Appendix 24

Paroxetine, SSRI Use and the Risk of Suicidal Behaviour

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Cover Sheet

Title:

Paroxetine, SSRI Use and the Risk of Suicidal Behaviour

Abstract: (For Internal Use Only – limit to 20 lines max):

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Revision Chronology:

Compound Numbers/Keywords (if applicable): **Paroxetine**

Electronic File name and location:

GlaxoSmithKline Research and Development – Worldwide Epidemiology

Title Page

Title:

Paroxetine, SSRI Use and the Risk of Suicidal Behaviour

Date of Protocol (dd/month/yyyy): **27th January, 2003**

Epidemiology Project/Protocol Number: **WE406**

Principal investigator(s) and center(s) involved in the study (as appropriate):

Dates of observation: **January, 1996-December, 2002**

Database source (if appropriate): **UK General Practice Research Database**

CONFIDENTIAL AA1997/NNNNN/nn

GlaxoSmithKline Research and Development – Worldwide Epidemiology

Approval Form

Product/Research Compound Name/TMT:

Epidemiology Study/Project #: _____

Study Title:

_____

Project Officer Name (Primary): **Project Officer Name (Secondary):**

_____ _____

_____

Name(s) of Principal Investigator(s) or Data Source(s):

_____

APPROVAL

Signatures	**Date**
Author (Project Officer)	
Line/Matrix Manager	
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1. INTRODUCTION

When evaluating a potential adverse effect of a medication, it is essential to disentangle the risks associated with the drug and the risks related to the disease for which the drug was given.[1] Selective pharmacotherapy has a clinical rationale, but it may also create a bias that needs to be taken into account. Confounding by indication is a bias that can be introduced by the selective prescribing of a drug to patients with an increased risk for the adverse health events of interest. It can result in the observation that users of a certain drug are experiencing these events at a high frequency, and this may be attributed to the drug, when in fact the patients were at an increased risk prior to starting medication. An illustration of this effect is provided by Miettinen concerning warfarin and an observed risk of thrombotic events. This counterintuitive result was partly the result of the selective prescribing of the anticoagulant warfarin to those already presenting signs of thrombosis.[2]

Paroxetine is an antidepressant that belongs to the class of selective serotonin reuptake inhibitors (SSRIs). It was launched in the United States in 1991 under the tradename Paxil, and in Europe in 1991 as Seroxat/Deroxat[3]. In addition to its original indication as treatment for major depression, the drug has gained FDA and worldwide approval for indications in generalized anxiety disorder (GAD), social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) , and panic disorder[3]. Paroxetine has proven to be an effective treatment for mood and anxiety disorders in over 6,700 studied patients worldwide[4]. Clinical trials of paroxetine have shown that the drug is well tolerated and has a favourable benefit-risk profile[5].

Clinical depression is major public health problem that can lead someone to suicidal behaviour (i.e. ideation, attempts, and completed suicide). There is a considerable body of population research that has shown major depression increases the risk of suicidal behaviour compared to people without depression[6-9]. Depressed patients have been found to have a 25-fold greater risk of suicide than those not depressed[10]. Research has shown that more than 90 percent of people who kill themselves have depression or another diagnosable mental or substance abuse disorder, often in combination with other disorders.[11] Additionally, the risk of death by suicide is believed to be related to the *severity* of depression. Those treated for depression as inpatients following suicidal ideation or suicide attempts have been found to be three times as likely to die by suicide as those who were only treated as outpatients[12].

Much less is known about the risk of suicide among those suffering with anxiety disorders, and most research has been conducted in those aged 18 and under. An investigation of 348 adolescent psychiatric inpatients found that the rate of attempted suicide was much lower in OCD patients, as compared to other mental disorders, and that there was an inverse relationship between depression and suicidality in these patients[29]. OCD and SAD were not found to be associated with suicidality in a sample of 1,979 adolescents referred to a general clinic[30]. Therefore, the relationship between anxiety disorder such as OCD or SAD and suicidality is largely unknown at this time.

The overall rate of completed suicide in the United States was 10.7/100,000 persons. In European nations, the rates of completed suicide in 1999 ranged from 7.5/100,000 persons in the U.K., 9.6/100,000 in the Netherlands, to 17.5/100,000 in France.

Suicidal behaviour is very complex with several factors working simultaneously. These risk factors vary with age, gender and ethnicity, and may even change over time. U.S. males are 4 times more likely to complete suicide, while females report attempting suicide 2 to 3 times more often than males[13]. Among age groups in the United States, the elderly and young adults have the highest rates of completed suicide[12].

Several types of major life events (bereavement, unemployment, divorce) in combination with other risk factors such as depression can lead to suicide[13]. Other known risk factors for suicidal behaviour are : prior suicidal acts; family history of mental disorder or substance abuse; family history of suicide; family violence, including physical or sexual abuse; firearms in the home; incarceration; and exposure to the suicidal behaviour of others, including family members, peers, or even in the media.[13] Also, there is evidence that alterations in neurotransmitters such as serotonin are associated with the risk for suicide.[14] Diminished levels of this brain chemical have been found in patients with depression, impulsive disorders, a history of violent suicide attempts, and also in post-mortem brains of suicide victims.

After the elderly, adolescents and young adults have the highest rates of completed suicide. According to the U.S. Surgeon General, for young people 15-24 years old, suicide is the third leading cause of death, behind unintentional injury and homicide[15]. In 1996, more teenagers and young adults died of suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia, influenza, and chronic lung disease combined. The rate of completed suicide appears to increase throughout adolescence and young adulthood. For children aged 10-14, the rate was 1.6/100,000 persons, the rate for children aged 15-19 was 9.7 per 100,000, and the rate for young people aged 20-24 was 14.5/100,000[15].

The suicide rate in the young has also increased over time. In England and Wales, the suicide rate among males aged 15-19 has increased by 72% between 1970 and 1990, and has remained high throughout the 1990s.28 From 1952-1996, the U.S. incidence of suicide among adolescents and young adults nearly tripled, although there has been a general decline in youth suicides since 1994. From 1980-1996, the rate of suicide among persons aged 15-19 years increased by 14% and among persons aged 10-14 years by 100%.

