (20/900) of women on carbamazepine monotherapy had pregnancies with a major congenital malformation.[17] With the rapid rise in the use of lamotrigine in pregnancy, I found a further five studies published in just the last five years which examined this comparison. An update on data from the UK Epilepsy and Pregnancy Register was published in 2014 using data up to 2012.[81] Since the 2006 study, the number of women on lamotrigine monotherapy tripled to 2,198. Of these, 49 (2.3%) had a major congenital malformation. There were also twice

as many women prescribed carbamazepine monotherapy in 2012 than in 2006. Of 1,718 women, 43 pregnancies were affected and after adjusting for confounders, there was no difference in risk between the two groups (OR 1.1; 95% CI 0.7-1.7) (Table 17). Data from the Australian Pregnancy Registry identified 5.5% (19/346) and 4.6% (14/307) of pregnancies exposed to carbamazepine monotherapy and lamotrigine monotherapy respectively with major congenital malformations and no difference in risk (OR 1.22; 95% CI 0.60-2.47 (Table 15)).[158] A large study came from the North American Antiepileptic Drug Pregnancy Registry by Hernadez-Diaz *et al*.[129] Of 1,862 women with exposure to lamotrigine monotherapy in the first trimester, 2.0% (n = 31) of babies had a major congenital malformation while in carbamazepine monotherapy exposed pregnancies, this was 3.0% (31/1033). After adjusting, there was no evidence that the risk differed (OR 1.5; 95% CI 0.9-2.5 (Table 16)). In Norway, the risks estimated by Veiby *et al* also suggested there was no differential between carbamazepine monotherapy and lamotrigine monotherapy exposed pregnancies (20/685 = 2.9% vs. 28/833 = 3.4% respectively; OR 0.86; 95% CI 0.48-1.55 (Table 19)).[131] In opposition to these studies, findings from the international collaboration, EURAP, found that women with carbamazepine monotherapy use were twice as likely to have a baby with a major congenital malformations than those who were using lamotrigine monotherapy (79/1402 = 5.6% vs. 37/1280 = 2.9%; OR 2.0; 95% CI 1.4-3.0 (Table 18)).[160] My study found no evidence of a difference in risk which was 4.4% in carbamazepine monotherapy pregnancies, 2.4% in lamotrigine monotherapy pregnancies (IRR 0.54; 95% CI 0.23- 1.26).

5. Sodium valproate monotherapy vs. carbamazepine monotherapy

This was examined in five studies in the original review. Two from the UK Epilepsy and Pregnancy Register and one from each of the Australian Pregnancy Registry, Swedish Medical Birth Registry and the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study from the UK and US. The later of the two studies from the UK Epilepsy and Pregnancy Registry found sodium valproate monotherapy to be twice as likely to lead to major congenital malformations (RR 2.35; 95% CI 1.57-3.57).[75] The Australian Pregnancy Registry also found an elevated risk (RR 4.34; 95% CI 1.79-10.53).[18] Population based data from linked

national registers in Sweden was analysed by Wide *et al* in 2004.[20] They found 26 (9.7%) cases of major congenital malformations in 268 women who took sodium valproate monotherapy and 28 (4.0%) in 703 women prescribed carbamazepine monotherapy. This was at least a twofold increase in risk (adjusted OR 2.51; 95% CI 1.43-4.86). The US/UK NEAD study identified major congenital malformations and foetal death in a relatively small number of pregnancies.[15] They found 5.8% (4/69) and 4.5% (5/110) pregnancies with a serious adverse outcome, and a relative risk of 3.83 (95% CI 1.41-10.39). Thus, overall from these studies, the conclusions were clear in that sodium valproate monotherapy was associated with a higher risk of major congenital malformations compared to carbamazepine monotherapy. The relative risk varied from around twice as likely to nearly four times. Since 2010, another six studies were published. Two were updates – one from the Australian Pregnancy Registry and another from the UK Epilepsy and Pregnancy Register, and both provided further data to reinforce their original findings. With more data, Vadja *et al* were able to double their denominators and refine risk estimates to 13.8% (35/253) vs. 5.5% (19/346) giving an unadjusted odds ratio of 2.76 (95% CI 1.54-4.96) (Table 15).[158] The UK Epilepsy and Pregnancy Register calculated an adjusted odds ratio of 2.7 (95% CI 1.9-3.9), which was not dissimilar to their research in 2009 (Table 17).[81] Figures from the North American Antiepileptic Drug Pregnancy Registry supported a roughly threefold increase in risk in sodium valproate monotherapy pregnancies (30/323 = 9.3% vs. 31/1033 = 3.9%; unadjusted OR 3.3 (95% CI 2.0-5.6) (Table 16).[129] Comparisons in the EURAP study estimated a slightly lower difference in risk – women with carbamazepine monotherapy use in pregnancy had a major congenital malformation in 79 of 1402 pregnancies (5.6%), whilst in sodium valproate monotherapy 98/1010 (9.7%), equivalent to an unadjusted odds ratio of 1.8 (95% CI 1.3-2.5) (Table 18).[160] In a case control study, Jentink *et al* used data from the malformation registry EUROCAT and found the risk of a specific malformation, *spina bifida*, was lower in carbamazepine monotherapy pregnancies than sodium valproate pregnancies (OR 0.2; 95% CI 0.1-0.6).[127] Veiby *et al* found a twofold elevated risk of major congenital malformations in sodium valproate monotherapy pregnancies compared to those exposed to carbamazepine monotherapy (unadjusted OR 2.2; 95% CI 1.2-4.2) (Table 19).[131] In my study, the risk of major congenital malformations in women prescribed sodium valproate monotherapy in the first

trimester was lower than expected (3.5%), and lower than in women prescribed carbamazepine monotherapy (4.4%). The difference was not statistically significant (IRR 0.80; 95% CI 0.34-1.86) thus conflicting with the overwhelming body of research that suggests a greater detrimental effect of sodium valproate monotherapy.

6. Sodium valproate monotherapy vs. lamotrigine monotherapy

In their earlier study, Vadja *et al* only had 61 women with lamotrigine monotherapy use in pregnancy, of which there were no cases of major congenital malformations. The risk in the sodium valproate monotherapy group relative to lamotrigine monotherapy was calculated as 5.58 (95% CI 2.06-15.09).[18] A similarly small study from NEAD found one case in 98 pregnancies with lamotrigine monotherapy exposure and a relative risk of 17.04 (95% CI 2.27-128.05).[15] The UK Epilepsy and Pregnancy Register found a relative risk of 2.4 (9% CI 1.6-3.7) in their 2009 study.[75] Apart from the UK Epilepsy and Pregnancy Register study where only the relative risk was reported, the size of these other two studies were very small compared to more recent studies. In the most recent study, Vadja *et al* were able to include 307 women with lamotrigine monotherapy exposure in pregnancy, finding a risk of 3.3%. The risk was threefold in women who were taking sodium valproate monotherapy (unadjusted OR 3.4; 95% CI 1.8-6.4) (Table 15).[158] Hernandez-Diaz *et al* also found a higher risk associated with sodium valproate monotherapy in their study of the North America Antiepileptic Drugs Registry (30/323 = 9.3% vs. 31/1862 = 2.0%; sodium valproate vs. lamotrigine monotherapy respectively; RR 5.1; 95% CI 3.0-8.5) (Table 16).[129] The UK Epilepsy and Pregnancy Register had the largest number of women with lamotrigine monotherapy use in pregnancy – 49 of 2,198 (2.3%) had a major congenital malformation. Sodium valproate monotherapy pregnancies were three times more likely to have a major congenital malformation (OR 3.0; 95% CI 2.1-4.3) (Table 17). [81] Data from EURAP further corroborated a threefold elevated risk – 98/1010 = 9.7% vs. 37/1280 = 2.9%; sodium valproate monotherapy vs. lamotrigine monotherapy respectively; OR 3.6; 95% CI 2.5-5.3) (Table 18).[170] Veiby *et al* examined 833 women with lamotrigine monotherapy, 28 (3.4%) of which had a major congenital malformation. There were 21 cases in 333 (6.3%) women with sodium valproate monotherapy exposure in pregnancy thus an odds

ratio of 1.94 (95% CI 1.08-3.46) (Table 19).[131] These studies vary in size however they are all in agreement that the risk of major congenital malformations is higher in pregnancies where the mother took sodium valproate monotherapy in pregnancy compared to those who took lamotrigine. In my study, the risk between sodium valproate monotherapy and lamotrigine monotherapy prescribed pregnancies was no different (IRR 1.47; 95% CI 0.55-3.92).

Sodium valproate polytherapy

The most recent study from the Australian Pregnancy Registry included 177 women on sodium valproate polytherapy in pregnancy of which 18 (10.2%) (Table 15) resulted in a major congenital malformation.[158] This was a threefold increase in risk compared to the untreated group (3.3%; unadjusted OR 3.35 95% CI 1.21-9.25), a twofold increase compared to lamotrigine monotherapy (4.6%; unadjusted OR 2.37 95% CI 1.15-4.89) and to carbamazepine monotherapy (5.5%; unadjusted OR 1.95 95% CI 1.00-3.82), whilst no difference was found compared to sodium valproate monotherapy (13.8%) (Table 15).

The study by Veiby *et al* from the Norwegian Birth Registry found a much lower rate – four in 77 (Table 19) women with sodium valproate polytherapy exposure in pregnancy had a major congenital malformation giving and absolute risk of 5.2%.[131] When compared to the untreated group, and each of the three monotherapy groups, there was no evidence of a difference in risk in this study.

The 2006 study from the UK Epilepsy and Pregnancy Register included 304 women with sodium valproate polytherapy exposure and found 9.0% (6.3% to 12.8%) were affected.[17] There was evidence of a higher risk in pregnancies with sodium valproate polytherapy use compared to lamotrigine monotherapy (unadjusted OR 2.9; 95% CI 1.6-5.2) and carbamazepine monotherapy (unadjusted OR 4.3; 95% CI 2.4-7.8), but not compared to sodium valproate monotherapy (unadjusted OR 1.5; 95% CI 0.9-2.4) (Table 21).

