Psychotropic co-medications among stimulant-treated children in the Netherlands

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Abstract

Objectives
To examine stimulant use from 1998 to 2002 among children in the Dutch pediatric population with emphasis on psychotropic co-medication.

Methods
A drug utilization study was based on community pharmacy dispensing data from 1998 to 2002 for children aged 0 through 19 years in the northern and eastern part of the Netherlands.

Results
The prevalence of stimulant use increased from 0.6% in 1998 to 1.2% in 2002. Duration of stimulant treatment was longest in children aged 5-14 years old. The use of any psychotropic co-medication in stimulant users increased from 12% in 1998 to nearly 15% in 2002. Of those youths prescribed stimulant medication in 2002, the most co-prescribed class was the antipsychotics (7.9%). In 1998 none of the stimulant-treated children received antidepressants for co-medication; in 2002 this was 1.8%.

Conclusions
The prevalence of stimulant use among children in the Netherlands has increased in recent years, mainly due to the duration of stimulant treatment. Psychotropic co-medication among stimulant-treated children increased moderately.
Introduction

During the 1990's there has been an explosive increase in the use of stimulants among children in several western countries. This increase has been reported in the United States of America, Canada, Australia and the Netherlands [1-4], with prevalence rates being highest in the USA. There is great concern about this increase, especially about the increased use in very young children [5]. The main reason for concern is the unknown long term effects of stimulant use, all the more since the duration of stimulant treatment has lengthened [3].

Another issue in psychotropic drug use in children is the rise of combined use of different psychotropic agents as reported in the USA [1]. After all, evidence supporting the effectiveness and safety of combined psychotropic drug use in children is lacking. Among stimulant users, a five-fold increase of psychotropic co-medication between 1993 and 1998 has been reported [6]. As drug utilization in the USA may not reflect practice in other countries, it is important to examine the combined use of psychotropic agents elsewhere.

Now that more recent data on stimulant use has become available from the Netherlands, we examined whether the increase in stimulant use among children has persisted and whether the use of psychotropic co-medication among these stimulant-treated children has increased.

Methods

Setting and study population
This study was performed with pharmacy dispensing data from the InterAction database (IADB) [7]. The IADB comprises all prescriptions from about 220,000 people in the northern part of the Netherlands from 1994 to present, and was more recently expanded to cover about 400,000 people. This database includes all prescriptions, regardless of prescriber, insurance or reimbursement status, apart from OTC drugs and drugs dispensed during hospital stay. Children aged 0 through 19 years to whom at least one stimulant prescription was dispensed during the period 1997 to 2002 were selected from the IADB.

Data analysis
Psychotropic agents were defined according to the ATC/DDD classification system and included the following subgroups: psychostimulants, antidepressants, antipsychotics, lithium, clonidine, hypnotics/anxiolytics, antiepileptics, and anticholinergic agents as a subgroup of the antiparkinson drugs (World Health Organization: http://www.whocc.no/atcddd).
Intravenous and rectal dosage forms with diazepam were excluded from the hypnotics/anxiolytics group and included in the antiepileptics group because of their primary use in the treatment of epilepsy. Melatonin is not classified in this system yet, and is dispensed in the Netherlands by means of compounded capsules.

Prevalence of stimulant use (in %) was estimated per year and was defined as the number of children to whom any stimulant prescription was dispensed per total number of children in the population covered by the IADB. The incidence was estimated analogously. E.g.: The incidence in 1998 was defined as the occurrence of one or more stimulant prescriptions in 1998 among youths without a stimulant prescription in 1997. Children were regarded incident users if they had not had any stimulant prescription before, despite being registered for at least one year in the IADB. Data from 1997 were used to identify incident users for 1998. Prevalence and incidence were stratified by gender and age group (0-4, 5-9, 10-14, 15-19 year olds).

Duration of stimulant use was estimated for all incident users in 2000-2002, using the Kaplan-Meier survival estimator. Stimulant treatment was considered stopped when a child had not received prescribed stimulants for at least 180 consecutive days after the end date of the final prescription. A log-rank test was used to test for differences in the duration of therapy between strata based on age and gender.

For calculations on dosages, the unit of analysis was a methylphenidate prescription. Since in the Netherlands dexamphetamine is only available as a substance for use in compounded capsules, no reliable data on prescribed daily dose were available for dexamphetamine. Calculations on dosage were stratified by year, gender and age group. The use of psychotropic co-medication among stimulant-treated children was estimated for each year considering another prescription as co-medication only when the other psychotropic drug was dispensed in the same week as a stimulant prescription. Confidence intervals (95%) were calculated according to the Wilson or Score method [8]. Statistical tests were considered significant when $p<0.05$ (two-tailed). For skewed distributions the three quartiles were given (1st, median and 3rd quartile) instead of mean and standard deviation. Statistical analyses were performed in SPSS 11.0.

