Stimulant treatment in children
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Use of double-blind, placebo-controlled N-of-1 trials among stimulant-treated youths in The Netherlands: A descriptive study

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Submitted
Abstract

Objectives
An N-of-1 trial is a double-blind, placebo-controlled, randomized trial to objectively and systematically evaluate the individual's response. This approach seems extraordinarily suitable for assessing the efficacy of stimulants in ADHD treatment. The aim is to examine the use of N-of-1 trials among youths in the Netherlands, the protocols used, and the continuation of stimulant treatment thereafter.

Methods
Physicians requesting N-of-1 trials with stimulants were interviewed about their rationale and protocol. Prevalence and continuation were investigated by extracting N-of-1 trials among youths <20 years for 2000-2004 from a large pharmacy dispensing database.

Results
Physicians mentioned as main purpose of N-of-1 trials assessing individuals’ response and dose-finding. Trial length, dosing schedule and efficacy assessment differed per physician. The annual percentage of youths starting stimulant treatment with an N-of-1 trial, fluctuated between 0.6% (3/462) and 3.3% (10/301). No statistical significant difference could be detected between continuation of stimulant treatment with and without an N-of-1 trial (p=0.71).

Conclusions
N-of-1 trials with stimulants are infrequently and not optimally used in the Netherlands. More uniformity in the protocols would make it easier to encompass the N-of-1 methodology in physicians’ daily practice.
Introduction

In many Western countries the use of stimulants among youths has increased markedly in the last decade [1-4]. Stimulants are the first-choice medication in the treatment of attention-deficit/hyperactivity disorder (ADHD). In 70-80% of the youths, stimulants reduce hyperactivity, impulsiveness and inattentiveness [5]. ADHD was once thought to disappear as children grew up, but follow-up studies in youths with ADHD have shown considerable persistence of the disorder into adulthood [6,7]. For these patients long-term treatment with stimulants may be indicated. The impact of long-term stimulant use, however, is still unclear [8].

As up to 20% of youths will not respond to stimulant treatment [5], it is important to evaluate the effect of stimulant treatment in the individual child in an early stage of treatment. A useful method that helps the physician and family to evaluate the effect of medication in individuals is the N-of-1 or single subject trial [9,10]. An N-of-1 trial is a double-blind, placebo-controlled randomized trial to objectively and systematically assess individual response. In an N-of-1 trial, a single patient undergoes a series of crossover trials with active treatment/placebo, high dose/low dose or first choice/alternative treatment. The order of administration is determined by random allocation and the patient and physician are blinded for the treatment order. Target symptoms are assessed and interpreted afterwards. The N-of-1 methodology is not suitable for all disorders and pharmacological treatments. Apart from the benefit-risk balance of the treatment being in doubt, the disorder should be chronic and relatively stable. Furthermore, treatment must have a rapid onset and termination of action, ruling out carry-over effect into the next treatment block.

An N-of-1 trial seems ideal for evaluating the efficacy of the stimulant methylphenidate in youths diagnosed with ADHD. First, ADHD is considered a chronic disorder nowadays, showing rather consistent symptoms. Second, methylphenidate has a rapid onset (1/2 -1 hours) and termination of action (4-6 hours) [11]. Furthermore, rational evaluation of behavior is hard, and the placebo-controlled, double-blind design enables a more objective evaluation of behavioral changes due to medication [9].

Several papers on stimulant treatment making use of the N-of-1 methodology have been published. The methodology was used for dose-finding and evaluation of side effects in several clinical trials on stimulant treatment in youths with ADHD [12-14], however, in these papers the N-of-1 methodology received no further attention. Parental acceptance, satisfaction and compliance of methylphenidate treatment after an N-of-1 trial were investigated by Johnston and Fine [15]. Other studies illustrated how N-of-1 trials with methylphenidate can be used in routine clinical practice [16,17] and Kent et al. promoted the technique as practical, useful and highly endorsed by families [18]. Furthermore, in the
literature several suggestions have been proposed to enhance reliable and unbiased interpretation of the effect of medication, such as assigning consistent raters, tailoring the outcome measures, blind evaluation of trial outcome and the use of statistical tests [9,19,20].

