Stimulant treatment in children
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Co-morbidity and patterns of care in stimulant-treated children with ADHD in the Netherlands

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Submitted
Abstract

Objectives
To investigate whether the presence of psychiatric co-morbidity in stimulant-treated children with ADHD was associated with the treatment modalities provided.

Methods
Stimulant users younger than 16 years were detected in 115 pharmacies. After informed consent from the parents and children aged 12 years and older, a questionnaire was sent to the physician currently prescribing stimulants.

Results
Of 773 questionnaires sent to physicians, 556 were returned and suitable for analysis (72%). A diagnosis of ADHD was reported in 510 stimulant-treated children (92%). For 350 of the 510 children with ADHD no other diagnosis was reported (69%), for 53 pervasive developmental disorder (PDD, 10%), for 50 oppositional defiant disorder/conduct disorder (ODD/CD, 10%), and for 57 children co-morbidity other than PDD or ODD/CD was reported (11%). We found an association between the presence of co-morbidity and the use of psychotropic co-medication (overall, p=0.012), antipsychotics (p<0.001) and melatonin (p=0.03). Use of antipsychotics was highest among stimulant-treated children with ADHD+PDD (17%), and melatonin use was highest among children with ADHD+ODD/CD (16%). Co-morbidity was also associated with higher use of non-pharmacological treatment for the child (p<0.001) and for the parents (p<0.001). In the ADHD-only group, 26% did not receive any non-pharmacological treatment, this percentage varied from 8-18% in children with ADHD + co-morbidity.

Conclusions
Stimulant-treated youths with ADHD and psychiatric co-morbidity received more psychotropic co-medication and non-pharmacological treatment than children with ADHD-only. The type of psychotropic co-medication and non-pharmacological treatment received by the children and the parents, depended on the specific co-morbid psychiatric disorder being present.
Co-morbidity and patterns of care

Introduction

Stimulants are first-line pharmacotherapy in the treatment of attention-deficit/hyperactivity disorder (ADHD). The rapid increase of stimulant use among children in the nineties [1-6] has raised concerns about injudicious prescribing of stimulants [1,3,6-9]. In Canada [3] as well as in the USA [9] excessive prescribing of stimulants by GPs was reported, which caused considerable concern and discussion. Also in the Netherlands, the lay media claimed excessive prescribing of stimulants by GPs. However, in a recent survey among parents of stimulant-treated children it was found that stimulant treatment in the Netherlands was mainly initiated by child psychiatrists and pediatricians [10]. Therefore, major concern about GPs frequently starting treatment appeared unnecessary for the Dutch situation.

Another point of concern is the application of stimulant drugs without other forms of treatment, especially since there has been increasing awareness that many children with ADHD also have other co-morbid psychiatric disorders that warrants special consideration in the treatment [11-13]. The few studies examining treatment patterns among children with ADHD and psychiatric co-morbidity originated from the USA. Two of these studies focused primarily on psychotropic pharmacotherapy patterns, and both found a significant association between the use of psychotropic medication and the presence of psychiatric co-morbidity [14,15]. Another study of Robison and co-workers examined the prevalence of single and combination treatment modalities for children with ADHD in relation to co-morbidity [16]. They reported that a larger proportion of children with ADHD without co-morbidity received stimulant medication without additional psychotherapy and/or mental health counseling compared to children with co-morbid disorders. However, psychotropic co-medication was not taken into account in this study.

Reflecting the above, we raised the following questions for the Dutch situation: Is the presence of specific psychiatric co-morbidity associated with the use of specific psychotropic co-medication among stimulant-treated children? Do physicians solely rely on pharmacotherapy or do children and parents also receive non-pharmacological therapies and are these treatment modalities associated with psychiatric co-morbidity? Therefore, we conducted a survey among physicians of a nation-wide sample of stimulant-treated children in the Netherlands, inquiring about the diagnoses made in these children and the non-pharmacological and pharmacological treatments provided in addition to stimulant use.

Methods

The questionnaire survey included only physicians of stimulant-treated children in 2003. To obtain a nationwide sample of stimulant-treated children irrespective of the prescribing
physician, pharmacies were used for detecting stimulant-treated children in their pharmacy information system. Since all prescriptions from medical doctors are entered in the pharmacy information system, regardless of particular health insurance or reimbursement status of the medication, the pharmacy is a reliable source of detecting medication users [17].