**Results**

**Characteristics of stimulant use**

The prevalence of stimulant use for children aged 0 through 19 years increased significantly from 0.6% in 1998 to 1.2% in 2002 (Table 1). This increase was strongest from 1998 to 1999 (0.3%) and then remained constant with 0.1% per year. This increase varied between
Table 1. Prevalence of stimulant use by children aged 0 - 19 years in 1998 and 2002.

<table>
<thead>
<tr>
<th>Group</th>
<th>1998</th>
<th></th>
<th>2002</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
<td>N</td>
</tr>
<tr>
<td>0 - 4 years</td>
<td>11</td>
<td>0.1</td>
<td>0.0 – 0.1</td>
<td>13</td>
</tr>
<tr>
<td>5 - 9 years</td>
<td>216</td>
<td>1.2</td>
<td>1.1 – 1.4</td>
<td>359</td>
</tr>
<tr>
<td>10 - 14 years</td>
<td>182</td>
<td>1.0</td>
<td>0.9 – 1.2</td>
<td>456</td>
</tr>
<tr>
<td>15 - 19 years</td>
<td>39</td>
<td>0.2</td>
<td>0.2 – 0.3</td>
<td>188</td>
</tr>
<tr>
<td>Total 0 - 19 years</td>
<td>415</td>
<td>0.6</td>
<td>0.5 – 0.6</td>
<td>919</td>
</tr>
<tr>
<td>Total study population</td>
<td>71879</td>
<td>100.0</td>
<td></td>
<td>75109</td>
</tr>
</tbody>
</table>

different age groups. No increased prevalence was found in children younger than 5 years, whereas prevalence among the oldest children increased nearly fivefold. The male-to-female ratio declined from 6.3:1 in 1998 to 4.5:1 in 2002. Incidence increased slightly from 0.20% in 1998 to 0.26% in 2002, but appears to have stabilized since 2000 (0.27%).

Figure 1. Duration of use in Dutch children who started stimulant treatment between 2000 and 2002 at the age of 0–4 years (n = 28), 5–9 years (n = 328), 10–14 years (n = 176), or 15–19 years (n = 72).
Children aged 5-14-years at start of stimulant treatment between 2000 and 2002 used stimulants much longer than younger and older children (Figure 1, p=0.001 with 3 df, after combining the 5-14 year olds p<0.001 with 2 df). The probability of stimulant treatment for over one year was 0.53 for the youngest children and 0.63 for the eldest children. For the 5-9 and 10-14-year old children these probabilities were 0.77 and 0.80. The probability of prolonged use for more than two years was about 0.54 for the youngest and oldest age groups and about 0.75 for the 5-14-year olds. No differences in duration of stimulant treatment were found between boys and girls (p=0.49).

More than 99% of the incident users started stimulant treatment with methylphenidate. The mean prescribed daily dose for methylphenidate increased from 22 mg in 1998 to 26 mg in 2002, due to an increased 1st and 3rd quartile. The median remained constant at 20 mg. The mean dose for girls was 23 mg, for boys 25 mg, a difference partly due to the 1st quartile being 5 mg lower in girls than in boys. The median prescribed daily dose increased with age from 10 mg for 0-4-year olds to 30 mg for 15-19-year olds.

**Use of psychotropic co-medication**

Table 2 shows psychotropic co-medication among children using stimulants, except for anticholinergic agents since they were used by less than 0.05%. The percentage of children using stimulants alone declined in the five year study period from 88.0% in 1998 to 85.3% in 2002. With 7.9% of the stimulant users receiving antipsychotics in 2002, antipsychotics are the most frequently co-prescribed psychotropic drugs, significantly more frequent than clonidine, the number two drug. The most often co-prescribed antipsychotic drug is risperidone. Number three of most frequently prescribed co-medications changed from antiepileptics with 1.0% in 1998 to antidepressants with 1.8% in 2002. Note that both co-medication with antidepressants and melatonin have increased significantly.

**Discussion**

The prevalence of stimulant use among children in the Netherlands has increased, mainly due to a long duration of use. The duration of treatment is longer in children starting at the age of 5-14 years than in the other age groups. The 3% increase in psychotropic co-medication among stimulants users could not be attributed to one drug class. Compared to earlier reports in the same population, our results suggest the incidence of stimulant use is leveling off to 0.3% per year [3]. Recent data on prevalence and incidence from South Australia also suggest this phenomenon [9]. The presented decrease in the male-to-female ratio of those being treated with stimulants is consistent with studies from other countries [9,10].
Table 2. Psychotropic co-medication among stimulant-treated children aged 0 through 19 years in 1998 and 2002.