Most studies on the use of N-of-1 trials in stimulant treatment in clinical practice were limited to single clinics in North America [15-18]. As far as we know, no research has been done to examine the use of N-of-1 trials with stimulants in the general pediatric population. In this study we examined the occurrence of N-of-1 trials when starting stimulant treatment in The Netherlands, and interviewed physicians about their protocols. Using this information, we derived the proportion of stimulant treatments starting with an N-of-1 trial, and the continuation of stimulant treatment using pharmacy data.

Methods

The data sources used were: physicians and a large pharmacy dispensing database.

Physicians’ interviews
To reach physicians conducting N-of-1 trials with stimulants for an interview, a brief questionnaire was sent to 102 randomly selected pharmacies. Pharmacists play an essential role in performing an N-of-1 trial, because they prepare the blinded stimulant and placebo capsules. Pharmacists were asked if they had provided an N-of-1 trial with stimulants in the past year. If so, pharmacists were asked for names of physicians who had requested an N-of-1 trial. Physicians then, were called to ask to participate in an interview. The questions asked were about considerations to use the N-of-1 method in stimulant treatment and details of the protocols used. During the interview, the physicians were given ample opportunity to provide additional information about their N-of-1 method. Information about these protocols was used to identify N-of-1 trials in the database part of the study. During the major part of the study period short-acting methylphenidate and dexamphetamine were the available and reimbursed stimulants on the Dutch market. Long-acting methylphenidate became available without regular reimbursement at the end of 2003.

Database study
The quantitative part of this study was performed with the InterAction database (IADB), which contains prescription drug dispensing data from about 50 community pharmacies in the northern and eastern part of the Netherlands. The IADB covers all prescriptions from an estimated population of approximately 450,000 since 1999 [21,22]. This database includes
all prescriptions, regardless of prescriber, insurance, or reimbursement status, apart from over-the-counter drugs and drugs dispensed during a hospital stay. Each prescription record comprises information about the drug, date of dispensing, amount dispensed, dose regimen and the prescribing physician. All drugs are coded according to ATC-classification. Each patient has a unique, though anonymous, identifier. Due to a high patient-pharmacy commitment in the Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete [23].

From the IADB we derived a study population of all incident stimulant users aged 0-19 years with a first-time prescription of stimulants dispensed during 2000-2004. Youths were regarded as incident users if they received a stimulant prescription, without any stimulant prescription in the year before, while being registered in the IADB. Data from 1999 were used to identify incident users in 2000.

Based on information on the N-of-1 protocols from the physician interviews, potential N-of-1 trials were defined as dispensation of compounded stimulant capsules and other compounded capsules to a person in the same pharmacy within a time frame of a month. Medication profiles of 10 selected patients from the IADB receiving a potential N-of-1 trial with stimulants were presented to four pharmacists. Within this group, consensus was quickly reached about what could be considered an N-of-1 trial at the start of stimulant treatment. Criteria were: (1) dispensation of compounded methylphenidate capsules and placebo capsules with inert excipients like lactose powder or corn starch only, (2) within a time frame of two weeks (3) to one person (4) in the same pharmacy. From the medication profiles of the incident stimulant users in the IADB, N-of-1 trials with methylphenidate were extracted using the criteria above. Of the initially 46 potential N-of-1 trials detected, 31 satisfied all four criteria. All 15 excluded cases received compounded capsules with adjunct medication besides stimulant capsules and had received no placebo capsules.

