WP2 Framework for pharmacoepidemiological studies

WG1 Databases

Study Protocol

Use of antiepileptics and risk of suicidality. An exploratory study using the UK Clinical Practice Research Datalink(CPRD) and data from Danish registries with an evaluation of available data from further European data sources.

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WG1 Drug AE group

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Contents

1. Context of the studies

The studies described in this protocol are all performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Workpackage 2 and Workgroup 1. Primary aim of these studies is to develop, test and disseminate methodological standards for the design, conduct and analysis of Pharmacoepidemiological (PE) studies applicable to different safety issues and using different data sources. To achieve this, results from PE studies on 5 key adverse events (AEs) performed in different databases will be evaluated. Therefore, emphasis will be on the methodological aspects of the studies in this protocol and not on the clinical consequences of the association under investigation. The standards to develop will contribute to decrease the discrepancies in results from different studies in the future and increase the usefulness and reliability of these studies for benefit-risk assessment in the EU.

2. Background

The term 'suicidality' includes diverse aspects such as completed suicide, suicide attempt, self-injurious behavior and suicidal ideation which have obviously different consequences for the patients (Meyer et al, 2010). However, there is evidence that less serious aspects of suicidality, such as suicidal ideation and preparatory suicidal behavior are risk factors for completed suicide (Posner et al, 2007).

Suicide is a major public heath concern.The estimated global burden of suicide is a million deaths per year. Self-inflicted death accounts for 1.5% of all deaths and is the thenth leading cause of death worldwide (Hawton et al, 2009).

Compiling evidence on suicidality is fraught with problems. E.g. suicide deaths are generally perceived as underreported or prone to misclassification during cause-of-death ascertainment procedures. The suicide rates may be underestimated by 10% to 22% (Mula et al, 2010; Kapusta et al, 2011).

The reliability of suicidality recording in electronic databases has recently been studied. Arana et al (2010) investigated data from the United Kingdom database THIN and found that the codes and the algorithm used to identify suicidality had a very high predictive value (97%). The positive predictive values for completed suicide was lower (88%) and 14% of 'true', completed suicides were not identified as having died. Hall (2009) who did a validation study of death and suicide recording in the same databases identified seven cases of suicide out of 1394 'true deaths' (0.5%). One had a record of 'suicide' as a Read code, a second case was identified by 'hanging' in the comments section, a third probable suicide case by the Read term 'overdose of drug' plus an additional comment 'paracetamol/propaxyphene', and the four remaining cases were identified by external documents such as death certificates. Hall excluded patients with 'major emotional events' and a history of cancer. This may be one of the reasons why the percentage of suicide deaths was lower than expected (0.5% versus 1.5%) as mentioned above.

Antiepileptic medications are a heterogeneous pharmacologic class characterized by various chemical structures and postulated mechanisms of actions (Patorno et al, 2010). The main therapeutic applications of antiepileptics include epilepsy, bipolar disorder, depression, neuralgia,

and migraine (Ettinger et al, 2007). Antiepileptic drugs (AEDs) are among the most commonly prescribed centrally active agents. In a survey, carried out in a Danish County, 1.1% of the studied people received AEDs. The use of these drugs increased with increasing age (Rochat et al 2001).

Patients with the above mentioned indication such as epilepsy, major depression, and bipolar disorders have a higher risk for suicide compared with the general population.

A possible association between antiepileptic drugs and suicidality has been studied using different data sources such as the UK Clinical Practice Research Datalink (CPRD) (Andersohn et al, 2010), the UK THIN (Arana et al, 2010), the US HealthCore Integrated Research Database (HIRD) (Patorno et al, 2010), Danish patient registries (Christensen et al, 2007; Bjerring Olesen et al, 2010), Swedish patient registries (Nilsson et al, 2002), and data from clinical trials (Statistical review FDA, 2008). The investigators applied different study designs such as cohort, matched case-control, case-crossover studies as well as a meta-analysis.

The published effects of antiepileptic drugs on suicidality covered a range between OR 0.24 (95% CI: 0.03-2.17) for pregabalin (Arana et al, 2010) and OR 6.42 (95% CI: 1.24-33.36) for levitiracetam (Anderson et al, 2010). The effects of individual AEDs differed considerably within studies and between studies. The same holds for different indications. Arana et al (2010) found the lowest OR in patients with epilepsy only (OR 0.59; 95% CI: 0.35 – 0.98) and the highest OR in patients with depression only (OR 1.65; 95% CI: 1.24 – 2.19). The authors compared current use of AEDs with no use of AEDs in different indications.