Non-fatal suicidal behaviour differs by gender and ethnicity among young adults. The 1997 Youth Risk Behaviour Surveillance System found that hispanics (10.7%) were significantly more likely than white students (6.3%) to have reported a suicide attempt. Among hispanic students, females (14.9%) were more than twice as likely as males (7.2%) to have reported a suicide attempt, while hispanic male students (7.2%) were significantly more likely than white male students (3.2%) to report this behavior15.

There has been a long debate concerning treatment with SSRIs, such as paroxetine, and their possible link to suicidality16. The issue started with case reports, then media coverage, followed by more case reports, which may have created a publicity bias. This issue has been investigated in both fluoxetine (Prozac) and paroxetine. Meta-analysis of controlled clinical data have not shown any evidence of an association between treatment-emergent suicidal ideation and these SSRIs17-18

Most recently, the FDA compared the rates of completed suicide for 48,277 adults depressed patients under treatment. Their conclusions were that there was "no difference in suicide risk between those receiving antidepressant and placebo, nor was there any difference between SSRIs and other antidepressants"19. However, this analysis was of spontaneous reporting data that has some inherent biases.

Recent experimental data, internal to GSK, of 1,000 children suggested that those receiving paroxetine were more likely to have suicidal thoughts, as compared to similarly depressed children on placebo. However, this data does not represent real-world utilization or outcomes of those receiving paroxetine. By design, trial participants are a select group and not representative of all patients. Clinical trials are not designed or powered to detect rare adverse events, such as suicidality. Therefore, the possible relationship seen in this data does not necessarily hold for the actual use population for paroxetine.

Several biological models have been proposed to explain a possible link between SSRIs and suicidal behavior. One hypothesis is that the acute effects of SSRI treatment include a compensatory decrease in 5-HT neuronal firing, which can lead to suicidality in certain vulnerable individuals20. Another theory is that after depressed patients begin therapy, they recover their initiative and energy before their mood improves21. This results in some acting upon or thinking about suicide during this period.

From these questions there emerges two distinct areas of inquiry that we will investigate.

- The prescribing patterns of SSRIs and paroxetine as they relate to baseline risks for suicidal behavior.
- The possible association between antidepressant use and suicide related events after initiation of therapy

We have designed an observational study, using the General Practice Research Database, that will investigate these two broad issues. This is the best approach to determine if these possible relationships exist in the actual treated population.

In the first phase of this research, we will be comparing new users of an SSRI to those started on a non-SSRI antidepressant. New paroxetine users will then be compared to users of other SSRIs (in aggregate and broken out individually). New, or incident users will be defined as those with no previous record of a prescribed antidepressant, and at least 18 months of "up to standard" registration prior to the new prescription. This phase will compare the baseline risks for suicidal behaviour across these groups by examining their medical history for risk factors present prior to their antidepressant prescription. We will then fully describe the patterns of patient characteristics between these groups. Information on any differential baseline risk for suicidal behaviour among users will help to inform the second phase of this study.

Our second phase will follow these defined cohorts forward in time and will determine the incidence of suicidal behaviour in each group. We will compare incidence and determine if there is an association between use of paroxetine, or any SSRI, and suicidal behaviour. As in the first phase, SSRIs will be compared to non-SSRIs, and paroxetine will be compared to other SSRIs both in the aggregate and against each SSRI

individually. Additionally, a nested case-control component will allow us to adjust for potential confounders and to obtain a second estimate of risk (first will be from the cohort comparison). In addition to matching cases and controls by practice and length of medical history, we will adjust for all potential confounding factors, that are contained in the GPRD data, occurring before or after initiation of therapy (i.e. indication, therapy duration, concomitant medications).

The primary goal of this study is to investigate an association between specific antidepressant use and suicidal behaviour and test whether such association can be explained by differences in baseline risk factors for suicidal behaviour across the cohorts.

2. OBJECTIVES

- Compare the patient characteristics and medical history between those prescribed SSRIs to those on a Non-SSRI , and then compare those prescribed paroxetine to those on all other SSRIs (as a group and each drug individually). Finally, describe any differences in these patient populations in regard to the risk of suicidal behavior (selective prescribing or channelling).
- Compare the incidence of suicidal behaviour (see Section 3.7 for definition), that occurs from initiation of therapy to 30 days after therapy overall and stratified by age (<=18 and over18) between SSRI users vs. Non-SSRIs, and paroxetine users vs. other SSRIs (as a group and individually by drug).
- Investigate whether any observed association between drug use and subsequent suicidal behavior may be explained by baseline risk for suicidal behavior or other patient factors during therapy.

3. METHODOLOGY

3.1. Data Sources

The UK General Practice Research Database (GPRD) is the world's largest computerised database of anonymised patient data from general practice[20]. It contains electronic medical records for approximately 35 million patient years of data. GPRD has been collecting patient records in the UK continuously since 1987. Currently, information is collected on approximately 3 million patients, equivalent to approximately 5% of the UK population. Data are provided by contributing general practices from all around the UK.

The GPRD has been found to be highly representative of the UK general population. Several studies have demonstrated nearly identical age and sex distributions when stratified by geographic region between the GPRD population and the entire UK population[21].

Since 1999, the UK Medicines Control Agency (MCA) (which became part of the newly created MHRA in April 2003) has assumed management of the GPRD.

The following patient information is collected electronically from each GP, as medical care is being administered: demographics (including age and gender of patient), medical diagnoses, all prescriptions, events leading to withdrawal of a drug or treatment, hospital referrals, treatment outcomes (including hospital discharge reports), miscellaneous patient care information (e.g. smoking status, height, weight, immunisations, lab results).

The GPRD is a widely used and well validated data source, with over 200 scientific papers , demonstrating its high quality and wide applicability[21].