The percentage of incident users starting stimulant treatment with an N-of-1 trial per total number of incident stimulant users was estimated per year. Confidence intervals (95%) were calculated according to the Exact method [24]. Continuation of stimulant treatment after an N-of-1 trial was compared to other starters using Kaplan-Meier survival estimators. Stimulant treatment was considered discontinued when a youth had not received stimulant prescriptions for at least 365 consecutive days after the dispersion date of the final prescription plus half the number of days of the final prescription. 95% Confidence intervals were calculated for the continuation probability after 5 weeks [25]. A log-rank test was used to test for overall differences in the continuation of therapy between starting treatment with and without an N-of-1 trial. Statistical tests were considered significant when p< 0.05 (two-tailed).
Table 1. Interview questions and answers from physicians (n=12) performing N-of-1 trials with methylphenidate.

<table>
<thead>
<tr>
<th>Question</th>
<th>No. physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>When do you offer an N-of-1 trial?</td>
<td></td>
</tr>
<tr>
<td>- Customary procedure if stimulant treatment is considered</td>
<td>8</td>
</tr>
<tr>
<td>- If stimulant treatment is considered, but not as a customary procedure</td>
<td>3</td>
</tr>
<tr>
<td>- Customary procedure if stimulant treatment is considered and also for evaluation of treatment</td>
<td>1</td>
</tr>
<tr>
<td>For what purpose do you use an N-of-1 trial with stimulants?</td>
<td></td>
</tr>
<tr>
<td>- Assessing effectiveness and optimal dose methylphenidate</td>
<td>8</td>
</tr>
<tr>
<td>- Assessing effectiveness</td>
<td>3</td>
</tr>
<tr>
<td>- To convince parents who are reluctant to stimulant treatment</td>
<td>1</td>
</tr>
<tr>
<td>Which dosing schedule do you apply?</td>
<td></td>
</tr>
<tr>
<td>- 4 blocks of 1 week, comparing placebo and 3 different dosages methylphenidate</td>
<td>5</td>
</tr>
<tr>
<td>- 4 blocks of 1 week, comparing placebo and 2 different dosages methylphenidate</td>
<td>4</td>
</tr>
<tr>
<td>- 4 blocks of 1 week, comparing placebo and 1 dosage methylphenidate</td>
<td>1</td>
</tr>
<tr>
<td>- 2 blocks of 1 week, comparing placebo and 1 dosage methylphenidate</td>
<td>1</td>
</tr>
<tr>
<td>- 4 blocks of 2 weeks, comparing placebo and 1 dosage methylphenidate</td>
<td>1</td>
</tr>
<tr>
<td>What is the frequency of dosing during a trial day?</td>
<td></td>
</tr>
<tr>
<td>- 2 x per day</td>
<td>11</td>
</tr>
<tr>
<td>- 2 or 3 x per day</td>
<td>1</td>
</tr>
<tr>
<td>How are target symptoms assessed during the trial? Use of</td>
<td></td>
</tr>
<tr>
<td>- Abbreviated Conners' rating scale</td>
<td>8</td>
</tr>
<tr>
<td>- Score list (self-made)</td>
<td>2</td>
</tr>
<tr>
<td>- DSM IV criteria</td>
<td>1</td>
</tr>
<tr>
<td>- Diary</td>
<td>1</td>
</tr>
<tr>
<td>How often are target symptoms assessed during the trial?</td>
<td></td>
</tr>
<tr>
<td>- Daily</td>
<td>6</td>
</tr>
<tr>
<td>- Weekly</td>
<td>5</td>
</tr>
<tr>
<td>- Minimal on 2 weekdays and during the weekend</td>
<td>1</td>
</tr>
<tr>
<td>Do you use an adverse effects questionnaire?</td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>9</td>
</tr>
<tr>
<td>- Yes</td>
<td>3</td>
</tr>
<tr>
<td>Do you use statistical tests to interpret the outcome of the trial?</td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>12</td>
</tr>
</tbody>
</table>
Use of N-of-1 trials

Results

Physicians’ interviews
Of 102 pharmacists to whom a questionnaire was sent, 51 responded of whom 24 pharmacists were able to mention names of 14 physicians requesting an N-of-1 trial in the past year. The 9 remaining pharmacists were unwilling or unable to give a name (e.g. only institute name available or physician moved office). Fourteen physicians were approached for an interview. One child psychiatrist and one pediatrician were not willing to participate due to busy schedules. The remaining 12 physicians were interviewed; 7 child psychiatrists, 1 adult psychiatrist, 2 pediatricians, 1 youth health care physician and one family doctor.