In the first three weeks of May 2003, 115 pharmacies located all over the Netherlands detected current users of methylphenidate and dexamphetamine in their information system and sent a questionnaire to the parents or guardians. Current users were defined as children younger than 16 years to whom at least two stimulant prescriptions were dispensed between November 1, 2002 and May 1, 2003, of which at least one prescription was in 2003. At the time of this study, immediate-release methylphenidate tablets and dexamphetamine were available, OROS-methylphenidate tablets became available in the course of 2003. The findings of the parents’ questionnaire were subject of another study and were published elsewhere [10]. For the present study, it was important that the parents’ questionnaire included a request for an informed consent to approach the stimulant prescribing physician. Informed consent was needed from the parents, and also from children if aged 12 years and older. After informed consent was received, a questionnaire and a copy of the informed consent were sent to the physician currently prescribing stimulants for the child. The questionnaire was tested especially for unambiguous wording of the questions, and completeness of the answer categories among five physicians. The resulting questionnaire contained open-ended and multiple choice questions about stimulant treatment, psychiatric diagnoses, co-medication, and several types of non-pharmacological treatment and counseling provided to the child and/or the parents. Behavioral interventions which took a maximum of two hours per week, were classified as non-intensive, whereas intensive training took more than two hours per week. The protocol was approved by the Medical Ethics Board of the University Medical Centre in Groningen. Questionnaires were regarded unsuitable for analysis if the questionnaires were returned blank or in case the physician reported not being the prescriber. A detailed description of the survey design and the response and consent analyses were published elsewhere [18].

Children were classified based on their diagnosis as reported by their physician. Only children diagnosed with ADHD were included in the present study. These children were classified as “ADHD-only” when no other diagnosis was reported, “ADHD + PDD” when pervasive developmental disorder (autistic disorder or PDD-NOS) was reported, “ADHD + ODD/CD” when one of these disruptive behavior disorders was reported, and “ADHD + other co-morbidity” when one or more psychiatric diagnoses other than PDD and ODD/CD were reported. Children with ADHD and both PDD and ODD/CD were excluded from the analysis.
We compared child characteristics and the use of additional therapy in the four diagnostic groups. Pearson Chi Square and one-way ANOVA tests (two-tailed) were used, and a p-value <0.05 was considered statistically significant. All analyses were performed using SPSS 11.0.

Results

The 115 pharmacies sent 1307 questionnaires to parents of stimulant users. Of these, 924 questionnaires (71%) were returned. In 811 of the 924 cases (88%) permission was given to approach the physician, of which 773 contained a valid address. Of the 773 questionnaires sent to physicians, 556 questionnaires were returned (72%). According to the physicians, 512 of the 556 children (92%) were diagnosed with ADHD. Two subjects were diagnosed with ADHD and both PDD and ODD/CD, leaving 510 cases for the present study. Almost half of these questionnaires were filled out by general practitioners (GPs, 47%). Child psychiatrists and pediatricians were responsible for respectively 27% and 23%. The mean age of the stimulant-treated children with ADHD in this study was 10.5 years, and the male-to-female ratio was approximately 5.7:1.

Co-morbidity

Of the 510 stimulant-treated children with ADHD, the physician reported only the diagnosis of ADHD in 69%. For the remaining children, the most frequently reported co-morbidities were PDD (53 children, 10%), ODD/CD (50 children, 9.8%), followed by learning disorder (28 children, 5.5%), mental retardation (22 children, 4.3%), tic disorder (10 children, 2.0%) and anxiety disorder (5 children, 1.0%). Of the 53 children in the PDD group, 49 were diagnosed PDD-NOS and 4 with autistic disorder. Of the 50 children in the ADHD + ODD/CD group, 48 children were diagnosed with ODD and 5 with CD; 3 children were reported to have both ODD and CD. For 57 children (11%) co-morbidity other than PDD or ODD/CD was reported.

Children with co-morbidity, and especially those with PDD were more likely to receive special education than children with ADHD-only (p<0.001, table 1). The type of physician prescribing stimulants was associated with the presence of co-morbidity too (p<0.001). Of the children with ADHD and a co-morbid disorder, 35% received their current stimulant prescriptions from a child psychiatrist, which was almost twice the percentage compared to children with ADHD-only. Stimulant prescriptions for children with ADHD-only, were mostly provided by GPs (54%). In 41% of the children with ADHD-only, stimulant prescribing was
Table 1. Characteristics of stimulant-treated children diagnosed with ADHD-only, ADHD with PDD, ADHD with ODD/CD and ADHD with other psychiatric co-morbidity.