3.2. Study Design

Our first phase will be a descriptive examination of prescribing patterns, and the second phase a retrospective cohort study, with a nested case-control component. The study will include all acceptible patients, and all years of observation deemed to be "up to research standard" data by the GPRD division at the MHRA. Data is deemed to be "up-to-standard" based on a routine examination of the continuity and completeness of recording within each gernal practice, and the consistecy of (registration) details within individual patient records. All checks are conducted by the data providors, prior to the data being made available to external customers.

3.3. Patient Confidentiality

The version of the GPRD that is accessed by GSK WWEpi contains only anonymised data. Patients are not identifiable at an individual level and no attempts will be made to contact individual patients.

3.4. Study Groups-Inclusion and Exclusion Criteria

Potential subjects will drawn from the population of those who are ages 10 and above, and registered with a general practitioner contributing data to the UK General Practice Research Database (GPRD).

In order to be eligible for this study, potential subjects need to meet the following criteria:

- Prescribed an antidepressant and with a record of either major depression, or an anxiety disorder (OCD, SAD, GAD, PTSD, or PD) in the 18 months prior to their first prescription for an antidepressant or within the following14 days..
- In order to restrict our study to only *new* users of antidepressants, subjects must have no previous record of a prescribed antidepressant. In order to validly and completely assess a subject's recent medical history, we will require **at least** 18 months of "up to standard" registration on the GPRD prior to their date of first antidepressant prescription. This mean that our subjects will have differential lengths of medical history. Therefore, we will adjust for time since GPRD registration in our analyses.

We will then classify eligible subjects into three study groups

1. Those that received an incident prescription for paroxetine as their first treatment during the study period.
2. Those that received an incident prescription for one of the other SSRIs (fluoxetine, sertraline, fluvoxamine, citalopram/escitalopram) as their first treatment, during the study period.

Those that received an incident prescription for one of the non-SSRI antidepressants as their first treatment (listed in appendix 7.1), during the study period..

3.5. Drug Exposure Definition and Measures

Antidepressants of interest will be all those that are currently marketed in the U.K, according to the British National Formulary (BNF) as of March, 2003. Therefore, antidepressants that have become unavailable before March, 2003 are not included in our study.

Drug exposure will be ascertained by examining all prescription records during the study period, and identifying the first occurrence of a prescription for paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram/escitalopram (SSRIs), or other non-SSRI antidepressants listed in Appendix 7.1. Prescriptions will be classified as incident if there is no previous record of a prescribed antidepressant prior to this prescription. We will exclude any subjects whose prescription records are found not to be new, according to this definition. Subsequently, the date of prescription for this medication will become the subject's index date. Patients will be categorized according to their initial antidepressant prescription during the study period. Switching to, and adding on, another antidepressant will be considered stoppage of initial treatment and the patient will be censored from that time onward, this includes those that switch from one SSRI to another SSRI

Indication for drug use is not explicitly stated in the GPRD. Therefore, we make inferences for the likely indication by looking for diagnoses of depression, and/or an anxiety disorder, in the 18 months previous to each patient's prescription date, or in the following 14 days. Initial analyses have suggested that many patients may have the depression/anxiety records on the date of prescribing, or in the following days.

During the follow-up phase of the study , we will follow patients forward, from their index date up to one of the following events: the initial drug is stopped, a suicidal endpoint is observed, death (from other causes), de-registration from the GPRD, or the end of the study period. For those who were censored because of initial treatment discontinuation (and who do not start an alternative therapy within 30 days), we will also include 30 days post treatment as a period of risk for suicidal events.

Duration of therapy will be calculated by looking at drug amount and prescription days. For those prescription records that are missing this information, we will estimate the duration of therapy by using the drug-specific median values for amount and prescription days from those in our cohort with these data.

Drug therapy will be defined as stopped when a greater than 30 day gap is observed between the end of one prescription and the beginning of the next, or a new antidepressant is either added to or replaces the initial drug, or antidepressant treatment is stopped altogether

Concomitant medications of interest will be defined as those that have been prescribed in the last 90 days, and in a quantity that will last to within 30 days of the index date, or beyond. Consistent with the definitions applied for antidepressant therapy, patients will be considered to be "at risk" during the period 30 days after the end of the last exposure. This will be done in order to look at possible short-term interactions with the antidepressants treatment. Medications known to increase suicidal behaviour or to produce depression or mania will be recorded (Appendices 7.6 & 7.7) .

The treatment period will also be divided into three sub-categories in order to assess whether the incidence of suicidal behavior has a temporal relationship following initiation of therapy. Our categories will be : initiation (first 30 days), maintenance, and discontinuation +30 days.

3.6. Diagnoses Definition and Measures

Medical diagnoses will be determined by examining all patient records prior to their index date. In addition to our inclusion criteria of a major depression or anxiety diagnosis , we will also examine each patients medical history to determine any past diagnosis of: substance abuse (including alcohol), insomnia, psychoses, malignant cancer (all sites), acute cardiovascular events (MI or unstable angina), stroke, epilepsy, multiple sclerosis, and Huntington's disease.

We will attempt to characterize depression/anxiety severity based upon the surrogate measure of psychiatric referral or hospitalization. Severity will be used to investigate this likely risk factor for suicidal behaviour across our study groups.

The MEDCODES codes for major depression, any anxiety disorder are in Appendix 7.3.

3.7. Suicidal Behaviour Definition and Measures

Incident suicidal behaviour will be determined based upon review of each patient's medical encounters from their index date until they are censored (see Section 3.5) from our analyses : a record of completed suicide, attempted suicide, suicidal ideation, or self-harm will be adequate to classify a subject as having had suicidal behaviour event. Past suicidal events will be ascertained in the same manner.

For those instances where a medical code related to completed suicide is recorded, but is then followed by more medical encounters, we will reclassify that event as an unsuccessful suicide attempt.

We will only record the first such event (after antidepressant prescribing) and will exclude any events that occur after 30 days post treatment. Initial analyses will consider all suicidal behaviours combined, without distinguishing between event types.

In an attempt to maximize our study's sensitivity for detecting suicidal behaviour, we will apply a two-tiered approach: initially examine the GP medical codes, as well as query the free text which GP can enter into patient records in order to refine our list of codes. The medical codes (Oxmis/Read codes), and the search terms and algorithm used for the free text queries are listed in Appendix 7.4 & 7.5.