Eight physicians (8/12 or 67%) perceived the N-of-1 methodology as a customary procedure when stimulant treatment was considered (Table 1). One physician also used the method to evaluate continuation of stimulant treatment. The main purpose for conducting an N-of-1 trial was assessing individuals’ response to stimulants and examining the optimal dose for most of the interviewed physicians. All physicians used a double-blind, placebo-controlled trial in which the pharmacist was responsible for the randomization and for preparing the blinded methylphenidate and placebo capsules. No protocol was the same, as trial length, dosing schedule and the frequency of rating outcome differed per protocol. According to most protocols the parents and teacher of the child assessed target symptoms during the trial, and scores were visually evaluated afterwards. The abbreviated Conners’ parent and teacher rating scales were used for measuring outcome by 8 of 12 physicians (67%). Adverse effects were assessed and evaluated in 3 of the 12 protocols (25%).

Database study
Using the pharmacy database IADB, a total of 1769 youths starting treatment with stimulants in the period 2000-2004 were detected. The median age was 9 years and the male-to-female ratio among these starters was 3.4:1. The percentage starting treatment with an N-of-1 trial with methylphenidate, fluctuated between 0.6% (3/462) and 3.3% (10/301) per year during 2000-2004 (Table 2).

Table 2. Prevalence of starting stimulant treatment in youths < 20 years with an N-of-1 trial in the period 2000 to 2004.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of starters</th>
<th>No. starting with N-of-1 trial</th>
<th>% Starting with N-of-1 trial</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>313</td>
<td>6</td>
<td>1.9</td>
<td>0.7 - 1.4</td>
</tr>
<tr>
<td>2001</td>
<td>301</td>
<td>10</td>
<td>3.3</td>
<td>1.6 - 6.0</td>
</tr>
<tr>
<td>2002</td>
<td>313</td>
<td>3</td>
<td>1.0</td>
<td>0.2 - 2.8</td>
</tr>
<tr>
<td>2003</td>
<td>380</td>
<td>9</td>
<td>2.4</td>
<td>1.1 - 4.4</td>
</tr>
<tr>
<td>2004</td>
<td>462</td>
<td>3</td>
<td>0.6</td>
<td>0.1 - 1.9</td>
</tr>
</tbody>
</table>
The median age in youths starting stimulant treatment with an N-of-1 trial was not statistically different from other starters (for both groups 9.0 years, p=0.84). The male-to-female ratio among youths starting stimulant treatment with an N-of-1 trial was 4.2:1 and did not differ statistically significantly from the male-to-female ratio in other starters (3.4:1, p=0.64). After 5 weeks, the cumulative probability of continuation of stimulant treatment was 0.89 (95%CI 0.77-1.0) among youths starting with an N-of-1 trial and 0.89 (95%CI 0.87-0.91) for other starters (Figure 1). Also, no overall statistically significant difference could be detected between continuation of stimulant treatment in youths starting with an N-of-1 trial and the other starters (p=0.71, 1df).

