11. QUESTION 11: FURTHER INVESTIGATIONS OF WITHDRAWAL REACTIONS AND/OR SUICIDAL BEHAVIOUR

Proposals for further investigation of withdrawal reactions and/or suicidal behaviour in relation to the use of paroxetine.

Response

11.1. Withdrawal Reactions – further investigation

Clinical studies already conducted using a standardised approach to collecting withdrawal reaction AEs have provided experience from over 5500 adult and over 700 paediatric patients. These extensive clinical data have allowed us to comprehensively characterise the nature, frequency and severity of withdrawal reactions. We do not believe that further studies would add appreciably to our knowledge of these events.

There are practical issues associated with conducting further work on approaches to discontinuation of therapy which are discussed in the response to a previous question (Question 8). Consequently, no new studies are planned in this area.

11.2. Suicidal behaviour – further investigation

11.2.1. Introduction

In GSK's placebo-controlled studies in paediatric patients, there was no difference between the paroxetine and placebo groups in change from baseline of Item 3 of the HAM-D and Item 10 of the MADRS (the items relating to suicidality) and no conclusive evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment group compared to the placebo group. However, the incidence of possibly suicide-related and self-harm adverse events was greater in paroxetine treated patients than in patients who received placebo, primarily in adolescents with major depressive disorder. These data, however, do not represent real-world utilisation or outcomes of those receiving paroxetine. There are several potential biases that may be present in the data. Since the trial patients are those who agreed to participate in the studies, they may be a select group and not representative of all patients. Also, there may have been some unmeasured confounding factor that was not balanced between the study groups through randomisation.

In order to further investigate paroxetine and the risk of suicidal behaviour, GSK is currently conducting an observational study, using data from the UK General Practice Research database (GPRD) [MHRA, website]. Our research objectives are to:

- Characterise the nature and the extent of selective prescribing for paroxetine as it relates to baseline risks for suicidal behaviour.

- Examine the possible association between paroxetine use and suicidal related events after initiation of therapy.

Those patients newly prescribed paroxetine will be compared to those on another SSRI, and those on a non-SSRI antidepressant. This will allow comparison of the baseline risks for suicidal behaviour across these groups, by examining their medical history for risk factors, which were present prior to their antidepressant prescription.

These defined cohorts will then be followed forward in time and the incidence of suicidal behaviour in each group will be determined. We will compare incidences and determine if there is an association between use of paroxetine, or any SSRI, and suicidal behaviour. This study will also have a nested case-control component in order to adjust for potential confounding factors and to obtain a second estimate of drug use effect (first will be from the cohort comparison). Our comparisons will be adjusted for all potential confounding factors occurring before or after initiation of therapy (e.g. indication, therapy duration, and concomitant medications).

The primary goals of this study are 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.

11.2.2. Methodology

11.2.2.1. Data Source

The UK General Practice Research Database (GPRD) is the world's largest computerised database of anonymised patient data from general practice [Walley, 1997]. 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 [MHRA, website].

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 (including indications), 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 [MHRA, website].

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

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.

11.2.2.3. Analysis Plan

Determine if selective prescribing of paroxetine (or SSRIs) is present, and if present, describe its nature.

We will pursue this objective by comparing the age, gender distributions, and the past 18 months of medical history between those that have been newly prescribed paroxetine, those newly prescribed another SSRI, and those prescribed a non-SSRI antidepressant. Medical history will be examined for the following events: an anxiety or conduct disorder, substance abuse, past suicidal behaviour, past depression, insomnia, psychoses, psychiatric hospitalisations, concomitant medications known to increase suicidal behaviour, and physical illness that is know to increase suicide risk such as cancer, acute cardiovascular events, stroke, epilepsy, multiple sclerosis, and Huntingdon's disease [Jick, 2003]. In order to determine if age (<=18, >18), gender, or indication is an effect modifier for the potential relationship between depression severity and choice of antidepressant, we will perform analyses where depression severity is compared across the three study groups, and these comparisons are stratified by age and gender.

Determine if the prescription of paroxetine (or SSRIs) is associated with the incidence of suicidal behaviour following initiation of therapy.

This objective will be pursued by following the three study groups forward from their initiation of therapy and observing any suicidal behaviour event that occurs during the period of on treatment to + 30 days after. We will calculate the unadjusted incidence of these events across our three groups. Exposure, or at risk time, will be defined as starting at drug initiation until either: an event is observed, therapy is stopped, or the 12-month follow-up period has ended. Treatment will be defined as continuous only if there is less than a 30-day gap between prescriptions, and the patient has not switched to another antidepressant.

We will look for associations by comparing the incidence rates and expressing them as rate ratios (relative risk). The relative risks will be stratified by age, gender, indication, and time since therapy initiation. This will allow us to determine if observed associations vary by age, gender, or indication, and to identify any patterns in the risk over time.

We also will confirm these finding by performing nested case-control analyses. We will compare the cases of suicidal behaviour to a random sample of controls that have been

matched on practice and index date. The odds of being a suicide case for the paroxetine group will be compared to the SSRI group, and the SSRI group will be compared separately to the non-SSRI group by using odds ratios to estimate the relative risk. As for rate ratios, we will stratify odds ratios by age, gender, indication, and time since therapy initiation

Attempt to explain any observed association between drug use and subsequent suicidal behaviour by investigating patient factors present before initiation, or during therapy.

We will conduct a survival analysis comparing incidence in our three cohorts after adjustment for confounding factors. Adjustment will be according to all baseline patient factors that are found to be related to prescribing, and information concerning antidepressant treatment such as: amount of drug received, and subsequent concomitant medications. We will implement these adjustments with Cox proportional hazard modelling (with time dependent covariates) and Kaplan-Meier survival curves. As part of this analysis phase, we will evaluate the proportional hazards assumption for our study.

Additionally, we will conduct adjusted analyses as part of the nested case-control study. Odds ratios will be adjusted by multivariate logistic regression. As above, adjustment will be according to all baseline patient factors, and information concerning treatment that follows initiation.

11.2.2.4. Limitations

The use of administrative data of this type carries some limitations. 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 our analyses of selective prescribing.

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 with suicidal behaviour 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 back for 18 months, 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.

11.3. References

Jick SS, Kaye JA, Vasilakis-Scaramozza C, Garcia Rodriguez LA, Ruigomez A, Meier CR, Schlienger RG, Black C, Jick H. Validity of the general practice research database. *Pharmacotherapy*. 2003 May; 23(5):686-9.

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Walley T, Mantgani A. The UK general practice research database. *Lancet* 1997; 350: 1097-1099.