<table>
<thead>
<tr>
<th></th>
<th>ADHD-only (n=350)</th>
<th>ADHD + PDD (n=53)</th>
<th>ADHD + ODD/CD (n=50)</th>
<th>ADHD + other co-morbidity (n=57)</th>
<th>(X^2)-test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>10.5y 350</td>
<td>10.6y 53</td>
<td>10.3y 50</td>
<td>10.4y 57</td>
<td>0.94</td>
</tr>
<tr>
<td>Male</td>
<td>85.7 300</td>
<td>83.0 44</td>
<td>88.0 44</td>
<td>80.7 46</td>
<td>0.69</td>
</tr>
<tr>
<td>Special education</td>
<td>28.2 98</td>
<td>60.4 32</td>
<td>40.0 20</td>
<td>43.9 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time since 1st prescription</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>22.3 78</td>
<td>15.1 8</td>
<td>16.0 8</td>
<td>26.3 15</td>
<td>0.42</td>
</tr>
<tr>
<td>1-2 years</td>
<td>18.3 64</td>
<td>18.9 10</td>
<td>28.0 14</td>
<td>21.1 12</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>58.0 203</td>
<td>62.3 33</td>
<td>52.0 26</td>
<td>52.6 30</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1.4 5</td>
<td>3.8 2</td>
<td>4.0 2</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td>Current prescriber stimulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GP</td>
<td>54.3 190</td>
<td>34.0 18</td>
<td>26.0 13</td>
<td>26.3 15</td>
<td></td>
</tr>
<tr>
<td>Pediatrician</td>
<td>22.6 79</td>
<td>24.5 13</td>
<td>16.0 8</td>
<td>31.6 18</td>
<td></td>
</tr>
<tr>
<td>Child psychiatrist</td>
<td>19.7 69</td>
<td>41.5 22</td>
<td>56.0 28</td>
<td>35.1 20</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.6 9</td>
<td>0 0</td>
<td>2.0 1</td>
<td>7.0 4</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0.9 3</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td></td>
</tr>
</tbody>
</table>
transferred from a child psychiatrist or pediatrician to a GP after initiation of treatment. For children with co-morbid PDD, ODD/CD or another psychiatric disorder this percentage was lower, respectively 30%, 18% and 23% (p<0.01, data not shown). No relation was found between the presence of co-morbidity and the factors age, gender, and time since first stimulant prescription (p≥0.42).

Additional therapy
We found an association between the presence of co-morbidity and the overall use of psychotropic co-medication (p=0.012, table 2). Use of psychotropic co-medication was most prevalent among stimulant-treated children with ADHD + PDD with 36%, which was twice as high compared to children in the ADHD-only group and ADHD + other co-morbidity group (both 18%). The use of antipsychotics (p<0.001) and melatonin (p=0.03) was significantly associated with the presence of co-morbidity. Antipsychotics use was most prevalent among stimulant-treated children with ADHD + PDD with 17%, compared to about 3% in the ADHD-only group. The frequency of melatonin use was highest among children with ADHD + ODD/CD (16%) and lowest among children with ADHD and a co-morbid disorder other than PDD or ODD/CD (7%). Clonidine, antiepileptics, antidepressants and hypnotics/anxiolytics were not frequently used as co-medication.