Due to the complexity of the present issue, adequate adjustment for the numerous potential confounders such as socioeconomic aspects, various comorbidities, and concomitantly prescribed medication, is an analytic challenge. Further to this, the availability of a sufficiently large number of patients for investigation is another issue.

In the present project, we use C-CASA definitions as a basis to specify the operational definitions of the different aspects of suicidality (Posner et al, 2007). The focus of the main analyses is on attempted suicide including completed suicide. This is due to statistical power issues. However, we will apply two additional outcome definitions in sensitivity analyses: 1) completed suicide only and 2) completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events. We will not include terms which clearly indicate an accidental event, or self-injurious behavior without a suicidal intent. These definitions are listed in the statistical analysis plan together with lists of terms from the dictionaries used in the different databases.

3. Objectives

1) Compare the study results which based on two data sources (UK CPRD and Danish registries) and different designs and evaluate the impact of design and population differences on the outcome of the study results.The UK database 'The Health Improvement Network' (THIN) may be included in these analyses as well.

2) Evaluate the strengths and weaknesses of the two data sources to study a possible association of antiepileptic drug use and suicidality, in particular the specific outcomes of death from suicide, hospitalization due to suicide attempt, and reports of the aspects of suicidality by the patients.

3) Estimate risks of completed suicide, completed suicide and attempted suicide, and completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events overall for all AEDs and by individual AEDs prescribed in UK and Denmark.

4) Describe the patterns of AED prescribing in six European databases (CPRD and THIN, UK; Danish registries; Mondriaan, Netherlands; Bavaria, Germany; BIFAP, Spain).

4. Methods

4.1. Data Source

The proposed studies will be conducted using different data sources. These populations are represented by the following databases:

4.1.1. National Databases (Denmark)

The Danish registries include computerized medical records of all hospital contacts, somatic diseases as well as psychiatric disorders, medication dispensing on a pharmacy level, causes of death for the entire population (5.3 million inhabitants) and contact information of visits to General Practitioners as well as contacts to specialists in private practice. The National Bureau of Statistics keeps computerized records of income, degree of education and working status. -The National Board of E-health keeps records of all inhabitants and their migrations and date of birth and death. The information on outcomes will come from the National Hospital Discharge Register and the Psychiatric Central Research Register. The National Hospital Discharge Register was founded in 1977. It covers all somatic inpatient contacts from 1977 to 1994 and from 1995 also all outpatient visits to hospitals, outpatient clinics, and emergency rooms. All psychiatric inpatient contacts have been registered since 1969 and from 1995 also all outpatient contacts. The somatic and psychiatric registers are based on the same kind of information: the physician codes the reason for the contact using the ICD system. The code used is at the discretion of the individual physician. The registries have a nationwide coverage and an almost 100 % capture of contacts. In general, the validity of registrations is high. The National Health Service keeps a register of all contacts to general practitioners for reimbursement purposes. The register does not contain ICD codes or any other medical code system for contacts but only codes for the nature of the contact (i.e. regular check-up visit, routine vaccination in children).

The Danish Medicines Agency keeps a nationwide register of all drugs sold at pharmacies throughout the country from 1994 onward (National Pharmacological Database run by the Danish Medicines Agency). Any drug bought is registered with ATC code, dosage sold, and date of sale for the period January 1, 1996, to December 31, 2009. As all sales are registered to the individual who redeemed the prescription, the capture and validity are high.

All registers can be linked through the use of a person specific code (the civil person number) given to all inhabitants, and used for all of the registrations mentioned before.

4.1.2. Clinical Practice Research Datalink (UK)

The UK Clinical Practice Research Datalink (CPRD) is the largest ongoing health care database available in the UK since 1987. The database contains approximately 5 million active patient data and historical data from 13 million people with data provided by primary care centres (more than 600 practices) based throughout the United Kingdom. Data included in the CPRD are collected by the UK Medicines Control Agency directly from the computerised recordings of primary care. The validity of a wide range of drug exposure data is routinely tested. The data covers 8.1 % of the population. Among recent additions to the database include external record linkage to other National Health Services (NHS) datasets, and increased availability of free text information format via new automated system.

4.1.3. The Health Improvement Network (THIN)

The Health Improvement Network (THIN) is a collaboration between two companies; In Practice Systems Ltd. (INPS), developer of Vision software used by general practices in the UK, and EPIC, provider of access to data for use in medical research. THIN data are collected during routine medical practice and regularly delivered to a central database. THIN data collection started in 2003, and the database currently contains the electronic medical records of almost 8 million patients (more than 3 million active patients) collected from over 386 general practices in the UK. THIN database consequently covers more than 5.7% of the UK population.

