**Use of SSRIs Among Children:**

**A Danish Drug Use Study**

Study Protocol

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**Introduction**

The use of selective serotonin reuptake inhibitors (SSRIs) in children has been subject to debate and controversy. Issues on efficacy and adverse reactions, especially reported cases of suicide-related behavior (1;2), have in the past decade sparked warnings and guidelines from several Regulatory Authorities (3;4). Among the currently marketed SSRIs in Denmark, only fluoxetine holds an indication for major depression in children, while sertraline and fluvoxamine are indicated in cases of obsessive-compulsive disorder in children (5).

The current knowledge of SSRI drug utilization in Danish children is limited. The Danish Ministry of Health and Prevention reported cross-sectional data on the utilization of SSRIs among children and adolescents in 2010 (6), identifying 2,802 new users of SSRIs below the age of 18 years among a total of 5,677 users in that year. There are no specific data on crucial drug utilization parameters such as regional differences, time-trends, co-medication or duration of therapy.

Using the powerful and validated nationwide Danish prescription database (7-9), we aimed to provide a detailed study of prescription patterns of SSRIs among children below the age of 18 in Denmark from 1995-2011.

**Methods**

In this study we described the use of SSRIs among children in Denmark, using descriptive statistics. We obtained prescription data for all children in Denmark aged 5-17 years during the period January 1, 1995 to December 31, 2011. On average, 1,233,165 children of this age resided in Denmark during the study years. We excluded children <5 years old as our preliminary analyses based on publicly available prescription data (10), showed negligible use of SSRIs in this age group.

**Data source**

National data on drug use in Denmark was extracted from the Danish National Prescription Database (11). The Registry contains complete information, from 1 January 1995 and onwards, on all prescriptions filled by Danish residents at outpatient pharmacies. For each filled prescription, the registry contains information on the following variables relevant for this study: drug type, quantity, strength, date of purchase, person age, gender and region of residence. Registered drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the World Health Organization (WHO) for purposes of drug use statistics (12), and the quantity dispensed for each prescription is expressed by the defined daily dose (DDD) measure, also developed by the WHO (12). In addition, the registry contains several other variables not used in this study. As described elsewhere, the registry is reported to have a high completeness and validity (11).

Population statistics were obtained from Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes (13).

**Study drugs**

SSRIs as a group were defined as all drugs within ATC-group N06AB. ATC-groups and DDD-definitions are shown for each single drug in table 1.

**Analysis**

To structure the description of the analysis and the presentation of the results, we divided the analysis into five research questions collectively describing the use of SSRIs among children in Denmark. All analyses were performed stratified by age and gender. We used age categories as defined by EMA (14), i.e. 5-11 years and 12-17 years.

*Which SSRIs were used and to what extent?*

We calculated the amount and type of SSRI use in 2011, by dividing the total number of dispensed DDDs for each specific SSRI by the total number of children in each age and gender category on January 1, 2011.

*What was the incidence of SSRI use?*

Incident use was defined as children’s first filled prescription for an SSRI in the Registry. As data were not available prior to 1995, only data from 1997 and onwards are shown, thus giving a 2-year run in period to avoid misclassification of previous uses as incident users. We calculated the annual incidence proportion by dividing the number of children who filled their first SSRI prescription by the total number of children within each age and gender category living in Denmark on January 1 of the relevant year. The incidence proportion was given per 1,000 persons.

To test whether the choice of first-line treatment with SSRIs changed during the study period, we further stratified all incidence analyses by type of SSRI.

*What was the prevalence of SSRI drug use?*

The point prevalence of SSRI use, i.e. current use, was defined as the number of children per 1,000 in the population, who on a given day either filled an SSRI prescription or had previously filled a prescription with enough SSRI doses to cover that day. When estimating whether SSRI doses covered a given day, we assumed one dispensed tablet to be the daily dose and then added 20% to the dispensed amount to account for non-compliance and irregular prescription refills. Prevalence proportions were calculated by dividing the number of current SSRI users by the total number of children within each age and gender category living in Denmark on January 1 of the relevant year. We further illustrated the age distribution of SSRI use by estimating the point prevalence proportion of use for each age year (as of December 31 2011) among boys and girls.

Lastly, to investigate regional differences in the use of SSRIs, we estimated the average prevalence of SSRI use during 2011 in each of the five Danish regions (North, Mid, South, Sealand and Capitol) and compared it to the national average during that same year.