This suicidal behaviour definition will also be used to identify our cases during the case-control analyses.

3.8. Other Covariates

In addition to those variables mentioned in the drug and diagnosis sections, the following will also be evaluated as possible confounding factors:

- age as determined by the age of the subject on their index date.
- gender
- past psychiatric referrals or hospitalizations
- length of medical history
- Major life events (i.e. death of a loved one, loss of employment, financial crises, separation/divorce, legal crises)
    - as recorded by the GP and ascertained by a query of the GP comments field. The search terms that will be used to query the comment fields are in Appendix 7.6.

3.9. Epidemiologic Measures

In phase one, we will calculate odds ratios and 95% confidence intervals which compare the proportion of subjects with past suicidal-behaviour risk factors between those on any SSRI with those on a non-SSRI antidepressant. Our second set of comparisons will be the paroxetine group to the group that received another SSRI (both in aggregate and for each SSRI). Because of the number of comparisons, we will describe , but not statistically test differences between paroxetine and other SSRIs. All ORs in this phase of the analysis will be adjusted for differential lengths of medical history.

During phase two, we will calculate crude incidence density rates, and estimate relative risks for suicidal behaviour during follow-up. Rates will be calculated considering all patient time at risk, and separately with time at risk divided between the periods of treatment initiation, maintenance and discontinuation. The risk across groups will be compared by calculating rate ratios (of incidence densities) and 95% confidence intervals. Confidence intervals for the rate ratios are Wald limits based upon the Poisson model.31. Rate ratios will be stratified by age (<18, 18 and over).

In addition, for our case-control analyses, we will calculate sets of odds ratios and 95% confidence intervals that compare risk of being a case among our three treated groups. During our adjusted analyses for the odds of being a case, we will calculate adjusted odds ratios with 95% confidence intervals. Factors that will be adjusted for include the

amount of drug prescribed, concomitant medication during follow-up, and any variable from the first phase of analyses that is found to differ across cohorts. For the case-control analyses, all variables presented in the initial description of baseline characteristics will be updated to reflect the patients status at the event date, rather than at the date of first prescribing.

3.10. Data Management

The study will be performed by the Worldwide Epidemiology department of GlaxoSmithKline, using in-house, full-featured, GPRD data. Several programmer/analysts will be dedicated to this research and the study will be managed by the psychiatric epidemiology team.

Queries of the GPRD comment fields will be requested from the MHRA and performed by the GPRD division of that agency.

Validation analyses will also require the collaboration of GSK and the MHRA.

The study protocol and final results will undergo internal GSK review by epidemiologic, clinical, suicide, and database experts.

3.11. Validation Procedures

3.11.1. Validation Process for Suicidal Events

The aim of this part of the study is to estimate the sensitivity and specificity of our claims-based definition of a suicidal event. We will follow-up with the reporting GPs for random samples of cases and non-cases, and ask the GP to confirm that this patient did/did not have a suicidal event on the date of interest. The physician response will be used as our gold standard. Therefore, we will estimate our algorithm's sensitivity by the proportion of non-cases that are found to actually have had an event. Conversely, the specificity of our approach will be estimated by the proportion of cases found to not have had a suicidal event. The physicians of the selected patients will be asked via the GPRD division of the MHRA to complete a questionnaire and to return it to the MHRA. The questionnaire is included in Appendix 7.9.

3.11.2. Previous Validation

Prior to our studies, the GPRD has been validated in several large scale studies22-23. The information on all patient referrals and hospitalizations contained in the manual records for the GP have been found to appear in the computerized database over 90% of the time.22-23 Most recently, Jick and colleagues (2003) have further demonstrated the quality and completeness of the computerized data24.

In addition, data quality is monitored continuously by the UK Medicines Control Agency and GP practices that fail to maintain the required standards are removed.

3.12. Data Analysis Plan

- **Compare the past medical history between those newly prescribed SSRIs to those on a non-SSRI antidepressant, and then compare those newly prescribed paroxetine to those on all other SSRIs (as a group and each individually drug). Finally, describe any differences in these patient populations in regard to the risk of suicidal behavior (selective prescribing or channelling).**

We will pursue this objective by comparing the age, gender and recent psychiatric diagnoses, and medical history between those that have been newly prescribed an SSRI, to those prescribed a Non-SSRI, and then those on paroxetine to the other SSRIs. Medical history will be examined for the following events: substance abuse, past suicidal behaviour, insomnia, psychoses, psychiatric referral/hospitalizations, recorded major life events, and physical illness that is know to increase suicide risk such as : cancer, acute cardiovascular events, stroke, epilepsy, multiple sclerosis, and Huntington's disease3. Because of differential lengths of medical history, we will adjust for time since GPRD registration in these analyses.

In order to determine if age (<=18, >18) is an effect modifier for the potential relationship between depression severity and choice of antidepressant, we will perform analyses where depression severity (as measured by psychiatric referral or hospitalization) is compared across SSRI users, Non-SSRI users, and paroxetine users, and these comparisons are stratified by age.

- **Compare the incidence of suicidal behaviour, that occurs from initiation of therapy to 30 days after therapy, between SSRI users vs. Non-SSRIs, and paroxetine users vs. users of other SSRIs (as a group and individually by drug).**

This objective will be pursued by following the various study groups forward from their initiation of therapy and observing any suicidal behaviour events that occur during the period of on treatment + 30 days after. We will calculate the incidence of these events across our study groups, and within the periods of initiation, maintenance and discontinuation within groups. Exposure, or at risk time, will be defined as starting at drug initiation until either : an event is observed, therapy is stopped, death from another cause has occurred, de-registration with the GPRD, or the study period has ended. Treatment will be defined as continuous only if there less than a 30 day gap between the end of the previous prescription and the start of the next, and the patient has not switched to, or added another antidepressant.

We will look for associations by comparing the incidence density rates expressing them as rate ratios (relative risk). The relative risks will be stratified by age as well.