Patient data are arranged in five standardised files per practice: patient, medical, therapy, additional health data and a file to enable data linkage containing postcodes. Additional data can be collected using the Additional Information Service which includes: questionnaires completed anonymously by the patient or general practitioner, copies of patient-related correspondence, a specified intervention (e.g. a laboratory test to confirm a diagnosis) and death certificates.

4.1.4. Mondriaan

The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP Institute Pharma. Under the umbrella of Mondriaan, the participating databases currently include: the Dutch General Practitioner (LINH) database, The Almere Health Care (ZGA) database, The General Practitioners of Utrecht (HNU) database and The Leidsche Rijn Julius Health Centre (LRJG) database. The cumulative number of persons having data in Mondriaan reached around 1.4 million comprising mainly of general practitioner (GP) data complemented by pharmacy dispensing data and linkages to survey data. The four databases within Mondriaan have different starting dates and scope of data. LINH is the Netherlands Information Network of General Practice and it holds a longitudinal data on morbidity, prescription, and referrals. The GPs record data on all patient contacts, including diagnoses, referrals and prescriptions. The ZGA is a GP and pharmacy database. The HNU is a GP database set up in 1995 and includes data dating till the end of 2005. The LRJG is a GP database with a linkage to additional survey records. Survey information is periodically up-dated through follow-up, including information on a wide range of health and lifestyle related variables.

4.1.5. BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiologica en Atencion Primaria), a computerised database of medical records of Primary Care) (14) is a non-profit research project operated by the Spanish Medicines Agency (AEMPS), a public agency belonging to the Spanish Department of Health, with the collaboration of the Spanish Centre for Pharmacoepidemiological Research (CEIFE). The project has started in 2001 having the goal to achieve a pool of collaborators in the range of 1000 general practitioners and paediatricians. Currently, 1190 physicians (995 GPs and 195 paediatricians) from 9 different autonomous communities in Spain collaborate with BIFAP and send their data to BIFAP every 6 months. BIFAP database includes clinical and prescription data from around 3.1 million patients covering around 6.8% of the Spanish population. The AEMPS has renewed its funding to BIFAP for project consolidation, for validation of information included in the databases, in addition to performing epidemiological studies.

4.1.6. Bavaria database

The Bavarian statutory health insurance physicians' association is based on accounting information of the Bavarian physicians. This German database includes a population-based data on diagnosis and medical services, covering 10.5 million people. It is a pharmacy (claims) database linked to outpatient treatment data through general practitioners and specialists. The database exists since 2001 and covers 84% of the Bavarian population excluding those with private insurance. A population-based study on asthma treatment resistance is done using this database (Brookhart et al, 2007).

4.2. Period of valid data collection

Each data source has a period of valid data collection, from the left censoring date, up to the right censoring date. This is defined as follows:

4.2.1. CPRD

The left censoring date is the latest of the following: the date that a practice became up to research standard, the date that a patient enrolled into a practice or the date that a practice was enrolled into the database, whichever came latest. The right censoring date is the earliest of the following: the date a patient died, the date a patient was transferred out of the practice, the end of the database's data collection, the date that the practice left the database, or the date the practice stops being up-to-standard.

4.2.2. Denmark

The left censoring date is the latest of the following: the date that a patient was born, 1 January 1995 (the date from which longitudinal dispensing data is available), or the date that a patient immigrated into the country. The right censoring date is the earliest of the following: the date on which a patient died, the date on which a patient emigrated out of Denmark, or the end of linked data collection.

5. Study Designs

5.0. Descriptive studies to compare the six European databases

Information for the use of antiepileptics will be obtained from individual databases comprising of records of GPs, national health system records and or claims data where prescription data are recorded.

5.0.1. Study populations, study period and description of drug prescriptions

The following assessments will be done for the study period between 1-Jan-2000 and 31-Dec-2009:

- Prevalence of AED use (overall and by the individual AEDs) stratified by age (using ten-year categories, i.e. 0-9, 10-19, … 80-89, 90+ years) and sex. This shall include a point prevalence (i.e. assessment on 01 Mar, 01 Jun, 01 Sep, 01 Dec 2000, …, 2009; to take seasonal variations into account) as well as a one year period prevalence (e.g. 01 Jan – 31 Dec 2000, …, 2009) assessment. The denominator should be the number of people that are present in the database on 01 Mar, 01 Jun, 01 Sep, or 01 Dec for the point prevalence and at mid-year for the one year period prevalence assessment.