Co-morbidity was associated with both higher use of non-pharmacological treatment for the child (overall, p<0.001) and counseling for the parents (overall, p<0.001, table 2). Non-pharmacological treatment was received by at least 74% of the children with ADHD and psychiatric co-morbidity, significantly more than the 54% in the ADHD-only group. Children with co-morbid PDD or ODD/CD received more intensive training and day treatment than the other children and were also more often treated in an inpatient clinic. Regardless of the type of counseling, counseling was most frequently offered to parents of children with ADHD + PDD or ODD/CD. Home training was especially applied when a PDD diagnosis was present, as it was applied in 23% of these families, and no more than 10% of the other families. Of the children in the ADHD-only group, 26% did not receive any non-pharmacological treatment, nor did their parents receive any counseling (data not shown). This percentage was 18% in the ADHD + other co-morbidity group, 10% in the ADHD + ODD/CD group and 8% in the ADHD + PDD group.
Table 2. Characteristics of additional treatment among stimulant-treated children diagnosed with ADHD-only, ADHD with PDD, ADHD with ODD/CD and ADHD with other psychiatric co-morbidity.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>ADHD-only (n=350)</th>
<th>ADHD + PDD (n=53)</th>
<th>ADHD+ODD/CD (n=50)</th>
<th>ADHD + other co-morbidity (n=57)</th>
<th>(\chi^2)-test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotropic co-medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>18.0</td>
<td>35.8</td>
<td>28.0</td>
<td>17.5</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>11.7</td>
<td>13.2</td>
<td>16.0</td>
<td>7.0</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>3.1</td>
<td>17.0</td>
<td>10.0</td>
<td>8.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>0.9</td>
<td>3.8</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0.3</td>
<td>1.9</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hypnotics/anxiolytics</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Non-pharmacological treatment child</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-intensive training</td>
<td>54.0</td>
<td>77.4</td>
<td>74.0</td>
<td>73.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>30.9</td>
<td>24.5</td>
<td>34.0</td>
<td>31.6</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>17.7</td>
<td>30.2</td>
<td>20.0</td>
<td>31.6</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Intensive training</td>
<td>4.3</td>
<td>11.3</td>
<td>2.0</td>
<td>1.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Day treatment</td>
<td>7.7</td>
<td>32.1</td>
<td>28.0</td>
<td>7.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Inpatient treatment</td>
<td>6.3</td>
<td>30.2</td>
<td>22.0</td>
<td>12.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Counseling parents - any</td>
<td>3.1</td>
<td>17.0</td>
<td>22.0</td>
<td>5.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Individual parent training</td>
<td>63.7</td>
<td>88.7</td>
<td>84.0</td>
<td>63.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Group-based parent training</td>
<td>55.1</td>
<td>77.4</td>
<td>80.0</td>
<td>59.6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Home training</td>
<td>8.3</td>
<td>17.0</td>
<td>14.0</td>
<td>1.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other training/course</td>
<td>8.0</td>
<td>22.6</td>
<td>10.0</td>
<td>7.0</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

- \(\chi^2\)-square not valid due to small numbers
Discussion

This study among prescribers of stimulant-treated youths with ADHD in the Netherlands showed that children with co-morbid psychiatric disorders received more psychotropic co-medication and non-pharmacological treatment than children with ADHD-only. The type of psychotropic co-medication and non-pharmacological treatment received, depended on the co-morbid disorder.

Co-morbidity

For 31% of cases psychiatric co-morbidity was reported in this sample of stimulant-treated children with ADHD, which is rather low. Other studies reported co-morbidity percentages ranging from 44% in community-derived samples to 87% in clinically referred children diagnosed with ADHD [19]. In particular, the presence of ODD/CD in our study (10%) was very low compared to e.g. the 50-60% reported by Gillberg [11]. These low co-morbidity figures may be partially explained by underdiagnosis of psychiatric disorders because not all children in our study were thoroughly screened by child psychiatrists. Another possibility is that physicians were inclined to report only a diagnosis that would fit the indication for stimulants, since stimulant use was the entry point for this study. Two studies from the USA reported that children with ADHD and psychiatric co-morbidity were less likely to use stimulants [14,15]. This may also be an explanation for the lower percentage of co-morbidity in our sample with stimulant-treated children with ADHD.

PDD as the most frequently mentioned co-morbid disorder, warrants special attention. Within the DSM-IV classification system, ADHD and PDD are exclusionary diagnoses, and therefore it is impossible to give a PDD and an ADHD classification to the same patient. There has been increasing debate about this issue [20-24]. The general point of the critics of the exclusionary criterion, is that the overlap in clinical symptoms between ADHD and PDD is evident in practice, and removing the exclusionary criteria may be beneficial for stimulating research and optimizing treatment in these children [20-24]. Obviously, many clinicians in the Netherlands apparently have dropped the DSM-IV exclusionary criterion in clinical practice.

Although most children in our study have been using stimulants for over 2 years, the majority of the children with co-morbidity still received their stimulant prescriptions from a specialist. In case of ADHD-only, prescribing responsibility was more often transferred to the GP.
Additional therapy

We found a significant association between the presence of psychiatric co-morbidity and the use of psychotropic co-medication among stimulant-treated children with ADHD. This is in line with the few earlier reports from the USA [14,15]. Where Radigan et al. reported an increased use of alpha agonists, antipsychotics, antidepressants, antiepileptics and anxiolytics among Medicaid children with ADHD and a co-morbid psychiatric disorder [15], we found an increased use of antipsychotics and melatonin. Part of this difference may be explained by the fact that the two US studies found that children with ADHD and a psychiatric co-morbidity were more likely to use non-stimulants only [14,15], whereas children without stimulants were not part of our study population. The difference may also be explained by different prescribing practices.