<table>
<thead>
<tr>
<th>Drug group</th>
<th>1998 N</th>
<th>% 95% CI</th>
<th>2002 N</th>
<th>% 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>26</td>
<td>6.3 4.3 – 9.0</td>
<td>73</td>
<td>7.9 6.4 – 9.9</td>
</tr>
<tr>
<td>Clonidine</td>
<td>21</td>
<td>5.1 3.3 – 7.6</td>
<td>29</td>
<td>3.2 2.2 – 4.5</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0</td>
<td>0.0 – 0.9</td>
<td>17</td>
<td>1.8 1.2 – 2.9</td>
</tr>
<tr>
<td>Melatonin</td>
<td>1</td>
<td>0.2 0.0 – 1.4</td>
<td>14</td>
<td>1.5 0.9 – 2.5</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>4</td>
<td>1.0 0.4 – 2.5</td>
<td>10</td>
<td>1.1 0.6 – 2.0</td>
</tr>
<tr>
<td>Hypnotics/anxiolytics</td>
<td>3</td>
<td>0.7 0.2 – 2.1</td>
<td>7</td>
<td>0.8 0.4 – 1.6</td>
</tr>
<tr>
<td>Lithium</td>
<td>1</td>
<td>0.2 0.0 – 1.4</td>
<td>1</td>
<td>0.1 0.0 – 0.6</td>
</tr>
<tr>
<td>Monotherapy stimulants</td>
<td>365</td>
<td>88.0 84.5 – 90.7</td>
<td>783</td>
<td>85.3 82.9 – 87.5</td>
</tr>
<tr>
<td>Any psychotropic co-medication</td>
<td>50</td>
<td>12.0 9.3 – 15.5</td>
<td>136</td>
<td>14.8 12.6 – 17.2</td>
</tr>
<tr>
<td>Total stimulant-treated children</td>
<td>415</td>
<td>100.0</td>
<td>919</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Earlier, a probability of stimulants use for over 20 months of 0.50 was reported [3], whereas in this study this probability has risen to 0.72. These findings emphasize the need for longitudinal studies on long term safety and efficacy.

Psychotropic co-medication among Dutch stimulant-treated children may be regarded low at nearly 15% in 2002. Although recent US data are not available, it is hypothesized that co-medication rates have increased since 1996 when 19% was reported for US youths [1,11]. Co-prescribing with clonidine declined slightly to about 3% of stimulant users in 2002, and reached the level reported for US youths in 1998-1999 [12].

In this study, antipsychotics were the most co-prescribed psychotropic drugs with nearly 6% in 1998 and 8% in 2002, whereas in the USA 1.8% is reported among stimulant-treated youths for 1998-1999 [12]. Conversely, in the USA stimulants are mostly combined with antidepressants [11,12]. This is probably partly due to the fact that the overall prevalence of antidepressant use among American youths is three to four times higher than among Dutch youths [3,13]. Another explanation may be that our database covers the general pediatric population, whilst other studies often report on specific groups, for example Medicaid enrollees.

The IADB covers an open population implying children who moved elsewhere may be wrongly identified as quitters. Also, not all children who moved into the region may be identified as incident users because they started stimulant treatment within one year after entering the database. The impact of these situations is likely to be limited, because of the low mobility in the region, particularly for these age groups.
The design of this study involved a one-week window to identify psychotropic co-medication, in accordance with other researchers [12,14]. Although this method may lead to an underestimation of concomitant drug use, it is less prone to false-positives than one-year prevalences. Indeed, our estimates of concomitant drug use based on one-year prevalence would have been higher, namely 21% for 2002. Note that this 6% increase is much smaller than the threefold increase Martin et al. reported, when widening the one-week window to a three-month window [12].

These data are the first to suggest melatonin has obtained itself a position in the treatment of sleep disorders in stimulant-treated children. We are not aware of any promotional paper or effort in the (Dutch) medical literature with regard to melatonin. Please note that in the Netherlands no activities to promote the use of prescription drugs in the lay press are legally allowed. It would be interesting to study whether the unlicensed use of yet another psychotropic agent is a typical Dutch phenomenon.

Conclusions

The prevalence of stimulant use among children in the Netherlands has increased in recent years, mainly due to the duration of stimulant use. Incidence rates appear to have stabilized. Duration of stimulant treatment is longer in children starting stimulant use at the age of 5-14 years old than in younger and older children. Since 1998, the use of psychotropic co-medication among Dutch stimulant-treated children has moderately increased.

References