- Point and one year period prevalence of AED use (overall and by the individual AEDs) stratified by indication, i.e. epilepsy, depression, bipolar disorder, neuralgia, migraine, and others. Indication will be assessed using the specific link between indication and prescriptions if these links exists in the respective database; if not, this will be assessed by searching for specific computer codes or free text within plus/minus two weeks of the first prescription in the year of interest (period prevalence).

- One year period prevalence of ever AED use (overall and by the individual AEDs) in the year of interest (e.g. 01 Jan – 31 Dec 2000, …, 01 Jan – 31 Dec 2009) stratified by number of prescriptions (0, 1, 2-4, 5-11, ≥ 12 Rx). The denominator should be the number of people that are present in the database at mid-year.

- 'Lifetime' prevalence of 1) completed suicide 2) suicide and suicide attempt 3) Completed and attempted suicide, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events in the first year (2000) stratified by age (in 10 year categories; see above) and sex. The 'lifetime prevalence' assessment is based on all available follow-back information for an individual in the database prior to 01 Jan 2000. The denominator should be the number of people that are present in the database at mid-year 2000.

- Cumulative yearly incidence of of 1) completed suicide 2) suicide and suicide attempt 3) Completed and attempted suicide, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events by age (in 10 year categories; see above) and sex per calendar year (2000, …, 2009). The follow-back period to determine whether the recorded episode is a 'first-time' event includes all available database information prior to 01 Jan of the year of interest. The denominator corresponds to the number of people that are present in the database at start of the calendar year of interest

(e.g. 01 Jan 2000) and who do not have a recorded history of suicide etc prior to Jan 1 of that year. If – for istance – a patient has a recorded attempted suicide in 2005 and another in 2008, these occurrences account only for the first-time incidence in 2005. In 2008 this person is excluded from the denominator as he is not "a person at risk" for getting his first event.

5.1. Cohort study

5.1.1. Study populations

We will use study cohorts consisting of patients who have received a first prescription to at least one AED at 1-Jul-1996 or later in the UK or Denmark. Further inclusion criteria are an age of 15 years and older at the index date, a registration history of at least 6 months prior to the index date (first date of AED prescription) and fulfilling research data criteria in C. Patients with records of coded suicidality (wide definition) in the six months prior to the index date will be excluded.

5.1.2. Additional descriptive analyses to compare the main study populations from the CPRD and Danish data sources

5.1.2.1. Study Population

In contrast to section 5.0., where we include data from all patients with at least one prescription to an AED between January 1, 2000 and December 31, 2009 and fulfilling quality criteria of the respective database, we will use here study cohorts consisting of patients who have received a first prescription to at least one AED at 1-Jul-1996 or later in the UK or Denmark. Further inclusion criteria are an age of 15 years and older at the index date, a registration history of at least 6 months prior to the index date (first date of AED prescription) and fulfilling research data criteria in CPRD. Patients with records of coded suicidality (wide definition, including suicidal ideation) in the six months prior to the index date will be excluded.

5.1.2.2. Definition of index date

The date of first prescription of an antiepileptic since 1 July 1996 and during the period of valid data collection, defines the start of follow-up (i.e. index date). Each patient is then followed until the date of an outcome, the date of death, the patient's transfer out of the database, the end of valid data collection of a practice, or the end of study (31 December 2009) whichever comes first.

5.1.2.3. Exposure definition

To get an overall risk estimate for the exposure to any AED, we will study all AEDs as one group. In the main study we will estimate possible effects by individual AEDs.

The follow up of the exposure to the individual antiepileptics will be divided into periods of current, recent past and distant past use, with patients moving between these periods according to their use. The expected duration of each prescription/dispensing will be estimated using the prescribed quantity and the prescribed daily dose (UK data). In case of missing data, on the estimated duration of use, the population-median duration of use of the database of interest will be used. In Denmark the duration of use of an individual prescription cannot be determined. The duration will be

estimated by assigning the population median duration of use (time between two prescriptions) between two antiepileptic dispensing. A new period of current use starts, when a new antiepileptic is prescribed. When a current use prescription is not renewed within the estimated exposure time period, a patient will become a recent past user for the next 90 days and afterwards a distant past user. The period of distant past use will be stratified into periods of 90 days, until he/she becomes a current user again or until the end of valid data collection.