We also will confirm these finding by performing nested case-control analyses. We will compare the cases of suicidal behaviour to a random sample from our cohort of new antidepressant users without any suicide record that have been matched on practice and on length of medical history. Cases will be matched to controls with a ratio of 4 controls to each case. Matched cases and controls will be given the same event date (suicidal event). The odds of being a case for the SSRI group will be compared to the Non-SSRI

group, and the odds of using paroxetine will be compared separately to other SSRIs group by using odds ratios to estimate the relative risk

- **Test whether any observed association between drug use and subsequent suicidal behavior may be explained by baseline risk for suicidal behavior, other patient factors during therapy.**

We will conduct adjusted analyses as part of the nested case-control study. Odds ratios will be adjusted by conditional multiple logistic regression. Adjustment will be according to all potential confounders such as the amount of drug prescribed, concomitant medication during follow-up, and any variable from the first phase of analyses that is found to differ across cohorts.

3.13. Sample Size and Study Power

3.13.1. Phase One: Selective Prescribing

Table 3.13 shows the levels of study power for detecting a difference in the prevalence of patient characteristics (from their medical history) between the exposed and unexposed groups. We have set the two-sided probability of a Type I error (alpha) at 0.05, and a range of prevalence estimates from 5% to 20% is being used. These calculations are based upon a sample size of 6,000 patients in each cohort. According to our calculations, we will have 90% power or greater to detect an odds ratios as small as 1.2 , assuming prevalence of the given factor of 15%.

Table 31. Study power (%) in detecting differences in patient medical history factors, according to prevalence of the factor and a range of odds ratios.

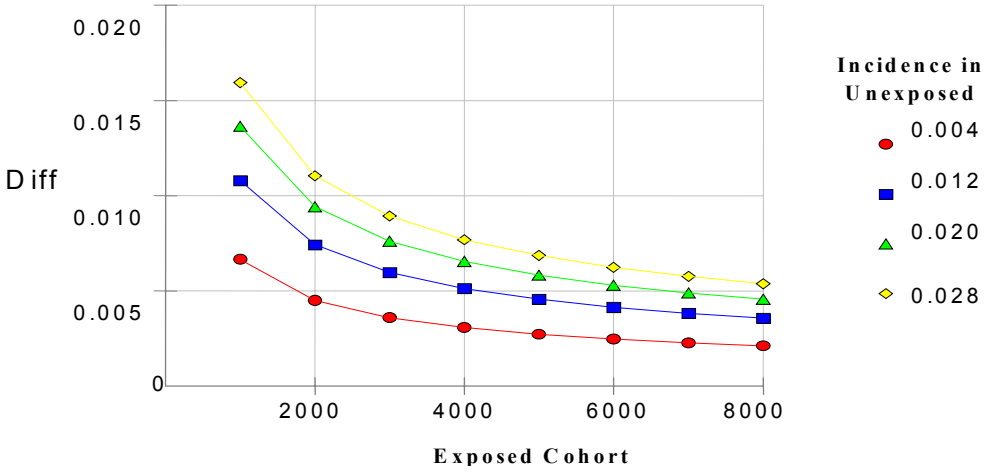
	Odds ratios				
Prevalence	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**
0.05	61	91	98	99	99
0.10	87	99	99	100	100
0.15	95	99	100	100	100
0.20	98	99	100	100	100

3.13.2. Phase Two : Cohort Study of Suicidal Behaviour

Figure 2 shows the detectable difference in incidence rates, between the index and comparison cohorts, for suicidal events , using various estimates of background incidence and number of eligible subjects in the exposed cohorts (can refer to either paroxetine or all SSRIs). We have set the study power at **80%,** and the probability of a Type I error (alpha) at **0.05.** A range of incidence estimates for the comparison group from **0.4 % up**

to 2.8% is being used. This range is based on our population estimate of suicide attempts among antidepressant users of **2.6%**. This estimate is based upon the reported incidence completed suicides among antidepressant users in the GPRD (**0.08%**)[26], and the estimate that **3%** of those that attempt suicide actually complete the act[27].(0.08/0.03=2.6%) This graph shows that if the incidence in the unexposed cohort is 0.012, and we have if we have 1,000 subjects in the exposed cohort , then we will be able to detect a difference in incidence of 0.011 (relative risk of 1.9) or more at 80% power. The risk that we can detect becomes smaller as our estimated sample size increases. At 4,000 exposed subjects, we are able to detect a relative risk of 1.4. Initial pilot analyses have revealed 3,261 incident paroxetine users in the GPRD during our study period. At this number of exposed subjects we would be able to detect a relative risk of 1.5.

Figure 2.



3.14. Strengths and Limitations

The GPRD is an electronic source of medical records that has been designed for epidemiologic research. As a result, there are distinct research advantages to its use. The GPRD represents clinical practice as it occurs in the real-world, so our findings are readily generalizable to UK antidepressant use. Therefore, our study should provide reliable population estimates of suicidality risk among those taking antidepressants. Previously, questions concerning paroxetine and suicidality have been based upon spontaneous reports and clinical trial data. In contrast, our study is specifically designed to investigate a rare adverse drug event.

Because of the GPRD's national catchment area, we should have a large number of subjects available for study, which will allow us to look at suicidal behavior in various sub-groups.

We will establish temporality because our study will follow subjects longitudinally backward and forward in time from their initial antidepressant prescription.

Finally, we intend to not only detect any possible drug-event associations, but also to explain any such relationships by looking at prescribing patterns.

The use of administrative data of this type carries some limitations. A primary limitation is our limited ability to control for confounding. We are only able to control for potential confounders that are contained in the GPRD data. We will be unable to address any imbalances between study groups for such suicide risk factors as physical or sexual abuse, or a family history of suicide.

The GPRD database represents those that have sought treatment for depression, OCD, GAD, SAD, suicidal behaviour, and the other medical conditions that we are evaluating. It is possible to have an ascertainment bias whereby the type of patient that is likely to seek care for suicidal behaviour is distinctly different from those that do not present to the GP. For example, those that seek care for suicidal behaviour may be only the most severely depressed , and therefore, not representative of the overall population of interest. However, this type of bias should be as likely to occur in any of the comparison groups, and therefore would only affect our results by weakening them.