Table 21 Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register, Morrow (2006)

Reference group	Malformations n/N (%)	OR (95% CI)†††
Lamotrigine monotherapy	21/647 (3.2)	2.9 (1.6-5.2)
Carbamazepine monotherapy	20/900 (2.2)	4.3 (2.4-7.8)
Sodium valproate monotherapy	44/715 (6.2)	1.5 (0.9-2.4)
Sodium valproate polytherapy	27/304 (9.0)	-

Two studies agree that there is an increased risk associated with sodium valproate polytherapy compared to carbamazepine and lamotrigine monotherapy, thus supporting my findings (vs. carbamazepine monotherapy IRR 2.72; 95% CI 1.23- 5.99; vs. lamotrigine monotherapy IRR 5.03 95% CI 1.99- 12.74). However, the effect sizes vary between all three studies, and one study conflicted these studies by finding no difference between sodium valproate polytherapy, lamotrigine monotherapy and carbamazepine monotherapy. Each of the three studies also found that the risk of malformations in sodium valproate polytherapy and monotherapy did not differ. This is in contrast to my study where women with sodium valproate prescribed in pregnancy were three times more likely to have a baby with major congenital malformations than those prescribed this drug as monotherapy (IRR 3.42 95% CI 1.35- 8.66).

Summary of current literature

Bringing together the research published elsewhere with those observed in my study, one can summarise the current understanding of the relative risks of major congenital malformations between specific antiepileptic drug regimens.

- Carbamazepine monotherapy and women with no antiepileptic drugs use in pregnancy exhibit similar risks of major congenital malformations in pregnancy.

- Sodium valproate monotherapy is associated with a higher risk of major congenital malformations compared to no antiepileptic drug use in the first trimester of pregnancy. The effect size is around fivefold, however

some studies found a slightly lower effect. My study did not support these findings.

- Lamotrigine monotherapy bears no differential risk of major congenital malformations compared to no antiepileptic drug use in pregnancy.

- Most studies, including my study, find no difference in risk between carbamazepine monotherapy and lamotrigine monotherapy. One study, which involved a large sample size, found higher rates in women who took carbamazepine monotherapy in pregnancy compared to those who took lamotrigine monotherapy. However, cross country differences may have confounded these estimates since the data examined was from an international malformation registry.

- Sodium valproate monotherapy increases the risk of major congenital malformations compared to carbamazepine monotherapy by around two to four times. Despite consistent evidence from several research studies, this was not observed in my study.

- Sodium valproate monotherapy increases risk to around threefold of that in lamotrigine monotherapy, however an association was not found in my study.

- There are few studies which examine sodium valproate polytherapy in comparison with monotherapy regimens. Bar one study, there is some evidence, including that from the main study of this thesis, that sodium valproate polytherapy use in pregnancy has a detrimental effect over other monotherapy regimens, however the studies are few and importantly lack adjustment for confounding factors.

The studies identified in the updated literature review built upon conclusions drawn from the original review by providing larger sample sizes particularly with respect to lamotrigine monotherapy. However, there are some key limitations to this combined review which have to be considered alongside the above summary.

Confounders

Most studies provided observations of risk in populations exposed to specific regimens in pregnancy. However, very few conducted a comparison to estimate the relative risk. In these cases, I calculated a crude odds ratio, however this would not account for baseline differences in the compared groups which may confound the observed effect.

Timing of exposure

It was not always clear whether or not women were exposed specifically in the first trimester. Two studies stated that their exposure definition spanned the length of pregnancy – these studies included for a different reason however it is important to restrict analyses to women who have used antiepileptic drugs in the first trimester since this is the period in which malformations occur. Including women who used antiepileptic drugs in later stages of pregnancy, but not in first trimester as "exposed" may dilute any true teratogenic effect of the drugs in question.

Non-live births

Some studies are able to provide data on foetal deaths and terminations (these were the two studies mentioned above which included women exposed to drugs at any point in pregnancy). Other studies, particularly the registries, provide some data on non-live births but are unable to capture all data due to loss to follow-up. Some studies actively exclude terminations and deaths with the reasoning that the cause is not certainly due to a malformation. There are two problems with not including non-live births. Firstly, this reduces the denominator and thus it may underrepresent the study population of pregnant women. Secondly, if there is a higher likelihood of death in pregnancies which have developed a malformation, then the risk estimated from a live birth population will not reflect this, but will underestimate the true effect.

Sample size

This was mainly an issue with regards to sodium valproate polytherapy. Polytherapy regimens are prescribed to fewer people, and are mainly to be prescribed for epilepsy, rarely for other indications (Table 12). Thus, the number of pregnant women taking such regimens is very low in comparison to

monotherapy regimens. Consequently, when estimating risks and comparing polytherapy to other regimens, studies may be underpowered to detect a difference if there is one. The studies in this review, and my study, have found evidence of a difference but a greater sample size is needed to improve the precision of the estimates.

It must be borne in mind that these comparisons are largely unadjusted for confounding factors. However, studies are substantially larger in numbers – from the Australian Pregnancy Registry alone, there were three times more pregnancies with lamotrigine use in 2013 than there were in 2006. Results from recent larger studies therefore provide a good base from which conclusions may be drawn. It is hoped that future studies will continue to accumulate larger samples of antiepileptic drug exposure in women in pregnancy, and adjusted analyses of teratogenic risk may be more prevalent.

8.3. Strengths and weaknesses

The main study in this PhD was a population representative study of pregnant women in the UK which used real time clinical data to examine the teratogenic effects of first trimester antiepileptic drug use. There were several strengths to this study which addressed some of the common weaknesses found in previous studies reviewed in Chapter 1.

Primary care in the UK is accessed freely, and for many women it is the first point of contact with a health care professional in pregnancy. The selection bias that can affect pregnancy registries is likely to be much lower in data which is collected out of routine visits, such as THIN, forming one of the major strengths of this study.

A second strength in this study is the accuracy of information on the use of antiepileptic drugs. Most GPs in the UK only use the computerised system for prescribing so the data captures nearly all prescriptions issued with details on the type of drug prescribed, and when it was prescribed. In a study of teratogenicity, the timing of exposure to drugs *in utero* is crucial to attribute the drug to a malformation, thus data with accurate information will reduce misclassification

bias. In addition to this, the use of prescription data extracted from medical records counteracts the problem of recall bias – where women may incorrectly recall details of antiepileptic drug exposure depending on whether or not their child was affected.

The benefits of THIN data to study the maternal population is overwhelmingly strong. The pregnancy cohort used in this study contained over 350,000 pregnancies. These numbers provide the potential to study rare exposures, such as specific drug regimens, and rare outcomes, such as major congenital malformations. Moreover, this study was able follow-up on child health outcomes, including major congenital malformations, in linked mother-child records for over 80% of pregnancies. There was also a substantial benefit of having a comprehensive medical history of the mother before and during pregnancy. One of the most difficult problems in studying teratogenicity is capturing information on potential confounding factors. Using THIN data, maternal history of behaviours such as smoking, alcohol dependency and substance misuse, alongside other possible contributing factors such as co-medications could be observed.

This study is not without its limitations. As discussed in Chapter 7, THIN data does not directly capture information on disease severity. If this is a factor which is independently associated with the type of drug prescribed and the risk of major congenital malformations, then the effects observed in my study may not be solely due to the drug. Despite the large amount of information on maternal demographic and clinical characteristics that is possible to determine from THIN data, information on disease severity is lacking. Unfortunately, there is no ideal solution to this problem. In real world practice, women with a worse form of e.g. epilepsy may have to be given multiple drugs to treat the condition – thus the likelihood of capturing a comparative sample of women with the same disease severity on a monotherapy, is low. However, a very large study population potentially from international collaborations or whole population birth registers could assess the effect of disease severity.

In my study, exposure in the first trimester included prescriptions made in the month before pregnancy. Drugs consumed prior to conception cannot have a teratogenic effect, however the inclusion of women prescribed in this period was

aimed at capturing women whose prescriptions continued into the early weeks of pregnancy prior to pregnancy being known. Despite this sensitive approach, there may have been women who were prescribed but did not take the drugs in the first trimester, perhaps if they were planning their pregnancy and chose to cease therapy. However, I have showed that the absolute risk estimates in my study were similar to several other studies for carbamazepine monotherapy, lamotrigine monotherapy and untreated pregnancies therefore suggesting misclassification may be only be minimal if at all.

A limitation which has become apparent is the lack of data on terminations, in particular those which were terminated following a pre-natal diagnosis of a malformation. In my study, I found it unusual to see a low prevalence of major congenital malformations in sodium valproate monotherapy exposed pregnancies, as I have discussed earlier in this chapter and in Chapter 7. A possible explanation is that terminations are not well recorded in THIN since it is a procedure conducted outside of primary care. Given the association between sodium valproate exposure and *spina bifida*, and the high rate of termination of babies with *spina bifida*, it could be that this study has underestimated the true effect of sodium valproate. Terminations were initially considered for this study, however it was found that there were numerous inconsistencies in identifying true terminations and relevant dates resulted in the decision not to identify this outcome. Primary care data alone is insufficient for this purpose – an additional data source is necessary.

Of the non-live births which were included in my analysis and counted as perinatal deaths, some of these might not be attributed to a major congenital malformation, thus the overall effect may be overestimated. In my study, there were seven perinatal deaths out of the 1,633 pregnancies in the study population. Incorrectly attributing all seven of these to a major congenital malformation would affect the absolute risks but the small number should have only minimal impact on the comparisons analysis.

This study has demonstrated that the effects of drugs in pregnancy can be examined without several biases that limit other study designs and data sources. It has its limitations, however, these are either problems that exist in all

observational studies and thus are not limited to my study, or can be addressed in future research with access to more data and additional linked data sources.

8.4. Clinical implications

The aim of this study was to enable women and healthcare professionals to be better informed with regards to antiepileptic drug treatment choices in pregnancy. At the time of the beginning of this PhD, the literature review in Chapter 1 demonstrated that high quality studies were lacking despite decades of research on older antiepileptic drugs. Furthermore, there was a clear paucity of information on the effects of newer antiepileptic drugs. In clinical practice, it may have been difficult to convey the risks if research studies had not provided consistent results and recent surveys of women with epilepsy have highlighted that this gap in knowledge exists. It is therefore important to consider how the studies conducted in this PhD can impact this aim to inform clinical practice.

In Chapter 5, I showed the use of lamotrigine has risen rapidly in pregnancy over time. Lamotrigine monotherapy should be considered for treatment for women of child-bearing age given its relatively low teratogenic risk but health care professionals must act cautiously so as not to compromise the management of the woman's condition. This is especially relevant for women due to faster clearance of lamotrigine from the blood during pregnancy, which could lead to relapses of the underlying condition and compromising the mother and baby's health. In these situations, lamotrigine dosage can be amended accordingly.

Whilst there has been much research on the risk associated with sodium valproate use in pregnancy, it remains more commonly prescribed in pregnancy than most other antiepileptic drugs. Sodium valproate continues to be highlighted as the drug of highest risk, however, this study shows that it is particularly high risk if prescribed in polytherapy. Sodium valproate should continue to be avoided. Where this is not possible, women should be given the minimum effective dose and monotherapy should be preferred over polytherapy in order to minimise the teratogenic risk as much as possible.