*For how long did SSRI use last?*

We produced a Kaplan–Meyer curve to estimate the duration of SSRI drug use among children in Denmark. For each SSRI user, the duration of treatment was calculated from the day the first prescription was filled. Treatment was defined as terminated when 180 days had passed without the individual filling a prescription for any SSRI drug. The long interval allowed between prescriptions was chosen to avoid false termination of use among children who had long pauses between prescriptions. Children were excluded from this analysis if their treatment episode was initiated in the first half of 1995 (i.e. the first 180 days of our dataset) to ensure that the correct starting date was assigned. In this analysis children were censored upon the time they turned 18, died, or at the end of the study period (31 December 2011). Only the first treatment episode of each child was included in the survival analysis. When specifying by age category we used the age at the time of the first prescription. We further conducted a sensitivity analysis to test whether extending the interval allowed between SSRI prescription fills from 180 to 365 days would alter our results on treatment duration.

*To what extent did children use other nervous system drugs concurrently with SSRI drugs?*

We assessed concurrent use of SSRI drug and other nervous system drugs (ATC-group N) among children in Denmark in 2011 by examining filled prescriptions for nervous system drugs, grouped down to the third ATC-level (e.g. N07B, psychostimulants). We calculated the percentage of prevalent SSRI users in 2011 who in that year also filled a prescription for another nervous system drug. We further calculated standardized morbidity rates (SMRs), i.e. the ratio between the actual concurrent drug use in the SSRI cohort and the expected concurrent drug use in the SSRI cohort if they had the same use pattern as the background population, standardized by sex and age in 1-year intervals.

**Other**

All calculations were performed using STATA Release 12.0 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency and Statistics Denmark’s Scientific Board. Approval from the Ethics Committee was not required.

**Results**

We identified a total xx children aged 5-17 using SSRIs during our study period (1995-2011), filling a total of xx prescriptions for SSRIs. The most used drug over the entire period was sertraline (xx fillings), followed by citalopram (xx fillings). In 2011, the most used drug in all age and gender categories was sertraline, followed by citalopram (table 2).

The highest incidence and prevalence proportion of SSRI use was seen among girls aged 12-17. [Description of changes in incidence proportions during study period]. Annual incidence proportions for both age groups and genders are shown in figure 1. [Description of changes in choice of first-line treatment based on drug-specific incidence proportions]. [Description of changes in prevalence proportion during study period] (figure 2). The full age and gender spectrum of prevalent children in 2011 is shown in figure 3. When stratifying by region we found […]. The use pattern specified by region is shown in table 3.

[Description of the kaplan-meier-plot] (figure 4). When allowing 365 days between prescriptions we saw that [...].

[Description of the co-med-analysis] (table 4).

**Tables**

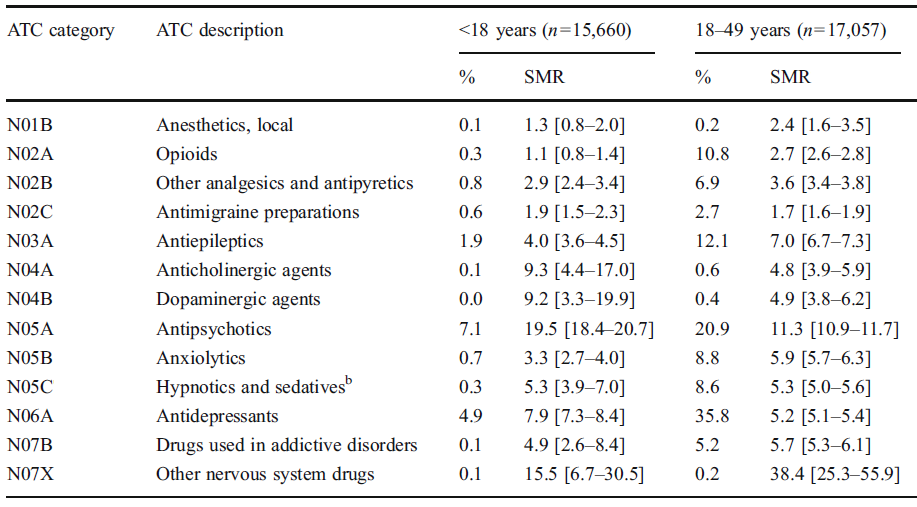
|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1:** SSRIs with marketing authorization in Denmark | | | |
| **Drug** | **ATC Class** | **DDD  (mg)** | **Marketed pediatric indication** |
| Fluoxetine | N06AB03 | 20 | Depression  (>8 years of age) |
| Citalopram | N06AB04 | 20 | None |
| Paroxetine | N06AB05 | 20 | None |
| Sertraline | N06AB06 | 50 | Obsessive-compulsive disorder  (>5 years of age) |
| Fluvoxamine | N06AB08 | 100 | Obsessive-compulsive disorder (>8 years of age) |
| Escitalopram | N06AB10 | 10 | None |
| ATC = Anatomical Theraputic Chemical  DDD = Defined daily dose | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 2:** Amount and type of SSRI use in 2011,  expressed in DDD per 1,000 children | | | | |
|  | **Boys** | | **Girls** | |
| **Drug** | **Age 5-12** | **Age 13-17** | **Age 5-12** | **Age 13-17** |
| Total |  |  |  |  |
| Fluoxetine |  |  |  |  |
| Citalopram |  |  |  |  |
| Paroxetine |  |  |  |  |
| Sertraline |  |  |  |  |
| Fluvoxamine |  |  |  |  |
| Escitalopram |  |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 3:** Regional differences in average prevalence proportion  of SSRI use in 2011 expressed as average number of users per 1,000  children and specified by gender and age category. | | | | |
|  | **Boys** | | **Girls** | |
| **Region** | **Age 5-12** | **Age 13-17** | **Age 5-12** | **Age 13-17** |
| Entire Denmark |  |  |  |  |
| North Region |  |  |  |  |
| Mid Region |  |  |  |  |
| South Region |  |  |  |  |
| Sealand Region |  |  |  |  |
| Capitol Region |  |  |  |  |