Our results may be inconclusive(high variability) because of limited sample size for some of our stratified comparisons. For example, there may be limited drug use in patients under 18 and with mild depression. We will have some indications of where our study samples are sparse from the results of phase one

There is the possibility of enhanced GP ascertainment/ patient reporting of non-fatal suicide events among SSRI users because of media attention related to this class of drug. However, this should not affect our paroxetine vs. all SSRIs comparison. Also, we may be able to adjust for this imbalance by controlling for past suicide behaviour. The possible effect of this bias would be an overestimation of an association between SSRIs vs. either other antidepressants, or the untreated. Therefore, if our results are negative, then we have greater assurance that no association exists.

Our study will only follow patients as far back as they were registered with an up-to-standard GPRD practice. We may be missing some events in the study groups that had occurred further back in time, but their effect on the baseline risk of suicidal behaviour is likely to be minimal.

Finally, we are using prescriptions received as a proxy for treatment compliance. It is possible that some patients are not taking their medications, but are still receiving prescriptions. Again, this occurrence should be non-differential across our treatment groups.

4. STUDY MANAGEMENT

4.1. Study Costs

Although the main study analyses will be performed by GSK, their will be costs associated with the comment field searches and validation work that will be requested from MHRA. Current estimate of study costs is 150,000 £. This estimate is based upon 120,000 £ for the validation study, and 30,000 £ for free text searches.

4.2. Study Reporting and Publication

This research will be performed by the GSK Worldwide Epidemiology Department and is planned for internal GSK decision-making , and to be shared with relevant regulatory agencies. A decision concerning peer-reviewed publication of this research will be made at a later date. This protocol will be submitted to the Scientific and Ethical Advisory Group (SEAG) within the MHRA so that the option of publication remains open.

4.3. Adverse Event Reporting

The procedure for reporting adverse events during the course of the study is in Appendix 7.10.

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6. TABLES SHELLS

Table 1. SSRIs vs. Non-SSRIs: Age, Gender , and Recent Psychiatric Diagnoses. All figures are based on details on the date of first antidepressant prescription.

.	SSRIs	Non-SSRIs	Chi-Square Test
.	N (%)	N (%)	X2, p-value
Total (N)			
Age			
Under 10			
10-14			
15-19			
20-24			
25-34			
35-44			
45-54			
55-64			
65+			
Sex			
Male			
Female			
Males			
<=18			
>18			
Females			
<=18			
>18			
Recent Psychiatric Diagnoses			
Depression alone			
Anxiety Disorder alone			
Depression + Anxiety			

Table 2. Paroxetine vs. Other SSRIs: Age, Gender , and Recent Psychiatric Diagnoses. All figures are based on details on the date of first antidepressant prescription.

	Paroxetine	All other SSRIs	Fluoxetine	Sertraline	Fluvoxamine	Citalopram	Chi-square test*	Chi-square test**	Chi-square test***
N									
Age									
Under 10									
10-14									
15-19									
20-24									
25-34									
35-44									
45-54									
55-64									
65+									
Sex									
Male									
Female									
Males									
<=18									
>18									
Females									
<-18									
>18									
Psychiatric Diagnoses									
Depression alone									
Anxiety Disorder alone									
Depression + Anxiety									

*refers to chi-square test of Paroxetine vs. All Other SSRIs
** refers to chi-square test of Paroxetine vs. Fluoxetine
***** refers to chi-square test of Paroxetine vs. Sertraline**

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Table 3. Medical History for those newly prescribed SSRI vs. Non-SSRI All figures are based on details on the date of first antidepressant prescription.

Medical Event ***	Non-SSRI (n/N) (%)	SSRI (n/N) (%)	Odds ratios*
(95% CI)			
Acute CV			
Insomnia			
Huntingdon's Disease			
Multiple Sclerosis			
Epilepsy			
Substance Abuse			
Psychoses			
Malignant Cancer			
Stroke			
Suicidal behaviour			
Had Major Life Event			
Had Major Life Evening in past 18 months			
Had Psychiatric Referral			
Had Psychiatric Hospitalisation			
Length of history**			
<=2 years			
3-4 years			
5-6 years			
7+ years			
Median Age			
Sex**			
Male			
Female			

* Reference group is non-SSRIs. OR is adjusted for length of history
** Chi-square test used to test for equal proportions
*** A minimum 18 months of medical history was searched for events.

Table 4. Medical History for those newly prescribed Paroxetine vs. Other SSRIs. All figures are based on details at time of first antidepressant prescription.

Medical Event***	Paroxetine (n/N) (%)	All other SSRIs (n/N) (%)	Fluoxetine (n/N) (%)	Sertraline (n/N) (%)	Fluvoxamine (n/N) (%)	Es/Citalopram (n/N) (%)	Odds Ratios* (95% CI)
Acute CV							
Insomnia							
Huntingdon's Disease							
Multiple Sclerosis							
Epilepsy							
Substance Abuse							
Psychoses							
Malignant Cancer							
Stroke							
Suicidal behaviour							
Length of history**							
<=2 years							
3-4 years							
5-6 years							
7+ years							
Had Major Life Event							
Had Major Life Evening in past 18 months							
Had Psychiatric Referral							
Had Psychiatric Hospitalisation							
Median Age							
Sex**							
Male							
Female							

* Reference group is All Other SSRIs. OR is adjusted for length of history
** Chi-square test used to test for equal proportions
*** A minimum 18 months of medical history was searched for events.

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Table 5. Past depression severity*, stratified by Age for those newly prescribed Paroxetine, Other SSRIs, or Non-SSRIs. All figures are based on details on the date of first antidepressant prescription.