Carbamazepine monotherapy should be considered as an alternative treatment to sodium valproate. Although my study found women on these monotherapies to bear similar risks of major congenital malformations, the strong evidence against sodium valproate in polytherapy suggests this drug should be avoided, and that carbamazepine may be a safer alternative treatment.

Since the original literature review was performed in 2010, there has been new advice on clinical practice in the UK related to the pharmacological treatment of women with antiepileptic drugs. In 2014, an update on the clinical guidelines for antenatal and postnatal management of women with mental health conditions was released.[120] This states several recommendations with regards to treatment with antiepileptic drugs:

- Sodium valproate and carbamazepine should not be offered to women planning pregnancy, pregnant or considering breastfeeding;
- In those already taking sodium valproate, the drug should be gradually stopped if planning pregnancy, or stopped if the woman is pregnant;
- In those already taking carbamazepine and who are either pregnant or planning to become pregnant, discontinuing treatment should be discussed;
- In women taking lamotrigine during pregnancy, lamotrigine levels should be checked frequently.[120]

In January 2015, the Medical Healthcare and Products Regulatory Agency in the UK strengthened warnings on the use of sodium valproate in women of child-bearing potential, advising against use if possible, publishing guides for both health care professionals and patients, accompanied by letters to health care professionals.[172] My study supports the recent advice on sodium valproate, reinforcing the need to discuss treatment decisions as soon as the woman reaches child bearing age, in anticipation of becoming pregnant in the future.

For all women, lifestyle and preferences change over time, so it would be sensible to review treatment regimens annually to revisit the woman's preferences for treatment should she fall pregnant, as well as to keep abreast of newer antiepileptic drugs which may provide more options.

8.5. Further research implications

There remain gaps in the research in the teratogenic effects of antiepileptic drugs in pregnancy which need to be addressed.

Clearly, efforts to study the teratogenicity of each of these antiepileptic drugs should continue in order to:

- Corroborate the current findings
- Obtain risk estimates with improved precision and accuracy
- Quantify the risk differences, if any, between lamotrigine, carbamazepine and sodium valproate monotherapy

This needs to be conducted on large samples with access to information on maternal health, antenatal events and perinatal outcomes. Particular attention needs to be paid to capturing information on disease severity and prenatal diagnoses in terminations.

Antiepileptic drug polytherapy regimens are still a poorly understood area in the study of teratogenicity. It has been difficult to examine due to the limited numbers who are prescribed such more than one antiepileptic drug in pregnancy – only about 20% of women treated with antiepileptic drugs for epilepsy are managed on a polytherapy regimen.[173] In addition to this, comparative estimates may be unattainable for polytherapy if there are no alternative medications for a particular types of condition or disease severity. Given these difficulties, it would be wise to firstly attain precise absolute risk estimates before considering the possibility of risk comparisons. The most important factor here is to ascertain large numbers of women with polytherapy regimens in pregnancy. Data from THIN could be used but would benefit from accumulating more pregnancies in order to increase the sample of women with polytherapy exposure. Population wide registers such as the Swedish Medical Birth Register may also be able to provide greater numbers since they cover the whole population.

Other than lamotrigine, newer antiepileptic drugs have not been researched to the same extent. Chapter 5 showed however, that newer antiepileptic drug use is on the rise and can rise significantly quickly (like lamotrigine) without a wide evidence base for their safety in pregnancy. Monitoring of the numbers of women

using newer antiepileptic drugs in pregnancy and planning stages of analysis dependent on numbers available would make the most of the available observational data as soon as it were possible to conduct formal pairwise comparisons.

At present, the utilisation of electronic health records in research is undergoing change in that such datasets are now being linked together to create richer data sources. One such example is the linkage of primary care data to secondary care data in the UK, in the form of Hospital Episode Statistics (HES). Since women give birth in secondary care, there may be a number of additional variables captured in secondary care data which primary care either lacks or poorly records. For example, demographic information such as ethnicity, delivery information such as method of delivery and information on the baby such as birthweight. However, preliminary explorations of such linked data found that, although there may be some increase in availability of variables, HES data has its shortcomings – particularly in the identification of a link between mothers and babies. Thus, further research needs to be completed on firstly how much richer studies in the effects of drugs in pregnancy be made if primary and secondary care data are linked, and furthermore do these gains in data outweigh the assumptions and difficulties associated with using HES data. A complement to the use of primary and secondary data would be the use of GP questionnaires to obtain information on disease severity. This is a service offered by some providers which helps to capture information not held in the medical records.

On a similar note, there would be gains in understanding more on non-live births, particularly terminations, and their prenatal scans and tests. My study was unable to ascertain such information, which, potentially, is key to identifying further cases of major congenital malformations that could have been caused by antiepileptic drugs. Secondary care data may hold some information, but there may be further data sources, particularly malformation registries such as the British Isles Network of Congenital Anomaly Registers (BINOCAR) which, if linked to primary care, could provide much greater insight in these teratogenic effects.

Women with bipolar disorder warrant further investigation. This PhD was only able to examine a small number of women with bipolar disorder who received

antiepileptic drug treatment. Generally, severe mental illnesses can be treated with other drugs – antipsychotics, antidepressants, lithium to name a few. Therefore the proportion on antiepileptic drugs is potentially always small. However, the study in Chapter 5 highlighted marked discontinuation of treatment in pregnancy – a larger study is needed to verify this finding, and to identify causes, subsequent treatment and consequences which would inform whether there is a need to change clinical practice.

8.6. Conclusion

Antiepileptic drugs are a necessity to some people who suffer from long term conditions including epilepsy and bipolar disorder which can be otherwise detrimental for one's health if it is not treated properly. Pregnant women and their health care professionals must seek up to date information on how best to manage drug therapy in pregnancy weighing up the teratogenic effects with the benefits of managing the underlying condition. Women should be counselled on this prior to becoming pregnant, and support should be provided throughout pregnancy to ensure women have access to advice should they become concerned about the effects of their treatment on the unborn child. The outstanding finding from my thesis is an excessive teratogenic risk which is associated with a sodium valproate polytherapy regimen in pregnancy. Whilst there is demand for additional research studies to be performed and corroborate these findings using larger and richer data sets, it is advisable that women and health care professionals consider alternatives to polytherapy to minimise the teratogenic harm to the foetus.

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Appendix 1

Search strategy for identifying literature in Chapter 1

Below is the strategy employed in the PubMed database. Each numbered section ran a different search and combinations of the sections were used to perform the overall search for each review.

1. pregnancy[MeSH Terms] OR children[MeSH Terms] OR foetus[MeSH Terms] OR in utero[MeSH Terms]
2. phenytoin[MeSH Terms] OR phenobarbital[MeSH Terms] OR sodium valproate[MeSH Terms] OR carbamazepine[MeSH Terms] OR lamotrigine[MeSH Terms] OR topiramate[MeSH Terms] OR levetiracetam[MeSH Terms] OR gabapentin[MeSH Terms] OR vigabatrin[MeSH Terms] OR zonisamide[MeSH Terms] OR tiagabine[MeSH Terms] OR oxcarbazepine[MeSH Terms] OR antiepileptic[MeSH Terms] OR lamotrigine[Title/Abstract] OR gabapentin[Title/Abstract] OR topiramate[Title/Abstract] OR levetiracetam[Title/Abstract] OR valproate[Title/Abstract] OR carbamazepine[Title/Abstract] OR phenytoin[Title/Abstract] OR phenobarbital[Title/Abstract] OR vigabatrin[Title/Abstract] OR zonisamide[Title/Abstract] OR tiagabine[Title/Abstract] OR oxcarbazepine[Title/Abstract]) OR antiepileptic[Title/Abstract]
3. abnormalities[MeSH Terms] OR teratogens[MeSH Terms] OR foetal diseases[MeSH Terms] OR infant newborn[MeSH Terms] OR teratogen[Title/Abstract] OR congenital defect[Title/Abstract] OR congenital malformation[Title/Abstract] OR congenital anomalies[Title/Abstract] OR birth defect[Title/Abstract]
4. Limits: Humans, English, Publication Date from 01/01/2007 to 01/10/2010

Appendix 2

Drug code list of ANTIEPILEPTIC DRUGS

Drug code	Generic name
52991979	Levetiracetam 250mg granules sachets sugar free
54822979	Phenytoin sodium 100mg capsules
54824979	Phenytoin sodium 50mg capsules
54828979	Phenytoin sodium 300mg capsules
54926979	PERAMPANEL 4mg tablets
54927979	Perampanel 4mg tablets
54928979	PERAMPANEL 2mg tablets
54929979	Perampanel 2mg tablets
55600979	Phenytoin sodium 100mg capsules
55601979	Phenytoin sodium 50mg capsules
55602979	Phenytoin sodium 25mg capsules
55603979	Phenytoin sodium 300mg capsules
57803979	Topiramate 25mg capsules
57805979	Topiramate 25mg tablets
58118979	PREGABALIN 20mg/1mL solution
58119979	Pregabalin 20mg/ml oral solution sugar free
58718979	RUFINAMIDE 40mg/mL oral susp
58783979	LACOSAMIDE 10mg/1mL s/f liquid
59577979	Clonazepam 500micrograms/5ml oral solution sugar free
59819979	Clonazepam 2mg/5ml oral solution sugar free
60175979	Levetiracetam 500mg tablets
61056979	Lacosamide 10mg/ml oral solution sugar free
63675979	Primidone 100mg/5ml oral suspension
64705979	Gabapentin 400mg/5ml oral solution
65303979	Topiramate 5mg/5ml oral solution
65489979	Sodium valproate 600mg/5ml oral solution
69586979	Clobazam 100mg/5ml oral suspension
79020979	Phenobarbital 50mg/5ml oral solution
80027979	Gabapentin 300mg/5ml oral solution
80572979	Clobazam 4mg/5ml oral suspension
80586979	Clobazam 20mg/5ml oral suspension
80590979	Clobazam 2.5mg/5ml oral suspension
80592979	Clobazam 2.5mg/5ml oral solution
80920979	LEVETIRACTAM 100mg/mL s/f soln
80964998	Levetiracetam 250mg tablets
81059998	Zonisamide 50mg/5ml oral suspension
81079998	Phenytoin 90mg/5ml oral suspension
81083998	Clonazepam 500micrograms/5ml oral solution
81126998	Clobazam 5mg/5ml oral solution
81127998	Clobazam 10mg/5ml oral solution
81134979	Acetazolamide 250mg/5ml oral solution
81142979	Acetazolamide 175mg/5ml oral suspension
81237998	Topiramate 50mg/5ml oral suspension
81396998	Retigabine 50mg tablets and Retigabine 100mg tablets
81399998	RETIGABINE 400mg tablets