The more frequent use of antipsychotics among children with ADHD and PDD, may be understood as confirmation that the presence of PDD symptoms in children with ADHD has significant practical implications for treatment. After all, several studies have reported a positive effect of antipsychotics in reducing aggressive behavior in children with PDD and disruptive behavior disorders [25-27].

In contrast to reports from the USA, we found antipsychotics to be the most prevalent co-medication instead of anti-depressants. In our study co-medication with antidepressants was reported in less than 2%, compared to 4% to 7% in the USA [4,28,29]. This lower use of anti-depressants may partly be explained by the lower male-to-female ratio in these American studies and differences in timing of the study periods, but is probably more likely to be explained by cross cultural differences in medical practice, including the attention paid to internalizing versus externalizing disorders.

Although melatonin is not a registered drug in the Netherlands, more than 11% of the stimulant-treated children used melatonin. The frequent use of melatonin in our study among children with ODD/CD could be explained by the more frequent difficulties regarding sleep routines in this group [30].

In this study stimulant-treated children with ADHD + co-morbidity and their parents had received considerable more treatment modalities than children with ADHD-only. This supports findings from the USA showing that children with ADHD and psychiatric co-morbidity were more likely to use mental health care services in addition to medication [14,16]. However, as in our study, a substantial portion of the children did not receive additional mental health care. Many guidelines such as the international consensus statement by Kutcher et al. [12], treatment of children with ADHD and co-morbid disruptive behavior disorders ought to consist of psychosocial interventions combined with pharmacotherapy. This statement is supported by recent evidence reporting a higher...
efficacy of multimodal interventions in case of ADHD and co-morbid disorders [31]. In our study, about 90% of the ADHD + ODD/CD and ADHD + PDD children received or had received multimodal interventions. One could conclude that some children with ADHD + co-morbidity and even more with ADHD-only, do respond adequately to pharmacological treatment only. But it is plausible that some children of the 18% to 26% with ADHD-only or ADHD + other co-morbidity did not receive optimal treatment by receiving pharmacotherapy only. Especially since other research from the Netherlands showed that almost 20% of the stimulant-treated youths were not monitored [10].

Limitations
Our study investigated the association between psychiatric co-morbidity and patterns of care according to the prescribing physicians of stimulant-treated children in the Netherlands. Hence, children with ADHD who did not receive stimulants were not included in our study and therefore the findings of our study cannot be generalized to all children with ADHD. This is even more so for children with ADHD and co-morbidities (especially PDD) because the chance of success with stimulants is less in those groups [24]. Another limitation of our study is that no information was available on how children were assessed, so no statements could be made about the appropriateness or the relative weight of the diagnoses. Because our study is an descriptive analysis of current practice in the Netherlands, our data also cannot address the appropriateness or effectiveness of the provided treatment.

Although the recruitment of children and their physicians may be unconventional, the median age and male-to-female ratio were very similar to those reported in other studies in children identified with ADHD [3,6,32]. Our two-step recruitment procedure implied, however, that physicians in our study could only be approached if the responding parents and child gave their consent, which may have led to selection bias. No association was found between giving consent and the child’s age, gender or the type of prescribing physician, but physician response rate differed significantly for the type of prescribing physician, being highest for pediatricians (83%) and lowest for child psychiatrists (62%) [18]. Since child psychiatrists probably see more complex cases of ADHD than pediatricians and GPs, this may have led to an underestimation of the presence of psychiatric co-morbidity.

Conclusions
Stimulant-treated youths with ADHD and psychiatric co-morbidity received more psychotropic co-medication and non-pharmacological treatment than children with ADHD-only. The type of psychotropic co-medication and non-pharmacological treatment received
by the children and the parents, depended on the specific co-morbid psychiatric disorder being present. So, it seems that some tailoring of treatment seems to take place in clinical practice. Whether this reflects what is known about the effectiveness of multimodal treatment for children with ADHD and co-morbidity is unknown and might be subject for further research. Also, the efficacy and safety of combining stimulants and antipsychotics in the treatment of children with both ADHD and PDD symptoms and the frequent use of the unlicensed drug melatonin warrants close attention.

Acknowledgments

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References