	Paroxetine n(%)	Other SSRI n(%)	Non-SSRI n(%)	OR* (95% CI)
Postive history of psychiatric referral/hospitalization				
Overall				
Age				
Under 10				
10-14				
15-19				
20-24				
25-34				
35-44				
45-54				
55-64				
65+				

*Paroxetine vs. Other SSRIs

Table 6. Incidence Density Rates, and Relative Risk of Suicidal Events following Initiation of Therapy*

Parameter	SSRIs	Non-SSRIs	Paroxetine	All Other SSRIs	Fluoxetine	Sertraline	Fluvoxamine	Citalopram
N								
Exposure Time (Pys)								
Events (All)								
Self harm								
Suicidal Ideation								
Attempted suicide								
Completed suicide								
Incidence Density (/100 person years)**								
Relative Risk (95% CI)***								

*Events occurring outside of therapy +30 days window will be excluded.
** Incidence rates consider the first event only (all event types combined).
*** SSRIs are compared to Non-SSRIs. Paroxetine is compared to all other SSRIs and to each individually.

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Table 7. Medicial history and patient characteristics of cases and controls. All figures are based on patient history on the date of the suicidal event (or matched date for controls).

Medical Event***	Cases	Controls
Acute CV		
Insomnia		
Huntingdon's Disease		
Multiple Sclerosis		
Epilepsy		
Substance Abuse		
Psychoses		
Malignant Cancer		
Stroke		
Suicidal behaviour		
Length of history**		
<=2 years		
3-4 years		
5-6 years		
7+ years		
Had Major Life Event		
Had Major Life event in past 18 months		
Paroxetine at time of event		
Any other SSRIs at time of event		
Fluoxetine at time of event		
Sertraline at time of event		
Fluvoxamine at time of event		
Es/Citalopram at time of event		
Any prior Paroxetine		
Any prior other SSRIs		
Any prior Fluoxetine		
Any prior Sertraline		
Any prior Fluvoxamine		
Any prior Es/Citalopram		
Had Psychiatric Referral		
Had Psychiatric Hospitalisation		
Median Age		
Sex**		
Male		
Female		

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Table 8. Crude and Adjusted Odds ratios for Suicidal Behavior between Cases and Controls. All figures are based on patient history on the date of the suicidal event (or matched date).

	OR	95% CI
Crude OR		
Adjusted ORs*		
SSRIs vs. Non-SSRIs		
Baseline Characteristics (details to be confirmed based on initial analyses)		
Amount of Drug		
Period of exposure (initiation/maintainence/discontinuation)		
Concomitant Medications (details to be confirmted based on initial analyses)		

*Odds ratios have been adjusted by all other factors in the model.

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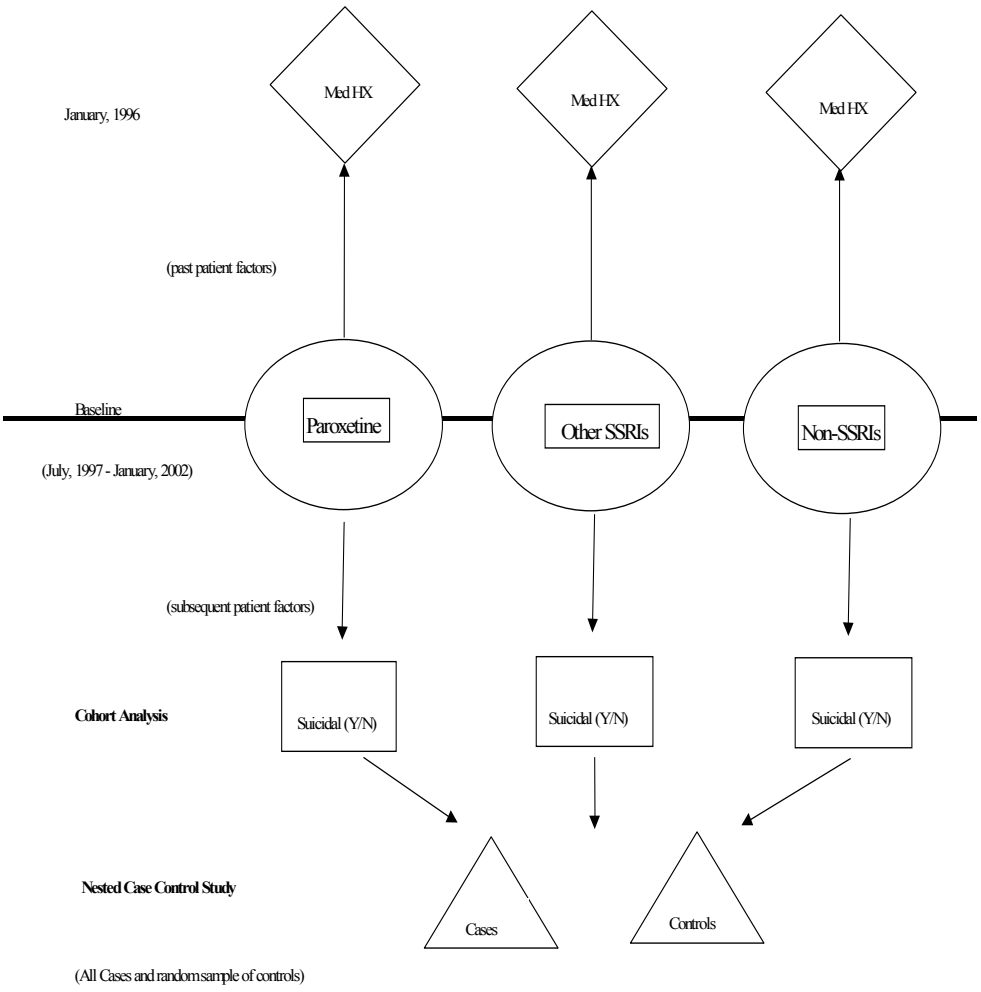
	OR	95% CI
Crude OR		
Adjusted ORs*		
Paroxetine vs. Other SSRIs		
Baseline Characteristics (details to be confirmed based on initial analyses)		
Amount of Drug		
Period of exposure (initiation/maintainence/discontinuation)		
Concomitant Medications (details to be confirmted based on initial analyses)		

*Odds ratios have been adjusted by all other factors in the model.