81400998	RETIGABINE 300mg tablets
81401998	RETIGABINE 200mg tablets
81402998	RETIGABINE 100mg tablets
81403998	RETIGABINE 50mg tablets
81404998	Retigabine 400mg tablets
81405998	Retigabine 300mg tablets
81406998	Retigabine 200mg tablets
81407998	Retigabine 100mg tablets
81408998	Retigabine 50mg tablets
81479998	CARBAMAZEPINE 400mg m/r tabs
81480998	CARBAMAZEPINE 200mg m/r tabs
81677998	Lamotrigine 50mg Suppository
81770998	Topiramate 25mg/5ml oral suspension
81830998	PRIMIDONE 50mg tablets
81842998	Primidone 50mg tablets
81954998	Sodium valproate 750mg modified-release granules sachets sugar free
81955998	Sodium valproate 250mg modified-release granules sachets sugar free
81956998	Sodium valproate 100mg modified-release granules sachets sugar free
81957998	Sodium valproate 50mg modified-release granules sachets sugar free
81991998	Gabapentin 250mg/5ml oral suspension
82051998	Phenobarbital 75mg/5ml oral suspension
82052998	Phenobarbital 75mg/5ml oral solution
82574998	ESLICARBAZPN ACETAT 800mg tabs
82576998	Eslicarbazepine 800mg tablets
82713998	Clobazam 25mg/5ml oral solution
82714998	Clobazam 25mg/5ml oral suspension
82857998	Sodium valproate 1g modified-release granules sachets sugar free
83073998	Phenobarbital 20mg/5ml oral solution
83321998	Sodium valproate 200mg modified-release tablets
83479998	SOD. VALPROATE 500mg e/c tabs
83480998	SOD. VALPROATE 200mg e/c tabs
83507998	LACOSAMIDE 50mg tablets
83508998	Lacosamide 50mg tablets
83509998	LACOSAMIDE 200mg tablets
83510998	Lacosamide 200mg tablets
83511998	LACOSAMIDE 150mg tablets
83512998	Lacosamide 150mg tablets
83513998	LACOSAMIDE 100mg tablets
83514998	Lacosamide 100mg tablets
83515998	LACOSAMIDE 15mg/1mL s/f liq
83516998	Lacosamide 15mg/ml oral solution sugar free
83518998	Lacosamide 200mg/20ml solution for infusion vials
83704998	SOD VALPROATE 750mg m/r grans
83705998	Sodium valproate 500mg modified-release granules sachets sugar free
83706998	SOD VALPROATE 250mg m/r grans
83707998	SOD VALPROATE 100mg m/r grans
83708998	SOD VALPROATE 50mg m/r grans
83709998	Sodium valproate with valproic acid 50mg modified release granules
83766998	Sodium valproate oral solution
83790998	Sodium valproate with valproic acid 1000mg modified release granules
83791998	Sodium valproate with valproic acid 750mg modified release granules
83792998	Sodium valproate with valproic acid 500mg modified release granules

83793998	Sodium valproate with valproic acid 250mg modified release granules
83794998	Sodium valproate with valproic acid 100mg modified release granules
84001998	Mesuximide 300mg Capsule
84089998	Sodium valproate 1g/10ml solution for injection ampoules
84095998	Stiripentol 500mg oral powder sachets
84096998	Stiripentol 250mg oral powder sachets
84097998	Stiripentol 500mg capsules
84098998	Stiripentol 250mg capsules
84127998	Primidone 100mg/5ml oral solution
84233998	PREGABALIN 225mg capsules
84234998	Pregabalin 225mg capsules
84311998	Carbamazepine 500mg/5ml oral suspension
84415998	RUFINAMIDE 400mg tablets
84416998	RUFINAMIDE 200mg tablets
84418998	Rufinamide 400mg tablets
84419998	Rufinamide 200mg tablets
84420998	Rufinamide 100mg tablets
84664998	SOD VALPROTE 1g/sach m/r grans
84665998	SOD VALPROATE 500mg m/r grans
84666998	SODUM VALPROATE 300mg m/r caps
84667998	SODUM VALPROATE 150mg m/r caps
84668998	Sodium valproate 1g modified-release granules sachets sugar free
84669998	Sodium valproate 500mg modified-release granules sachets sugar free
84670998	Sodium valproate 300mg modified-release capsules
84671998	Sodium valproate 150mg modified-release capsules
84720998	Sodium valproate 300mg suppositories
85030998	Sodium valproate 300mg/3ml solution for injection ampoules
85180998	Primidone 50mg/5ml oral suspension
85423998	Clobazam 2.5mg capsules
85466998	Primidone 62.5mg/5ml oral suspension
85486998	Acetazolamide 250mg/5ml oral suspension
85559998	Clonazepam 250micrograms/5ml oral solution
85954998	ETHOSUXIMIDE 250mg/5mL syrup
85968998	LEVETIRACETAM 500mg/5mL inj
85969998	Levetiracetam 500mg/5ml solution for infusion vials
86019998	Lamotrigine 50mg dispersible tablets sugar free
86109998	ETHOSUXIMIDE 250mg capsules
86161998	Clobazam 5mg/5ml oral suspension
86349998	Primidone 25mg/5ml oral suspension
86362998	Gabapentin 400mg/5ml oral suspension
86429998	Acetazolamide 125mg/5ml oral suspension
86457998	Clobazam 10mg/5ml oral suspension
86485998	Gabapentin 250mg/5ml oral solution
86604998	Clonazepam 500micrograms/5ml solution sugar free
86669998	Sultiame 50mg tablets
86670998	Sultiame 200mg tablets
86671998	Sultiame 50mg tablets
86841998	ZONISAMIDE 100mg capsules
86842998	ZONISAMIDE 50mg capsules
86843998	ZONISAMIDE 25mg capsules
86844998	Zonisamide 100mg capsules
86845998	Zonisamide 50mg capsules

86846998	Zonisamide 25mg capsules
87030998	Phenobarbital 50mg/5ml oral suspension
87106998	PRIMIDONE 250mg tablets
87193998	LEVETIRACTAM 100mg/mL s/f soln
87194998	LEVETIRACETAM 750mg tablets
87195998	Levetiracetam 100mg/ml oral solution sugar free
87196998	Levetiracetam 750mg tablets
87395998	PREGABALIN 300mg capsules
87396998	PREGABALIN 200mg capsules
87397998	PREGABALIN 150mg capsules
87398998	PREGABALIN 100mg capsules
87399998	PREGABALIN 75mg capsules
87400998	PREGABALIN 50mg capsules
87401998	PREGABALIN 25mg capsules
87402998	Pregabalin 300mg capsules
87403998	Pregabalin 200mg capsules
87404998	Pregabalin 150mg capsules
87405998	Pregabalin 100mg capsules
87406998	Pregabalin 75mg capsules
87407998	Pregabalin 50mg capsules
87408998	Pregabalin 25mg capsules
88177998	SOD VALPROATE 300mg m/r tabs
88178998	SOD VALPROATE 500mg m/r tabs
88217997	CARBAMAZEPINE 400mg m/r tabs
88396998	Topiramate 50mg capsules
88422998	Clonazepam 2.5mg/ml drops sugar free
88423996	Clonazepam 2mg/5ml oral solution sugar free
88423997	Clonazepam 500micrograms/5ml oral suspension
88423998	Clonazepam 2.5mg/ml drops sugar free
88868996	TOPIRAMATE 50mg beads in caps
88868997	TOPIRAMATE 25mg beads in caps
88868998	TOPIRAMATE 15mg beads in caps
89008998	ACETAZOLAMIDE 250mg m/r caps
89087979	PREGABALIN 150mg capsules
89210996	Levetiracetam 1g tablets
89210997	Levetiracetam 500mg tablets
89210998	Levetiracetam 250mg tablets
89231998	OXCARBAZEPINE 600mg tablets
89384997	CARBAMAZEPINE 400mg m/r tabs
89384998	CARBAMAZEPINE 200mg m/r tabs
89408996	TIAGABINE 15mg tablets
89408997	TIAGABINE 10mg tablets
89408998	TIAGABINE 5mg tablets
89409996	Tiagabine 15mg tablets
89409997	Tiagabine 10mg tablets
89409998	Tiagabine 5mg tablets
89991998	Fosphenytoin 750mg/10ml solution for injection vials
90211979	Primidone 250mg/5ml oral suspension
90424998	GABAPENTIN 300mg cap/600mg tab
90425998	Gabapentin 600mg tablets and Gabapentin 300mg capsules
90426997	GABAPENTIN 800mg tablets
90426998	GABAPENTIN 600mg tablets

90505998	Sodium valproate 500mg modified-release tablets
90776998	Phenytoin sodium 300mg capsules
90780996	Phenytoin sodium 100mg capsules
90780997	Phenytoin sodium 50mg capsules
90780998	Phenytoin sodium 25mg capsules
90858998	TIAGABINE 15mg tablets
91044996	Topiramate 25mg capsules
91044997	Topiramate 15mg capsules
91044998	Topiramate 25mg tablets
91045998	TOPIRAMATE 25mg tablets
91050996	Topiramate 200mg tablets
91050997	Topiramate 100mg tablets
91050998	Topiramate 50mg tablets
91051996	TOPIRAMATE 200mg tablets
91051997	TOPIRAMATE 100mg tablets
91051998	TOPIRAMATE 50mg tablets
91218998	OXCARBAZEPINE 60mg/mL s/f susp
91465997	Lamotrigine 2mg dispersible tablets sugar free
91465998	Lamotrigine 200mg tablets
91596997	LAMOTRIGINE 2mg disp tablets
91596998	LAMOTRIGINE 200mg tablets
91625996	Oxcarbazepine 600mg tablets
91625997	Oxcarbazepine 300mg tablets
91625998	Oxcarbazepine 150mg tablets
91626998	OXCARBAZEPINE 300mg tablets
91643998	ACETAZOLAMIDE 500mg injection
91690990	Sodium valproate 200mg gastro-resistant tablets
91839998	Oxcarbazepine 60mg/ml oral suspension sugar free
91881990	Levetiracetam 100mg/ml oral solution sugar free
92064998	FOSPHENYTOIN NA 750mg/10mL inj
92131997	Carbamazepine 400mg modified-release tablets
92131998	CARBAMAZEPINE 200mg m/r tabs
92345998	Sodium valproate 300mg modified-release tablets
92375996	LEVETIRACETAM 1g tablets
92375997	LEVETIRACETAM 500mg tablets
92375998	LEVETIRACETAM 250mg tablets
92463990	Gabapentin 600mg tablets
92700996	Lamotrigine 100mg dispersible tablets sugar free
92700997	Lamotrigine 25mg dispersible tablets sugar free
92700998	Lamotrigine 5mg dispersible tablets sugar free
92709996	LAMOTRIGINE 100mg disp tablets
92709997	LAMOTRIGINE 25mg disp tablets
92709998	LAMOTRIGINE 5mg disp tablets
92734997	Carbamazepine 250mg suppositories
92734998	Carbamazepine 125mg suppositories
92735997	CARBAMAZEPINE 250mg supps
92735998	CARBAMAZEPINE 125mg supps
92796990	Clonazepam 500microgram tablets
92802996	SOD. VALPROATE 200mg/5mL sfliq
92802997	Sodium valproate 500mg gastro-resistant tablets
92802998	SOD. VALPROATE 200mg e/c tabs
92812998	Phenytoin 90mg/5ml oral solution sugar free