5.1.2.4. Description of drug exposure and outcome

From each patient, a period of current use will be randomly selected. The following drug utilization characteristics will be determined on the start date, or within the three months before: number of previous antiepileptic Rx (0, 1, 2-4, 5-11, ≥ 12); the proportion of first time users, the proportion of patient with prior use of one or more other AEDs, the proportion of patients with a medication possession ratio <0.8 and 0.8+ in the 6 months before (defined as the proportion of the estimated duration of prescription coverage compared to the whole period of observation), and repeat antiepileptic Rx in the next 3 months.

Additionally, the following information will be provided:

Point prevalence of AED use (at 1-Jul-1999, 1-Jul-2004, and 1-Jul-2009) overall and by indication, gender, and age bands (15-19,20-29, 30-39, 40-49,etc.; 80+ years) and by number of prescriptions to any AEDs.

The proportion of patients with epilepsy/seizure, depression, bipolar disorder, neuralgic pain, migraine, and other medically relevant diseases, recorded in the 6 months prior to the index date.

Incidence of three different outcomes (1) completed suicide 2) suicide and suicide attempt 3) Completed and attempted suicide, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events) by gender and age groups overall and stratified by drug and kind of exposure (current use, recent past, and distant past use) for the period from 1-Jul-1996 to 31-Dec-2009.

For the present investigations, we will study AEDs prescribed in UK and Denmark.

5.1.2.5. Evaluation of a possible channeling effect

A frequency table of potential risk factors for suicidality recorded in the six months before the index date by the AEDs will be created. This should help to identify a possible channeling effect for the drugs studied as observed for antidepressive drugs (Rubino et al, 2007).

5.1.3. Start and end of follow-up

The date of first prescription of an antiepileptic of interest since 1 July 1996, and during the period of valid data collection, defines the start of follow-up (i.e. index date). Each patient is then followed until the occurrence of a suicide attempt or completed suicide, the end of data collection, date of

death, the patient's transfer out of the database, the end of valid data collection of a practice, or the study end (31 December 2009) whichever comes first.

5.1.4. Exposure definition

The follow up of the exposure to the individual antiepileptics studied will be divided into periods of current, recent past and distant past use, with patients moving between these periods according to their use. The expected duration of each prescription/dispensing will be estimated using the prescribed quantity and the prescribed daily dose (UK data). In case of missing data, on the estimated duration of use, the population-median duration of use of the database of interest will be used. In Denmark the duration of use of an individual prescription cannot be determined. The duration will be estimated by assigning the population median duration of use (time between two prescriptions) between two antiepileptic dispensing. A new period of current use starts, when a new antiepileptic is prescribed. When a current use prescription is not renewed within the estimated exposure time period, a patient will become a recent past user for the next 90 days and afterwards a distant past user. The period of distant past use will be stratified into periods of 90 days, until he becomes a current user again or until the end of valid data collection.

At each antiepileptic drug prescription, the exposure will be characterized by the prescribed daily dose of this specific AED, the number of previous prescriptions for this AED up to this date, and concomitant exposure to one or more of the other remaining AEDs up to this date (number of the remaining AEDs).

5.1.5. Outcome Definition

The outcome for the main analyses will be suicide attempt including completed suicide. For CPRD we will use electronically recorded medical terms, cause of death information available in full CPRD to identify patients with completed suicide. To define completed suicide, a term of suicide/suicide attempt plus information on death (+/- 4 weeks), or death as reason for registering out and a final date of any administrative activity in the database or disenrollment within 6 months after suicidality code is necessary. In a sensitivity analysis we plan to use cause of death information from national, centrally held UK death data. We will use this information for analysis and will ignore information recorded in CPRD sources in case of discrepancies.

For CPRD data, we will calculate sensitivity, specificity, positive and negative predictive values for the outcome using different combinations of additional information on suicidality (free text information, HES data and cause of death information from UK Office for National Statistics (ONS).

For the Danish data we are using cause of death information from the Danish Cause of Death Registry, and medical information from registry data based on information from hospitals and emergency wards (the National Hospital Discharge Register and the Psychiatric Central Research Register). Additionally, ICD codes listed in section 7.2.2 of the statistical analysis plan will be used to identify patients with suicide attempt. A medical code from section 7.2.2 of the statistical analysis plan as recorded on a death certificate defines suicide; if the code is recorded in the patient registry but at least 7 days before the date of death, it defines a suicide attempt. In Denmark, it is not needed

to include a time-window of 4 weeks between the date of death and the date of recording of the suicide code.

We will apply in sensitivity analyses the following additional outcome definitions:

- completed suicide only
- completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events (wide definition).