7. APPENDICES

7.1. Schematic of Study Design



7.2. Non-SSRI Antidepressants

Available from authors on request.

7.3. Medical Codes for Major Depression, and Anxiety Disorders.

Available from authors on request.

7.4. Medical Codes for Suicidal Behaviour.

Available from authors on request.

7.5. Search Terms for Major Life Events.

Available from authors on request.

7.6. Search Terms for Suicidal Behaviour.

Available from authors on request.

7.7. Concomitant Medications linked to a risk of suicidal behavior

Available from authors on request.

7.8. GP Questionnaire for Validation of Suicidal Events

Has this patient ever experience any of the following medical events?

If YES, please record the <u>first-ever</u> occurrence of each event within the time periods specificed.

Please attempt to answer every question.

Decisions about the classification of self-harm, suicidial idealitions, and suicide attempts should be made based on your clinical judgement, and knowledge of the patients history and medical records.

1. Has this patient ever been diagnosed with depression, an anxiety disorder, or a related psychological condition?

Depression? YES □NO □ Date of first record __ __ ____ (DD/MM/YYYY)

Anxiety? YES □NO □ Date of first record __ __ ____ (DD/MM/YYYY)

Other (please specify) _____ Date of first record __ __ ____ (DD/MM/YYYY)

Prescribed Psychotropics ? YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY

2. SUICIDAL THOUGHTS
Did this patient ever report serious thoughts about committing suicide before xx/xx/xxxx?

YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY)

Did this patient ever report serious thoughts about committing suicide on, or after, xx/xx/xxxx?

YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY)

3. SUICIDAL ATTEMPTS

Did this patient ever make a serious attempt to commit suicide before xx/xx/xxxx?

YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY)

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Did this patient ever make a serious attempt to commit suicide on, or after, xx/xx/xxxx?

YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY)

4. COMPLETED SUICIDES
Did this patient die, with the cause of death recorded as suicide before xx/xx/xxxx?

YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY)

Did this patient die, with the cause of death recorded as suicide on, or after, xx/xx/xxxx?

YES □ NO □ Date of first record __ __ ____ (DD/MM/YYYY)

5. Has this patient ever reported intending to cause themselves harm, or inflicted actual self-harm?

Thoughts of self harm before xx/xx/xxxx? YES □ NO □ Date of first record __ __ ____
Thoughts of self harm on, or after, xx/xx/xxxx? YES □ NO □ Date of first record __ __ ____

Inflicted actual self harm before xx/xx/xxxx? YES □ NO □ Date of first record __ __ ____

Inflicted actual self harm on, or after, xx/xx/xxxx? YES □ NO □ Date of first record __ __ ____

6. Are paper records, case notes, or referral/hospital discharge letters available for this patient?

Paper records available □

Computer records only □

7.9. Reporting and Evaluation of Individual Serious Adverse Events (SAEs) Standard Operating Procedure

Safety Reporting from Epidemiology Studies and Analyses of Epidemiology Databases (effective Feb, 2000)

"Adverse event reports are processed in Global Clinical Safety and Pharmacovigilance (GCSP) and reported to regulatory authorities by GCSP. Worldwide Epidemiology will handle adverse events arising from epidemiology studies and analyses of epidemiology databases as outlined in this SOP".

Safety Assessments of Marketed Medicines (SAMM) study

“Formal investigations conducted for the purpose of assessing the clinical safety of marketed medicine(s) in clinical practice.” These include not only those studies performed to investigate a known or suspected safety issue but also those studies in which the number of patients to be included (> 500) will add significantly to the existing safety data for the product. SAMM studies may include those conducted using automated databases (GPRD, MEMO) or pharmacovigilance data collection mechanisms (PEM).

Disease natural history studies, resource utilisation studies, and studies of drug effectiveness are not SAMM studies. Safety studies of non-GlaxoSmithKline products are not SAMM studies unless they are likely to influence utilisation of GlaxoSmithKline products. This point should be discussed with European Regulatory Affairs prior to designing the study. In addition, for studies conducted for registration purposes or as a requirement of registration, interactions between GSK and MCA will be handled entirely by European Regulatory Affairs. However, Epidemiology is responsible for sending MCA a courtesy copy of the protocol and a cover letter stating the MCA division with primary oversight of the study.

Epidemiologists should note that interim reports are required by MCA at 6-month intervals and final reports are due within 3 months of study completion. If final reports require more than 6 months to prepare, a brief report should be submitted 3 months post study completion.

GSK has access to numerous observational databases that include information on patients, drug therapy, clinical events, costs, deaths, and other information. These are secondary databases that originate from either governmental or private sources. The epidemiology databases have a variety of uses in describing disease natural history, treatment patterns, and disease burden. Some of the questions addressed in these databases warrant the full development of a study protocol. Often the searches do not

require a study protocol. Only rarely would database searches be conducted to explicitly evaluate a GSK drug safety signal.
If in the process of searching a database a hospitalization due to an adverse reaction to a GlaxoSmithKline product is detected, the report is to be sent to Global Clinical Safety and Pharmacovigilance (GCSP) as there may be regulatory reporting obligations. It is important to note, however, that all hospitalizations in patients taking GSK products do NOT need to be sent, only those where there was clearly a relationship to the drug. Further, regarding non-serious events, GCSP is to be notified if, as a result of analysis of the study data, you detect a safety signal. It is not necessary to notify GCSP if only a few reports are noted.

Reportable Events and Timeframe for Reporting

In the circumstance that serious events identified through epidemiology studies or database searches are explicitly attributed to a GSK drug by health care professionals, the Epidemiology Department forwards these reports to GCSP. The event is to be forwarded to GCSP by the Epidemiology within 24 hours if the event is fatal or life-threatening, within 3 calendar days for other serious events, and within 7 calendar days for nonserious events. Expedited reports are submitted to regulatory authorities by IPSP/NAPS as appropriate. Note that EU guidelines require that the company use the reporter's assessment of causality, while the FDA regulations allow the sponsor (GSK) to make this determination.