92837996	CARBAMAZEPINE 400mg tablets
92837997	CARBAMAZEPINE 200mg tablets
92837998	CARBAMAZEPINE 100mg tablets
92917996	Sodium valproate with valproic acid 500mg modified release tablets
92917997	Sodium valproate with valproic acid 300mg modified release tablets
92917998	Sodium valproate with valproic acid 200mg modified release tablets
92918996	SOD VALPROATE 500mg m/r tabs
92918997	SOD VALPROATE 300mg m/r tabs
92918998	SOD VALPROATE 200mg m/r tabs
93015996	Valproic acid 500mg gastro-resistant capsules
93015997	Valproic acid 300mg gastro-resistant capsules
93015998	Valproic acid 150mg gastro-resistant capsules
93016996	VALPROIC ACID 500mg e/c caps
93016997	VALPROIC ACID 300mg e/c caps
93016998	VALPROIC ACID 150mg e/c caps
93037992	PHENOBARBITONE SODIUM ALCOHOL FREE 50 MG/5ML MIX
93058996	Piracetam 333.3mg/ml oral solution sugar free
93058997	Piracetam 1.2g tablets
93058998	Piracetam 800mg tablets
93059996	PIRACETAM 333.3mg/mL solution
93059997	PIRACETAM 1.2g tablets
93059998	PIRACETAM 800mg tablets
93148998	Sodium valproate 400mg powder and solvent for solution for injection vials
93404992	PHENOBARBITONE 10 MG TAB
93443990	Sodium valproate 500mg gastro-resistant tablets
93444990	Sodium valproate 200mg gastro-resistant tablets
93454996	Phenobarbital 60mg/1ml solution for injection ampoules
93454997	Phenobarbital 30mg/1ml solution for injection ampoules
93454998	Phenobarbital 15mg/1ml solution for injection ampoules
93460992	LAMOTRIGINE 50mg tablets
93530997	Carbamazepine 200mg chewable tablets sugar free
93530998	Carbamazepine 100mg chewable tablets sugar free
93531997	CARBAMAZEPINE 200mg chew tabs
93531998	CARBAMAZEPINE 100mg chew tabs
93532997	CARBAMAZEPINE 400mg m/r tabs
93532998	CARBAMAZEPINE 200mg m/r tabs
93579997	Carbamazepine 400mg modified-release tablets
93579998	Carbamazepine 200mg modified-release tablets
93720992	PHENOBARBITONE SODIUM 100 MG TAB
93768992	PHENOBARBITONE 100 MG SPA
93769997	VIGABATRIN 500mg pdr sachets
93769998	VIGABATRIN 500mg tablets
93770996	Vigabatrin 125mg capsules
93770997	Vigabatrin 500mg oral powder sachets sugar free
93770998	Vigabatrin 500mg tablets
93913990	Clonazepam 500micrograms/5ml solution sugar free
94010990	Lamotrigine 200mg tablets
94011990	Lamotrigine 100mg tablets
94012990	Lamotrigine 50mg tablets
94013990	Lamotrigine 25mg tablets
94068997	VALPROIC ACID 500mg e/c tabs
94068998	VALPROIC ACID 250mg e/c tabs

94118990	Lamotrigine 100mg tablets
94120990	Lamotrigine 25mg tablets
94256992	OSPOLOT 200 MG TAB
94278992	PHENOBARBITONE S/R 100 MG CAP
94279992	PHENOBARBITONE 22.5 MG TAB
94281992	PHENOBARBITONE SODIUM 50 MG TAB
94282992	PHENOBARBITONE 15 MG CAP
94284992	PHENOBARBITONE 7.5 MG TAB
94285992	PHENOBARBITONE 50 MG CAP
94288992	PHENYTOIN 150 MG SUS
94408996	SODIUM VALPROATE 400mg/4mL inj
94408997	SOD. VALPROATE 200mg/5mL sfliq
94408998	SODIUM VALPROATE 200mg/5mL syr
94409996	SOD VALPROATE 100mg crush tabs
94409997	SOD. VALPROATE 500mg e/c tabs
94409998	SOD. VALPROATE 200mg e/c tabs
94455992	EPANUTIN + PHENOBARB CAP
94521992	PHENOBARBITONE 30 MG CAP
94525992	PHENYTOIN 25 MG SYR
94568996	Sodium valproate 200mg/5ml oral solution
94568997	Sodium valproate 200mg/5ml oral solution sugar free
94568998	Sodium valproate 100mg tablets
94606997	Sodium valproate 500mg gastro-resistant tablets
94606998	Sodium valproate 200mg gastro-resistant tablets
94834996	GABAPENTIN 400mg capsules
94834997	GABAPENTIN 300mg capsules
94834998	GABAPENTIN 100mg capsules
94835996	Gabapentin 400mg capsules
94835997	Gabapentin 300mg capsules
94835998	Gabapentin 100mg capsules
94848979	LEVETIRACETAM 250mg tablets
94854979	Levetiracetam 500mg tablets
94858979	LEVETIRACETAM 500mg tablets
94914979	TOPIRAMATE 25mg beads in caps
94921979	TOPIRAMATE 15mg beads in caps
95045979	Gabapentin 100mg capsules
95112979	LAMOTRIGINE 25mg tablets
95157990	Gabapentin 600mg tablets
95159990	Gabapentin 300mg capsules
95160979	SODIUM VALPROATE 200mg/5mL syr
95161990	Gabapentin 100mg capsules
95172979	SOD VALPROATE 500mg m/r tabs
95177979	SOD VALPROATE 300mg m/r tabs
95180979	Sodium valproate 300mg modified-release tablets
95184979	SOD VALPROATE 200mg m/r tabs
95186979	SOD VALPROATE 200mg m/r tabs
95187990	Gabapentin 600mg tablets
95189990	Gabapentin 300mg capsules
95190990	Gabapentin 100mg capsules
95216990	Sodium valproate with valproic acid 500mg modified release tablets
95217990	Sodium valproate with valproic acid 300mg modified release tablets
95266979	CARBAMAZEPINE 400mg m/r tabs

95361992	OSPOLOT 50 MG TAB
95403997	Primidone 250mg/5ml oral suspension
95403998	Primidone 250mg tablets
95404996	LAMOTRIGINE 25mg tablets
95404997	LAMOTRIGINE 100mg tablets
95404998	LAMOTRIGINE 50mg tablets
95409992	PHENOBARBITONE 10 MG PUL
95411992	PHENOBARBITONE 30 MG ELI
95415992	PHENOBARBITONE SODIUM 15 MG TAB
95417992	PHENOBARBITONE 5 MG ELI
95418992	PHENOBARBITONE 20 MG TAB
95419992	PHENOBARBITONE 60 MG SPA
95420992	PHENOBARBITONE 5 MG TAB
95421992	PHENOBARBITONE 50 MG TAB
95444996	Lamotrigine 25mg tablets
95444997	Lamotrigine 100mg tablets
95444998	Lamotrigine 50mg tablets
95531998	Phenytoin sodium 250mg/5ml solution for injection ampoules
95532996	Phenytoin 300mg capsule
95532997	Phenytoin 30mg/5ml oral suspension
95532998	Phenytoin 100mg capsule
95533996	Phenytoin 50mg capsule
95533997	Phenytoin 25mg capsule
95533998	Phenytoin 50mg chewable tablets
95553998	PHENOBARBITAL 200mg/1mL inj
95554998	Phenobarbital 200mg/1ml solution for injection ampoules
95750992	ZARONTIN 300 MG CAP
95810990	Sodium valproate 200mg/5ml oral solution
95838992	PHENYTOIN SODIUM/ PHENOBARBITONE SODIUM TAB
95852996	Methylphenobarbital 200mg Tablet
95852997	Methylphenobarbital 60mg Tablet
95852998	Methylphenobarbital 30mg Tablet
96096992	PIRACETAM 400 MG CAP
96127990	Carbamazepine 400mg modified-release tablets
96128990	Carbamazepine 200mg modified-release tablets
96159990	Sodium valproate 200mg/5ml oral solution sugar free
96160992	CLOBAZAM 5 MG TAB
96386992	PHENOBARBITONE 60MG & PHENYTOIN 100MG MG TAB
96446989	Carbamazepine 400mg modified-release tablets
96446990	Carbamazepine 200mg modified-release tablets
96463992	SOD VALPROATE C/R 200 MG TAB
96479992	CARBAMAZEPINE 100mg/5mL sf liq
96536989	Carbamazepine 400mg modified-release tablets
96536990	Carbamazepine 200mg modified-release tablets
96571990	Clonazepam 2mg/5ml oral solution sugar free
96634996	Clonazepam 1mg/1ml solution for injection ampoules and diluent
96634997	Clonazepam 2mg tablets
96634998	Clonazepam 500microgram tablets
96648997	Clobazam 10mg tablets
96648998	Clobazam 10mg capsules
96697988	Carbamazepine 200mg tablets
96697989	Carbamazepine 100mg tablets