5.1.6. Analysis

Incidence rates will be calculated as the number of completed suicides and suicide attempts divided by person-time, overall and stratified by kind of exposure (current, recent past, distant past) to the AEDs and by indication to the AEDs. Crude incidence density ratios (IDRs) and 95% confidence intervals (95% CI) will be calculated by dividing the incidence rate in the current users by the incidence rate in the distant past users.

Time dependent Cox regression analyses will be used to estimate age, gender, and fully adjusted IDRs. Final regression models will be determined as follows (manual selection of potential confounders that change the age-gender HR at least 5%). Potential confounders evaluated in this study will be shown in the next paragraph. Concomitantly prescribed additional AEDs will be handled as time varying covariates. Statistical analyses will be conducted using SAS for data management and STATA for the statistical analyses. The proportional hazard (PH) assumption will be evaluated.

5.1.7. Potential confounders

We will consider the following potential confounders recorded in the six months prior to index date: gender, age, marital status, socio-economic status, employment status (for Danish data), BMI (BMI <20, 20-24.9; 25-29.9; etc), smoking status (no, ex, smoker), alcohol abuse (categorical: 0: no medical term records or missing; 1: terms recorded for alcohol abuse, alcohol addiction/dependence or prescription of alcohol dependence, drug and medication abuse (binary, as for alcohol), number of different drugs (any, except AEDs) prescribed in the six months prior to index date, and calendar period. We will further consider epilepsy/seizure, bipolar disorder, depression, anxiety disorders (including anxiety, phobia, adjustment disorders, obsessive-compulsive disorders, severe stress), neuralgic pain, migraine, anxiety, schizophrenia, and personality disorders as binary variables (medical terms recorded yes/no). In a sensitivity analysis we will handle these covariates additionally as categorical: 0: no/missing information; 1: at least one medical term; 2: medical term plus >1 prescription for the respective diseases of interest.

Various aspects of exposure to AEDs will be handled as time varying variables: At each antiepileptic drug prescription, the exposure will be characterized by the prescribed daily dose of this specific AED, the number of previous prescriptions for this AED up to this date, the number of previous prescriptions to other AEDs, and concomitant exposure to one or more of the other remaining AEDs..

Concomitant prescription to anti-depressive treatment during the study period will be handled as AEDs as time varying variable.

5.1.8. Sensitivity analyses for cohort study

We plan to perform the following sensitivity analyses:

1) Using completed suicide only as an outcome.

2) Using a population with a restricted age range from 18 to 60 years to reduce the potential of difficult to control confounding in elderly (e.g. not reported depressive mood, not recorded diseases such as not diagnosed cerebrovascular disorders or not diagnosed malignancies).

CPRD only:

3) Using wide definition of suicidality (completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation plus indeterminate or potentially suicidal events as outcome).

4) Use of patients only from practices linked to hospital episode statistics (HES) and national, centrally held death data to realize a more direct comparison to Danish data sources which contains data originating from hospitals and emergency wards only. The study period will be adjusted accordingly, because this information is available only since a few years.

5) Use of categorical instead of binary covariates (e.g. Comorbidities: 0 = no information; 1 = medical term only; 2 = medical term plus ≥1 prescription to the respective comorbidity).

6) Start of follow-up is first record of epilepsy/seizure. Study drug is the most frequently prescribed AED. Exposure classifications: no AED exposure, current exposure, recent past exposure, distant past exposure.

7) Use of dummy variables to account for missing values of the variables BMI, socio-economic status, marital status, and smoking status. Otherwise as main analysis.

5.2. Nested case-control study

The cohort consists of all patients with at least one AED prescription. Within this cohort, a nested-case control study will be conducted.

5.2.1. Definition of cases

Cases will be patients (men and women) aged 15 years and older at the time of their case-control-index date, with a record/diagnosis for a completed or an attempted suicide after start of follow-up. The date of the suicide/suicide attempt defines the case-control-index date. Patients are required to have a registration history of at least 6 months.

5.2.2. Selection of controls

To each case, up to six control patients will be matched using the incidence density sampling method, i.e. control patients were not allowed to have sustained a suicide attempt or completed

suicide at their index date. The case-control-index date for each control will be the same as the date of suicide for the matched case.

5.2.3. Exposure definition

The estimation of the exposure to AEDs (current use, recent past, and distant past use) before the index date will be determined using the prescription/refill information as for the cohort study. Patients with history of using more than one AED before the index date will be classified as appropriate. A patient may qualify to be classified as current user of more than one AED. The average daily dose will be calculated by dividing the cumulative exposure by the total treatment time.