**Table 4:** Concurrent use of other psychotropic drugs among children using SSRI in 2011, expressed as the percentage of users using any drug from the given drug category and the standardized morbidity ratio, i.e. the ratio between the actual drug use among children using SSRIs and the drug use of the background population.

[The table is copied from another study, but I’ll aim for something that resembles this!]

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**Figures (Warning: Fake data!)**

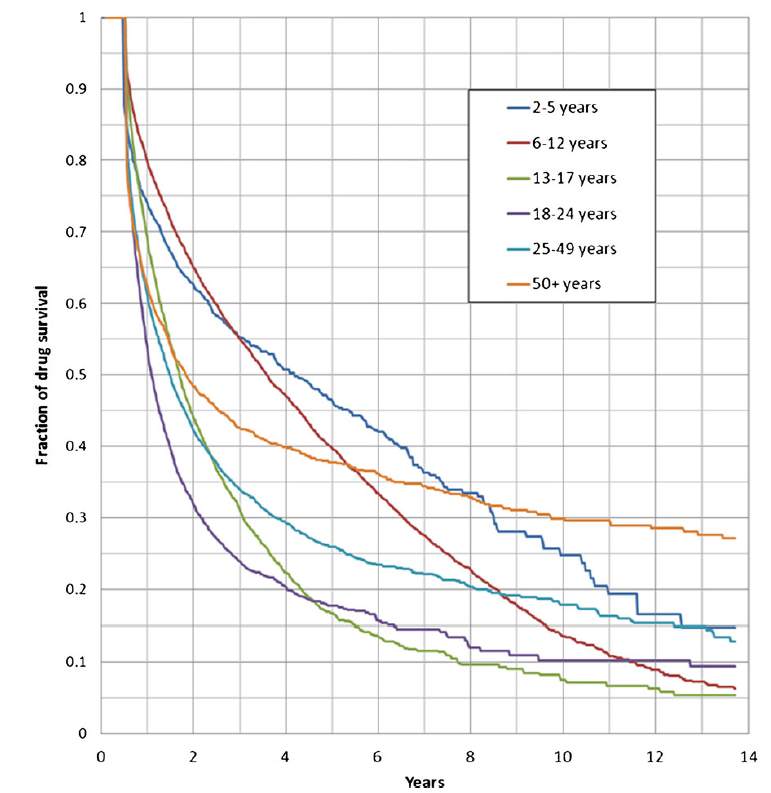
**Figure 1:** Annual incidence proportions from 1997 to 2011, specified by gender and age category.

**Figure 2:** Prevalence proportion from 1995 to 2011, specified by gender age category.

**Figure 3:** Full age and gender spectrum of children using any SSRI at some point during 2011.

**Figure 4:** Kaplan-Meier curve of drug survival. Treatment was considered terminated when 180 days had passed without the child filling a new SSRI prescription.

[The figure is copied from another study, but I’ll aim for something that resembles this!]



References

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