96767997	Ethosuximide 250mg/5ml oral solution
96767998	Ethosuximide 250mg capsules
96817992	METHSUXIMIDE 300 MG CAP
96885998	Carbamazepine 100mg/5ml oral suspension sugar free
96914998	Beclamide 500mg tablets
96916988	Carbamazepine 400mg tablets
96916989	Carbamazepine 200mg tablets
96977989	Sodium valproate 200mg gastro-resistant tablets
96977990	Sodium valproate 500mg gastro-resistant tablets
96978990	Phenytoin sodium 100mg tablets
96986990	Sodium valproate 200mg gastro-resistant tablets
96986998	Acetazolamide 500mg powder for solution for injection vials
96987997	Acetazolamide 250mg modified-release capsules
96987998	Acetazolamide 500mg modified-release capsules
96988996	Acetazolamide 40mg/ml oral solution
96988997	Acetazolamide powder
96988998	Acetazolamide 250mg tablets
97033996	Carbamazepine 400mg tablets
97033997	Carbamazepine 200mg tablets
97033998	Carbamazepine 100mg tablets
97080997	Phenobarbital sodium 60mg tablet
97080998	Phenobarbital sodium 30mg tablet
97086998	CARBAMAZEPINE 200mg tablets
97128989	Carbamazepine 400mg modified-release tablets
97128990	Carbamazepine 200mg modified-release tablets
97140989	Phenytoin sodium 100mg tablets
97158992	CLOBAZAM 1 MG SUS
97159992	CLOBAZAM 2.5 MG CAP
97160992	CLOBAZAM 7.5 MG CAP
97161992	CLOBAZAM 5 MG CAP
97185990	Acetazolamide 40mg/ml oral solution
97202998	Phenobarbital 100mg tablet
97203996	Phenobarbital 60mg tablets
97203997	Phenobarbital 30mg tablets
97203998	Phenobarbital 15mg tablets
97402992	ETHOSUXIMIDE POW
97514997	PHENYTOIN 50mg chew tabs
97514998	PHENYTOIN SODIUM 300mg caps
97628997	Valproic acid 500mg gastro-resistant tablets
97628998	Valproic acid 250mg gastro-resistant tablets
97721990	Sodium valproate 200mg gastro-resistant tablets
97736992	METHSUXIMIDE 3000 MG CAP
97736997	PHENYTOIN 100mg tablets
97736998	PHENYTOIN 50mg tablets
97779988	Carbamazepine 400mg tablets
97779989	Carbamazepine 200mg tablets
97779990	Carbamazepine 100mg tablets
97782998	ACETAZOLAMIDE 250mg m/r caps
97884992	PHENOBARBITONE & PHENYTOIN 60 MG CAP
97896992	PHENYTOIN SODIUM/ PHENOBARBITONE CAP
97897992	PHENYTOIN 30 MG TAB
97910989	Sodium valproate 200mg gastro-resistant tablets

97910990	Sodium valproate 100mg tablets
97911989	Sodium valproate 200mg gastro-resistant tablets
97911990	Sodium valproate 200mg/5ml oral solution sugar free
97949992	PRIMIDONE 200 MG TAB
98049988	Phenobarbital 60mg tablets
98075990	Phenytoin 90mg/5ml oral solution sugar free
98084990	Sodium valproate 500mg gastro-resistant tablets
98087997	Phenobarbital 50mg/5ml oral solution
98087998	Phenobarbital 15mg/5ml elixir
98090997	Phenytoin sodium 100mg tablets
98090998	Phenytoin sodium 50mg tablets
98112988	Phenobarbital 15mg tablets
98112989	Phenobarbital 30mg tablets
98112990	Phenobarbital 60mg tablets
98147992	SULTHIAME 50 MG TAB
98152992	SULTHIAME 200 MG TAB
98200998	TIAGABINE 5mg tablets
98315996	PHENYTOIN SODIUM 100mg caps
98315997	PHENYTOIN SODIUM 50mg capsules
98315998	PHENYTOIN SODIUM 25mg caps
98328998	ACETAZOLAMIDE 250mg tabs
98338988	Carbamazepine 400mg tablets
98338989	Carbamazepine 200mg tablets
98338990	Carbamazepine 100mg tablets
98360998	CARBAMAZEPINE 100mg/5mL sf liq
98361996	CARBAMAZEPINE 400mg tablets
98361997	CARBAMAZEPINE 200mg tablets
98361998	CARBAMAZEPINE 100mg tablets
98385989	Sodium valproate 500mg gastro-resistant tablets
98385990	Sodium valproate 200mg gastro-resistant tablets
98430990	Phenytoin sodium 100mg tablets
98461996	METHYLPHENOBARB 200mg tabs
98461997	METHYLPHENOBARBITONE 60mg tab
98461998	METHYLPHENOBARBITONE 30mg tab
98476997	PHENOBARBITAL 60mg tablets
98476998	PHENOBARB SODIUM 30mg tablets
98517998	CLONAZEPAM 1mg/1mL injection
98658998	PHENYTOIN 30mg/5mL suspension
98730998	OXCARBAZEPINE 150mg tablets
98739990	Phenobarbital sodium powder
98764990	Phenobarbital sodium powder
98928998	ACETAZOLAMIDE 250mg tabs
98929988	Sodium valproate 200mg/5ml oral solution sugar free
98929989	Sodium valproate 500mg gastro-resistant tablets
98929990	Sodium valproate 200mg gastro-resistant tablets
98949997	ETHOSUXIMIDE 250mg/5mL syrup
98949998	ETHOSUXIMIDE 250mg capsules
98989997	Gabapentin 800mg tablets
98989998	Gabapentin 600mg tablets
99121989	Phenytoin sodium 100mg tablets
99122990	Phenytoin sodium 50mg tablets
99176997	CLONAZEPAM 2mg tablets

99176998	CLONAZEPAM 500mcg tablets
99383997	PRIMIDONE 250mg/5mL susp
99383998	PRIMIDONE 250mg tablets
99453990	Phenytoin sodium 100mg tablets
99454989	Phenytoin sodium 100mg capsules
99455989	Phenytoin sodium 100mg tablets
99457990	Phenobarbital 15mg/5ml elixir
99458989	Phenobarbital 30mg tablets
99458990	Phenobarbital 15mg tablets
99459989	Phenobarbital 30mg tablets
99459990	Phenobarbital 60mg tablets
99622997	CLOBAZAM 10mg tablets
99622998	CLOBAZAM 10mg capsules
99692998	PHENYTOIN 250mg/5mL injection
99697997	ETHOSUXIMIDE 250mg/5mL syrup
99697998	ETHOSUXIMIDE 250mg capsules
99751988	Carbamazepine 400mg tablets
99751989	Carbamazepine 200mg tablets
99751990	Carbamazepine 100mg tablets
99752989	Carbamazepine 200mg tablets
99752990	Carbamazepine 100mg tablets
99762998	Acetazolamide 500mg modified-release capsules
99880998	TIAGABINE 10mg tablets

Read code list for EPILEPSY

Read code	Description
1473.00	h/o: epilepsy
1B1W.00	transient epileptic amnesia
1O30.00	epilepsy confirmed
282..13	o/e - a seizure
2828.00	absence seizure
6110.00	contraceptive advice for patients with epilepsy
667..00	epilepsy monitoring
6671.00	initial epilepsy assessment
6672.00	follow-up epilepsy assessment
6674.00	epilepsy associated problems
6675.00	fit frequency
6676.00	last fit
6677.00	epilepsy drug side effects
6678.00	epilepsy treatment changed
6679.00	epilepsy treatment started
667A.00	epilepsy treatment stopped
667B.00	nocturnal epilepsy
667C.00	epilepsy control good
667D.00	epilepsy control poor
667E.00	epilepsy care arrangement
667F.00	seizure free >12 months
667G.00	epilepsy restricts employment
667H.00	epilepsy prevents employment
667J.00	epilepsy impairs education
667K.00	epilepsy limits activities
667L.00	epilepsy does not limit activities
667M.00	epilepsy management plan given
667N.00	epilepsy severity
667P.00	no seizures on treatment
667Q.00	1 to 12 seizures a year
667R.00	2 to 4 seizures a month
667S.00	1 to 7 seizures a week
667T.00	daily seizures
667V.00	many seizures a day
667W.00	emergency epilepsy treatment since last appointment
667X.00	no epilepsy drug side effects
667Z.00	epilepsy monitoring nos
67AF.00	pregnancy advice for patients with epilepsy
67IJ000	pre-conception advice for patients with epilepsy
8BIF.00	epilepsy medication review
8IAg.00	contraceptive advice for patients with epilepsy decli
8IAh.00	pre-conception advice for patients with epilepsy decl
8IAi.00	pregnancy advice for patients with epilepsy declined
8IB2.00	contraceptiv advice for patients with epilepsy not in
8IB3.00	pre-conception advic fr patients with epilepsy not in
8IB4.00	pregnancy advice for patients with epilepsy not indic
9h6..00	exception reporting: epilepsy quality indicators
9h61.00	excepted from epilepsy quality indicators: patient un
9h62.00	excepted from epilepsy quality indicators: informed d

9N0r.00	seen in epilepsy clinic
9Of..00	epilepsy screen administration
9Of0.00	epilepsy screen invite 1
9Of1.00	epilepsy screen invite 2
9Of2.00	epilepsy screen invite 3
9Of3.00	epilepsy monitoring verbal invite
9Of4.00	epilepsy monitoring telephone invite
9Of5.00	epilepsy monitoring call first letter
9Of6.00	epilepsy monitoring call second letter
9Of7.00	epilepsy monitoring call third letter
Eu05212	[x]schizophrenia-like psychosis in epilepsy
Eu05y11	[x]epileptic psychosis nos
Eu06013	[x]limbic epilepsy personality
Eu80300	[x]acquired aphasia with epilepsy [landau - kleffner]
F132100	progressive myoclonic epilepsy
F132z12	myoclonic seizure
F25..00	epilepsy
F250.00	generalised nonconvulsive epilepsy
F250000	petit mal (minor) epilepsy
F250011	epileptic absences
F250100	pykno-epilepsy
F250200	epileptic seizures - atonic
F250300	epileptic seizures - akinetic
F250400	juvenile absence epilepsy
F250500	lennox-gastaut syndrome
F250y00	other specified generalised nonconvulsive epilepsy
F250z00	generalised nonconvulsive epilepsy nos
F251.00	generalised convulsive epilepsy
F251000	grand mal (major) epilepsy
F251011	tonic-clonic epilepsy
F251100	neonatal myoclonic epilepsy
F251111	otohara syndrome
F251200	epileptic seizures - clonic
F251300	epileptic seizures - myoclonic
F251400	epileptic seizures - tonic
F251500	tonic-clonic epilepsy
F251600	grand mal seizure
F251y00	other specified generalised convulsive epilepsy
F251z00	generalised convulsive epilepsy nos
F252.00	petit mal status
F253.00	grand mal status
F253.11	status epilepticus
F254.00	partial epilepsy with impairment of consciousness
F254000	temporal lobe epilepsy
F254100	psychomotor epilepsy
F254200	psychosensory epilepsy
F254300	limbic system epilepsy
F254400	epileptic automatism
F254500	complex partial epileptic seizure
F254z00	partial epilepsy with impairment of consciousness nos
F255.00	partial epilepsy without impairment of consciousness
F255000	jacksonian, focal or motor epilepsy