5.2.4. Analysis

Conditional logistic regression analysis will be used to estimate the risk of suicidality with the use of AEDs. We will consider the same potential confounding variables as mentioned under the cohort study. The risks will be calculated in terms of odds ratios (OR) with corresponding 95% confidence interval (CI). Adjusted ORs for suicide attempt or completed suicide will be estimated by comparing current antiepileptic use with distant past use using conditional regression analysis. Final regression models will be determined by manual selection of potential confounders using a significance level of 0.05 similar as described for the Cox regression analysis. We will stratify the population by age and sex to assess the risk.

5.2.5. Potential confounders

We will consider the same potential confounders as in the cohort study. However, in the case-control study, potential confounders will be determined before the suicide attempt/completed suicide index date, and not before the start date of a current use period as in the cohort study.

5.2.6. Planned sensitivity analyses for nested case-control study

- We will use completed suicide only as outcome.

- We will apply a high dimensional propensity score matching.

- We will use a smaller cohort containing patients with at least one prescription to the most frequently prescribed AED.

5.3. Case-crossover analysis

Based on the results of the description studies it will be decided whether this design can be applied.

5.3.1. Study population

The study population comprises patients with at least one prescription to an AED as for the other study types, who had a completed or an attempted suicide during follow-up.

5.3.2. Analysis

The analysis uses a case-crossover design. For each case (patients with completed suicide or suicide attempt), the drug exposure during the case period, defined as the three months before a case event (suicide attempts or completed suicide) will be compared to the drug exposure in the control period, defined as the period three to six months before a case event. Drug exposure will be defined as at least one prescription to an AED. The same potential confounders will be considered as for the two other study designs. Only information from patients with discordant exposures (exposed in case period and not exposed in control period or not exposed in case period and exposed in control period) will be used for the analysis.

5.3.3. Sensitivity analyses for case-crossover study

1) We will use completed suicide only as outcome.

2) Instead of using 3 months exposure periods, we will use six months (case period: six months before the case event; control period: 12 to six months before the case event).

6. Instrumental variable analysis

A method that potentially controls for both observed and unobserved confounding is instrumental variable (IV) analysis [Martens 2006, Hernan 2006]. An IV is a variable that is strongly related to exposure, and only related to the outcome through exposure. Hence, an IV should neither directly nor indirectly through (unobserved) confounders be associated with the outcome. Importantly, if the IV is independent of observed confounders, it is assumed to be independent of unobserved confounders. This is in analogy with the comparability of observed and unobserved prognostic variables between the intervention and control group achieved by randomization in a trial.

A key example of instrumental variable approach in pharmacoepidemiology for the assessment of gastrointestinal complications in relation to COX-2 inhibitors compared to non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has illustrated this approach [Brookhart 2006]. It may however not be possible to identify valid IVs for every pharmacoepidemiologic research question [Groenwold 2010].

We aim to apply IV analysis to assess the unconfounded association between prescriptions for antiepileptics and suicidality. Several potential IVs will be evaluated, including physician preference (e.g. as indicated by the prescription to the previous patient with a prescription for the same indication), regional variation (e.g. different regions or countries, possibly with different prescribing guidelines), and calendar time (e.g., periods prior to and after establishment of new guidelines) [Brookhart 2007, Chen 2010]. These variables may be related to prescriptions for antiepileptics, yet are unlikely to be directly related to suicidality, nor indirectly through the potential confounder(s) listed in the paragraph “potential confounders”. Estimation will be conducted via a two-stage instrumental variable model [Rassen 2009]. This analysis will be a separate from the main analyses described in this proposal and focuses on the (methodological) application of IV analysis in pharmacoepidemiology.

7. Change log

22-Feb-2011: Study start date changed to 1-Jul-1996 (Section 4.1.4.). Reason for this is concern about reliability of data recording for Danish data (Frank deVries, personal communication).

24-Mar-2011: Change of abuse/addition/dependence. Now use of two categorical variables: 1) alcohol abuse/addiction/dependence and 2) drug plus medication abuse/addiction/dependence. Values for both variables: 0 = no; 1 = abuse; 2 = addiction/dependence (cf. Appendices 7.5.6 and 7.5.7).

31-Mar-2011: Small changes to make it more consistent.

29/30-Apr-2011: Added objective 3, to clarify study intention. Age range changed from ≥18 to ≥15 years. Various minor changes to take into account comments from coleads.

14-Jun-2011: Section added in introduction on underreporting of suicidality. Objective 3: added: overall analysis considering all AEDs as one group.Section on THIN deleted. Section 'potential confounding factors' Covariate 'alcohol abuse' changed from categorical to binary. Same for drug and medication abuse.