F255011	focal epilepsy
F255012	motor epilepsy
F255100	sensory induced epilepsy
F255200	somatosensory epilepsy
F255300	visceral reflex epilepsy
F255311	partial epilepsy with autonomic symptoms
F255400	visual reflex epilepsy
F255500	unilateral epilepsy
F255600	simple partial epileptic seizure
F255y00	partial epilepsy without impairment of consciousness
F255z00	partial epilepsy without impairment of consciousness
F256.00	infantile spasms
F256.11	lightning spasms
F256.12	west syndrome
F256000	hypsarrhythmia
F256100	salaam attacks
F256z00	infantile spasms nos
F257.00	kojevnikov's epilepsy
F258.00	post-ictal state
F259.00	early infant epileptic encephalopathy wth suppression
F259.11	ohtahara syndrome
F25A.00	juvenile myoclonic epilepsy
F25B.00	alcohol-induced epilepsy
F25C.00	drug-induced epilepsy
F25D.00	menstrual epilepsy
F25E.00	stress-induced epilepsy
F25F.00	photosensitive epilepsy
F25G.00	severe myoclonic epilepsy in infancy
F25G.11	dravet syndrome
F25X.00	status epilepticus, unspecified
F25y.00	other forms of epilepsy
F25y000	cursive (running) epilepsy
F25y100	gelastic epilepsy
F25y200	locl-rlt(foc)(part)idiop epilep&epilptic syn seiz loc
F25y300	complex partial status epilepticus
F25y400	benign rolandic epilepsy
F25y500	panayiotopoulos syndrome
F25yz00	other forms of epilepsy nos
F25z.00	epilepsy nos
F25z.11	fit (in known epileptic) nos
Fyu5000	[x]other generalized epilepsy and epileptic syndromes
Fyu5100	[x]other epilepsy
Fyu5200	[x]other status epilepticus
Fyu5900	[x]status epilepticus, unspecified
R003400	[d]nocturnal seizure
R003z11	[d]seizure nos
SC20000	traumatic epilepsy
ZS82.00	acquired epileptic aphasia

Read code list for DEPRESSION

Read code	Description
1465.00	h/o: depression
1B17.00	depressed
1BT..00	depressed mood
2257.00	o/e - depressed
62T1.00	puerperal depression
8BK0.00	depression management programme
8CAa.00	patient given advice about management of depression
8HHq.00	referral for guided self-help for depression
9H90.00	depression annual review
9H91.00	depression medication review
9H92.00	depression interim review
9HA0.00	on depression register
9HA1.00	removed from depression register
9Ov..00	depression monitoring administration
9Ov0.00	depression monitoring first letter
9Ov1.00	depression monitoring second letter
9Ov2.00	depression monitoring third letter
9Ov3.00	depression monitoring verbal invite
9Ov4.00	depression monitoring telephone invite
9hC..00	exception reporting: depression quality indicators
9hC0.00	excepted from depression quality indicators: patient
9hC1.00	excepted from depression quality indicators: informed
9k4..00	depression - enhanced services administration
9k40.00	depression - enhanced service completed
9kQ..00	on full dose long term treatment depression - enh ser
9kQ..11	on full dose long term treatment for depression
E112.00	single major depressive episode
E112.11	agitated depression
E112.12	endogenous depression first episode
E112.13	endogenous depression first episode
E112.14	endogenous depression
E112000	single major depressive episode, unspecified
E112100	single major depressive episode, mild
E112200	single major depressive episode, moderate
E112300	single major depressive episode, severe, without psyc
E112500	single major depressive episode, partial or unspec re
E112600	single major depressive episode, in full remission
E112z00	single major depressive episode nos
E113.00	recurrent major depressive episode
E113.11	endogenous depression - recurrent
E113000	recurrent major depressive episodes, unspecified
E113100	recurrent major depressive episodes, mild
E113200	recurrent major depressive episodes, moderate
E113300	recurrent major depressive episodes, severe, no psych
E113500	recurrent major depressive episodes,partial/unspec re

E113600	recurrent major depressive episodes, in full remissio
E113700	recurrent depression
E113z00	recurrent major depressive episode nos
E11y200	atypical depressive disorder
E11z200	masked depression
E135.00	agitated depression
E200300	anxiety with depression
E204.00	neurotic depression reactive type
E204.11	postnatal depression
E2B..00	depressive disorder nec
E2B0.00	postviral depression
E2B1.00	chronic depression
Eu32.00	[x]depressive episode
Eu32.11	[x]single episode of depressive reaction
Eu32.12	[x]single episode of psychogenic depression
Eu32.13	[x]single episode of reactive depression
Eu32000	[x]mild depressive episode
Eu32100	[x]moderate depressive episode
Eu32200	[x]severe depressive episode without psychotic sympto
Eu32211	[x]single episode agitated depressn w'out psychotic s
Eu32212	[x]single episode major depression w'out psychotic sy
Eu32213	[x]single episode vital depression w'out psychotic sy
Eu32400	[x]mild depression
Eu32500	[x]major depression, mild
Eu32600	[x]major depression, moderately severe
Eu32700	[x]major depression, severe without psychotic symptom
Eu32800	[x]major depression, severe with psychotic symptoms
Eu32B00	[x]antenatal depression
Eu32y00	[x]other depressive episodes
Eu32y11	[x]atypical depression
Eu32y12	[x]single episode of masked depression nos
Eu32z00	[x]depressive episode, unspecified
Eu32z11	[x]depression nos
Eu32z12	[x]depressive disorder nos
Eu32z13	[x]prolonged single episode of reactive depression
Eu32z14	[x] reactive depression nos
Eu33.00	[x]recurrent depressive disorder
Eu33.11	[x]recurrent episodes of depressive reaction
Eu33.12	[x]recurrent episodes of psychogenic depression
Eu33.13	[x]recurrent episodes of reactive depression
Eu33.14	[x]seasonal depressive disorder
Eu33000	[x]recurrent depressive disorder, current episode mil
Eu33100	[x]recurrent depressive disorder, current episode mod
Eu33200	[x]recurr depress disorder cur epi severe without psy
Eu33211	[x]endogenous depression without psychotic symptoms
Eu33212	[x]major depression, recurrent without psychotic symp
Eu33214	[x]vital depression, recurrent without psychotic symp

Eu33y00	[x]other recurrent depressive disorders
Eu33z00	[x]recurrent depressive disorder, unspecified
Eu33z11	[x]monopolar depression nos
Eu34111	[x]depressive neurosis
Eu34113	[x]neurotic depression
Eu34114	[x]persistant anxiety depression
Eu3y111	[x]recurrent brief depressive episodes
Eu41200	[x]mixed anxiety and depressive disorder
Eu41211	[x]mild anxiety depression
Eu53011	[x]postnatal depression nos
Eu53012	[x]postpartum depression nos

Read code list for BIPOLAR DISORDER

Read code	Description
146D.00	h/o: manic depressive disorder
212T.00	psychosis, schizophrenia + bipolar affective disord r
212V.00	bipolar affective disorder resolved
E11..11	bipolar psychoses
E111.00	recurrent manic episodes
E111000	recurrent manic episodes, unspecified
E111100	recurrent manic episodes, mild
E111200	recurrent manic episodes, moderate
E111300	recurrent manic episodes, severe without mention psyc
E111400	recurrent manic episodes, severe, with psychosis
E111500	recurrent manic episodes, partial or unspecified remi
E111600	recurrent manic episodes, in full remission
E111z00	recurrent manic episode nos
E114.00	bipolar affective disorder, currently manic
E114.11	manic-depressive - now manic
E114000	bipolar affective disorder, currently manic, unspecif
E114100	bipolar affective disorder, currently manic, mild
E114200	bipolar affective disorder, currently manic, moderate
E114300	bipolar affect disord, currently manic, severe, no ps
E114400	bipolar affect disord, currently manic,severe with ps
E114500	bipolar affect disord,currently manic, part/unspec re
E114600	bipolar affective disorder, currently manic, full rem
E114z00	bipolar affective disorder, currently manic, nos
E115.00	bipolar affective disorder, currently depressed
E115.11	manic-depressive - now depressed
E115000	bipolar affective disorder, currently depressed, unsp
E115100	bipolar affective disorder, currently depressed, mild
E115200	bipolar affective disorder, currently depressed, mode
E115300	bipolar affect disord, now depressed, severe, no psyc
E115400	bipolar affect disord, now depressed, severe with psy
E115500	bipolar affect disord, now depressed, part/unspec rem
E115600	bipolar affective disorder, now depressed, in full re
E115z00	bipolar affective disorder, currently depressed, nos
E116.00	mixed bipolar affective disorder
E116000	mixed bipolar affective disorder, unspecified
E116100	mixed bipolar affective disorder, mild
E116200	mixed bipolar affective disorder, moderate
E116300	mixed bipolar affective disorder, severe, without psy
E116400	mixed bipolar affective disorder, severe, with psycho
E116500	mixed bipolar affective disorder, partial/unspec remi
E116600	mixed bipolar affective disorder, in full remission
E116z00	mixed bipolar affective disorder, nos
E117.00	unspecified bipolar affective disorder
E117000	unspecified bipolar affective disorder, unspecified

E117100	unspecified bipolar affective disorder, mild
E117200	unspecified bipolar affective disorder, moderate
E117300	unspecified bipolar affective disorder, severe, no ps
E117400	unspecified bipolar affective disorder,severe with ps
E117500	unspecified bipolar affect disord, partial/unspec rem
E117600	unspecified bipolar affective disorder, in full remis
E117z00	unspecified bipolar affective disorder, nos
E11y.00	other and unspecified manic-depressive psychoses
E11y000	unspecified manic-depressive psychoses
E11y100	atypical manic disorder
E11y300	other mixed manic-depressive psychoses
E11yz00	other and unspecified manic-depressive psychoses nos
Eu30.11	[x]bipolar disorder, single manic episode
Eu31.00	[x]bipolar affective disorder
Eu31.11	[x]manic-depressive illness
Eu31.12	[x]manic-depressive psychosis
Eu31.13	[x]manic-depressive reaction
Eu31000	[x]bipolar affective disorder, current episode hypoma
Eu31100	[x]bipolar affect disorder cur epi manic wout psychot
Eu31200	[x]bipolar affect disorder cur epi manic with psychot
Eu31300	[x]bipolar affect disorder cur epi mild or moderate d
Eu31400	[x]bipol aff disord, curr epis sev depress, no psycho
Eu31500	[x]bipolar affect dis cur epi severe depres with psyc
Eu31600	[x]bipolar affective disorder, current episode mixed
Eu31700	[x]bipolar affective disorder, currently in remission
Eu31800	[x]bipolar affective disorder type i
Eu31900	[x]bipolar affective disorder type ii
Eu31911	[x]bipolar ii disorder
Eu31y00	[x]other bipolar affective disorders
Eu31y11	[x]bipolar ii disorder
Eu31y12	[x]recurrent manic episodes
Eu31z00	[x]bipolar affective disorder, unspecified
Eu33213	[x]manic-depress psychosis,depressd,no psychotic symp
Eu33312	[x]manic-depress psychosis,depressed type+psychotic s
ZRby100	profile of mood states, bipolar
ZV11111	[v]personal history of manic-depressive psychosis
ZV11112	[v]personal history of manic-depressive psychosis

Appendix 3

Minor Anomalies for Exclusion (EUROCAT)

For EUROCAT for use from 2005

Reports of cases with the following anomalies are not to be transmitted to the EUROCAT Central Registry if the anomalies are isolated. It is, however, important to report all minor anomalies for cases with major malformations or syndromes.

“Minor” anomalies are excluded, when isolated, because they have lesser medical, functional or cosmetic consequences (although they may be indicators of other problems) and experience shows that their definition and diagnosis and reporting varies considerably. At the present time, it is not useful to collect data at a European level on these anomalies. We also exclude anomalies which are not always truly congenital in origin, sometimes associated with immaturity at birth. In addition, we exclude poorly specified conditions and recommend that for any such cases more specific information be sought from medical records.

Cases reported to EUROCAT should always be confirmed cases of congenital anomaly. Cases which had diagnosed ultrasound soft markers but who were found to be normal at birth or with unknown outcome should not be reported.

Note that exclusions should be made locally, where all information is available. Many minor anomalies do not have specific ICD10-BPA codes, but we give specific codes where they exist. For the codes given in the list, if any cases with only one or more of these codes has been inadvertently transmitted to Central Registry, they will be
subsequently excluded from the central files on the basis of the code only. For allocation of cases to EUROCAT subgroups (see Chapter 8), only major malformations will be considered (codes for minor anomalies will be excluded).

	Specified ICD10-BPA – if present
Head	
Aberrant scalp hair patterning	
Flat occiput	
Dolichocephaly	Q67.2
Plagiocephaly – head asymmetry	Q67.3
Bony occipital spur	
Third fontanel	
Macrocephalus	Q75.3
Facial asymmetry	Q67.0
Compression facies	Q67.1
Other cong deformities of skull, face and jaw	Q67.4
Eyes	
Epicanthic folds	
Epicanthus inversus	
Upward slanting palpebral fissures	
Downward slanting palpebral fissures	
Short palpebral fissures	
Congenital ectropion	Q10.1
Congenital entropion	Q10.2
Other congenital malformations of eyelid	Q10.3
Dystopia canthorum	
Hypertelorism	Q75.2
Hypotelorism	
Stenosis or stricture of lacrimal duct	Q10.5
Synophrys	Q18.80
Blue sclera	Q13.5
Crocodile tears	Q07.82
Ears	
Primitive shape	Q17.3
Lack of helical fold	Q17.3
Asymmetric size	Q17.3
Posterior angulation	Q17.3
Microtia	Q17.2
Macrotia	Q17.1
Protuberant ears	Q17.3
Absent tragus	
Double lobule	Q17.0
Accesorry auricle, preauricular appendage, tag or lobule	Q17.0
Auricular pit	
Preauricular sinus or cyst	Q18.1
Narrow external auditory meatus	
Low set ears	Q17.4
Bat ear, prominent ear	Q17.5
Unspecified and minor malformation of ear	Q17.9

Nose	
Small nares	
Notched alas	
Oral regions	
Borderline small mandible/ minor micrognathia	
Aberrant frenula	
Enamel hypoplasia	
Malformed teeth	
High arched palate	Q38.50
Tongue tie or cyst of tongue	Q38.1
Macroglossia	Q38.2
Macrostomia	Q18.4
Microstomia	Q18.5
Macrocheilia	Q18.6
Microcheilia	Q18.7
Ranula	
Neck	
Mild webbed neck	
Sinus, fistula or cyst of branchial cleft	Q18.0
Preauricular sinus or cyst	Q18.1
Other branchial cleft malformations	Q18.2
Congenital malformation of face and neck, unspecified	Q18.9
Torticollis	Q68.0
Hands	
Duplication of thumbnail	
Enlarged or hypertrophic nails	Q84.5
Single/abnormal palmar crease	Q82.80
Unusual dermatoglyphics	
Clinodactyly (5^{th} finger)	
Short fingers (4. 5. th finger)	
Accessorry carpal bones	Q74.00
Feet -Limb	
Syndactyly (2nd-3rd toes)	
Gap between toes (1st-2nd)	
Short great toe	
Recessed toes (4th, 5th)	
Enlarged or hypertrophic nails	Q84.5
Prominent calcaneus	
Clicking hip, subluxation or unstable hip	Q65.3-Q65.6
Metatarsus varus or metatarsus adductus	Q66.2
Hallux varus – other cong varus deformities of feet	Q66.3
Talipes or pes calcaneovalgus	Q66.4
Congenital pes planus	Q66.5
Metatarsus varus – other cong valgus deformities of feet	Q66.6
Pes cavus	Q66.7

Clubfoot of postural origin - other cong deformities of feet	Q66.8
Congenital deformity of feet, unspecified	Q66.9
Skin	
Hemangioma (other than face or neck)	
Pigmented naevus – cong non-neoplastic naevus	Q82.5
Neavus flammeus	Q82.50
Strawberry naevus	Q82.51
Lymphangioma	
Angioma	
Persistent lanugo	
Mongoloid spot (whites)	Q82.52
Depigmented spot	
Unusual placement of nipples	
Accessory nipples	Q83.3
Cafe-au-lait spot	
Skeletal	
Cubitus valgus	
Prominent sternum	Q67.7
Depressed sternum	Q67.6
Sternum bifidum	Q76.71
Shieldlike chest, other cong deformities of chest	Q67.8
Congenital deformity of spine	Q67.5
Genua valgum	
Genua varum	
Genu recurvatum	Q68.21
Congenital bowing of femur	Q68.3
Congenital bowing of fibula and tibia	Q68.4
Congenital bowing of long bones of leg, unspecified	Q68.5
Spina bifida occulta	Q76.0
Sacral dimple	
Cervical rib	Q76.5
Absence of rib	Q76.61
Accessory rib	Q76.62
Congenital lordosis, postural	Q76.43
Brain	
Arachnoid cyst	
Choroid plexus cyst	
Anomalies of septum pellucidum	
Cardiovascular	
Absence or hypoplasia of umbilical artery, single umbilical artery	Q27.0
Functional or unspecified cardiac murmur	
Patent ductus arteriosus if GA < 37 weeks	Q25.0 if gestational age <37 weeks
Peripheral pulmonary artery stenosis	

Patent or persistent foramen ovale	Q21.11
Pulmonary	
Accessory lobe of lung	Q33.1
Congenital laryngeal stridor	Q31.4
Laryngomalacia	Q31.4, Q31.5
Tracheomalacia	Q32.0
Azygos lobe of lung	Q33.10
Gastro-intestinal	
Hiatus hernia	Q40.1
Pyloric stenosis	Q40.0
Diastasis recti	
Umbilical hernia	
Inguinal hernia	
Meckel's diverticulum	Q43.0
Functional gastro-intestinal disorders	Q40.21, Q43.20, Q43.81, Q43.82
Transient choledochal cyst	
Anterior anus	
Renal	
Vesico-ureteral-renal reflux	Q62.7
Hydronephrosis with a pelvis dilatation less than 10 mm	
Hyperplastic and giant kidney	Q63.3
Single renal cyst	Q61.0
External genitals	
Deficient or hooded foreskin	
Undescended testicle	Q53
Unspecified ectopic testis	
Retractile testis	Q55.20
Hydrocele of testis	
Phymosis	
Bifid scrotum	Q55.21
Curvature of penis lateral	
Hypoplasia of penis	
Hymen imperforatum	Q52.3
Fusion of labia	Q52.5
Prominent labia minora	
Enlarged clitoris	
Vaginal skin tag	
Cysts of vulva	
Transient ovarian cyst	
Other	
Congenital malformation, unspecified	Q89.9
Chromosomal	

Balanced translocations or inversions in normal	Q95.0, Q95.1

“Non-congenital” anomalies

- Pyloric stenosis – there is controversy about the congenital nature of the majority of cases.
- Patent ductus arteriosus in babies <37 weeks.
- Hydrocephaly where a result of preterm birth rather than congenital: all cases among preterm births should be thoroughly checked before registration.

Poorly specified anomalies

- Functional or unspecified cardiac murmur. Laryngomalacia and tracheomalacia. Functional gastro-intestinal disorders.
- Undescended testicle. Registries may choose to record this locally if they can follow-up
- all babies to ascertain whether the testis descends normally. Unspecified ectopic testis.
- Vesico-ureteral reflux. Registries should record and transmit to EUROCAT the underlying anomaly, if present.
- Clicking hip.
- Clubfoot where there is no further specification of whether malformation or postural origin.

Read code list used to identify cases of perinatal death in Chapter 6

Read code	Description
633..12	stillbirth [prevention record]
6332.00	single stillbirth
6335.00	twins - both still born
6339.00	triplets - 3 still born
L264.00	intrauterine death
L264.11	fetal death in utero
L264000	intrauterine death unspecified
L264100	intrauterine death - delivered
L264200	intrauterine death with antenatal problem
L264z00	intrauterine death nos
Q48D.00	[x] stillbirth
Q48D000	[x]fresh stillbirth
Q48D100	[x]macerated stillbirth
Q48y600	early neonatal death
Q48y700	late neonatal death
Q4z..11	infant death
Q4z..12	neonatal death
Q4z..13	newborn death
Q4z..14	perinatal death
Q4z..15	stillbirth nec
ZV27.12	[v]stillbirth
ZV27100	[v]single stillbirth
ZV27400	[v]twins, both stillborn
ZV27700	[v]other multiple birth, all stillborn
ZVu2C00	[x]other multiple births, all stillborn
L39X.00	obstetric death of unspecified cause
Lyu7500	[x]obstetric death of unspecified cause
Q211.00	fetal death due to labour anoxia
Q210.00	fetal death due to prelabour anoxia