28-Aug-2011: Modification of the introduction, adding information on the reliability of the recording suicidality in electronic databases. Specification of the outcome definitions used in the main and the sensitivity analyses. Objective 4 added: Descriptive studies on AED prescriptions in the six European databases CPRD, Danish registries, THIN, Mondriaan, Bavaria and BIFAP plus short guidelines for descriptive studies to compare the six European databases.

16-Sep-2011: As requested by WP2/WG1 coleads, the outcome definition for the main analyses was changed to completed suicide. Completed suicide plus suicide attempt will be considered in sensitivity analyses.

14-Dec-2011: Due to results from a feasibility study using CPRD data, the main outcome was changed back to suicide attempt plus suicide completed due to statistical power issues.

13-Dec-2012: Additional specifications on Danish data sources in sections 4.1.1. and 5.1.5.

5/11-Feb-2012: Concomitant anti-depressive treatment will be handled as time varying variable. Text search for suicidality in CPRD was only possible for a 1% random sample of the patients. Therefore, this information cannot be used to determine outcome events in the main study. To assess the reliability of the outcome we will calculate sensitivity, specificity, positive and negative predictive values using additional suicidality information (free text, HES data, ONS cause of death information).

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10. Appendices

10.1. C.f. Statistical analysis plan / data specifications

10.2. Amendment 1

Protocol: PROTECT_Final protocol_Suicide_Anticonvulsants_Dec 16 2011
Amendment number: *Nº 1*
Amendment date: *June 2012*
Protocol Owners and reviewers:

Name	Role
Markus Schuerch [1] and Frank de Vries [2]	Protocol lead
Yolanda Alvarez [3]	Protocol backup
Lamiae Grimaldi [4]	Protocol reviewer
Mark de Groot[2] and Raymond Schlienger[11]	WG1 colead
Olaf Klungel[2] and Robert Reynolds[12]	WP2 coleads

1. Reason(s) for Amendment:

The order of some sections of the protocol is rearranged for clarity (see details below). The content of the sections remains unchanged.

2. Protocol Section(s) Amended

Section entitled “Additional descriptive analyses to compare the main study populations from the CPRD and Danish data sources” originally under section “Descriptive studies to compare the six European databases” is moved to section “Cohort study”. The numbering of subsequent sections is modified accordingly.

10.3. Amendment 2

Protocol: PROTECT_Final protocol_Suicide_Anticonvulsants_Dec 16 2011
Amendment number: *Nº 2*
Amendment date: *December 2012*
Protocol Owners and reviewers:

Name	Role
Markus Schuerch [1] and Frank de Vries [2]	Protocol lead
Yolanda Alvarez [3]	Protocol backup
Lamiae Grimaldi [4]	Protocol reviewer
Mark de Groot[2] and Raymond Schlienger[11]	WG1 colead

Olaf Klungel[2] and Robert Reynolds[12]	WP2 coleads

1. Reason(s) for Amendment:

Clarification and specification of the Danish data sources used

2. Protocol Section(s) Amended

4.1.1. and 5.1.5.

10.4. Amendment 3

Protocol: PROTECT_Final protocol_Suicide_Anticonvulsants_Dec 16 2011
Amendment number: *Nº 3*
Amendment date: *February 2013*
Protocol Owners and reviewers:

Name	**Role**
Markus Schuerch [1] and Frank de Vries [2]	Protocol lead
Yolanda Alvarez [3]	Protocol backup
Lamiae Grimaldi [4]	Protocol reviewer
Mark de Groot[2] and Raymond Schlienger[11]	WG1 colead
Olaf Klungel[2] and Robert Reynolds[12]	WP2 coleads

1. Reason(s) for Amendment:

Due to unknown reasons, the concomitant exposure to anti-depressives as time varying variable is not in the present version. This was a request of ISAC. It has been added in the Amendment 3. Concomitant anti-depressive treatment will be handled as time varying variable.

Because it was not possible for CPRD to perform a text search on suicidality terms for all patients we have to change the wording in the outcome section. It has been changed in the Amendment 3. Text search for suicidality in CPRD was only possible for a 1% random sample of the patients. Therefore, this information cannot be used to determine outcome events in the main study.To assess the reliability of the outcome we will calculate sensitivity, specificity, positive and negative predictive values using additional suicidality information (free text, HES data, ONS cause of death information.

2. Protocol Section(s) Amended

5.1.5 Outcome definition
5.1.7 Potential confounders
5.1.8 Sensitivity analisys for cohort study