![Figure 1. Continuation of stimulant treatment in youths <20 years, who started stimulant treatment in 2000-2003 without an N-of-1 trial (A: n=1279) and with an N-of-1 trial (B: n=28, including 95% CI) (UL = upper limit 95% confidence interval, LL = lower limit 95% confidence interval).](image)

Discussion

Two thirds of the responding Dutch pharmacists had provided an N-of-1 trial with stimulants in the last year. Usually, requests came from child psychiatrists or pediatricians who used the N-of-1 methodology for determining individuals’ response and dose-finding, and each of these physicians used his or her own protocol.
Similar to other studies, we found assessing individuals’ response and dose-finding were the main purposes for physicians to apply an N-of-1 trial [15,16,18]. Other reasons mentioned in the literature were discouraging both overenthusiastic prescribing or a prior rejection of stimulant therapy [16], and positively influencing parents’ views regarding the acceptability of methylphenidate [15]. The latter was reported by one physician in our study, who performed an N-of-1 trial only in a case parents were reluctant to stimulant treatment.

Although none of the Dutch physicians followed exactly the same N-of-1 procedure, most of the N-of-1 procedures were roughly similar to the ones used in outpatient clinics in Canada [15,16,18]. Mostly placebo and methylphenidate blocks of 1 week were used, different methylphenidate doses were compared and Conners rating scales were used to measure effectiveness. However, trial length was 3 weeks in the Canadian centers, while 4 weeks was most commonly found in our study. In two other North American studies among institutionalized youths with ADHD, placebo and methylphenidate treatment blocks were shorter, as randomization took place per day or per 4 days, resulting in a trial length of 6-16 days [16,20]. Probably in our community setting and in the Canadian outpatient clinics, blocks of 1 week were chosen because shorter treatment blocks were difficult to implement in an outpatient setting.

The frequency of measuring outcome during an N-of-1 trial varied between daily to weekly ratings in our study, a variation also found in the literature [15,16,18,20]. We would prefer daily outcome measurements, because in that manner day-to-day variation in ADHD symptoms and treatment effect (caused by multiple factors) will be represented, something that will be ignored when rating only once a week. After all, it may be hard to give a well-considered overall judgment of behavior at the end of a treatment block of seven days.

All physicians evaluated the trial outcome measurements by visual inspection. A study by Wallace and Koefoed showed that visual inspection resulted in a greater likelihood of falsely accepting a treatment as effective, than would be generally acceptable by a statistical inspection [20]. However, adjunct statistical evaluation of N-of-1 trials is possible though very cumbersome [9,10,19].

The database part of the study showed that the proportion of youths starting stimulant treatment with an N-of-1 trial ranged from 0.6% to 3.3% per year. No statistically significant difference could be detected between the continuation curves of stimulant treatment after starting with and without an N-of-1 trial. One would expect a steeper curve when N-of-1 trials were mainly used to discourage overenthusiastic prescribing [16]. Analogously, one would expect a less steep curve when N-of-1 trials were predominantly used to convince reluctant parents [15,16]. However, the vast majority of the interviewed physicians in the current study did not mention these reasons for conducting an N-of-1 trial. Moreover, the number of
youths starting stimulant treatment with an N-of-1 trial was probably too small to detect difference, if any.

The presented study has certain limitations that need to be taken into account. For the first part of the study we used pharmacies as a starting point for our search for physicians performing N-of-1 trials with stimulants. Therefore, no estimations could be made about the proportion of child psychiatrists and pediatricians in the Netherlands actually using the N-of-1 methodology. There are two forms of ‘non-response’ in this study. Firstly, 50% of the pharmacists responded. Although this is not a high percentage, still all regions were represented. The other source of being unable to approach physicians is that nine pharmacists were unable or unwilling to give names of physicians for us to interview. However, we think we covered most of the different aspects of N-of-1 trials procedures, because no new information was obtained after the tenth interview.

To detect N-of-1 trials with stimulants in our database, inclusion criteria were formulated based on a consensus discussion with pharmacists, which may have lead to an underestimation of the proportion of stimulant treatments starting with an N-of-1 trial in theory. The chosen time frame of maximally 2 weeks between dispensation of compounded methylphenidate capsules and placebo capsules was chosen because none of the interviewed physicians used treatment blocks longer than 2 weeks. To investigate the effect of this time window we repeated the selection of N-of-1 trials using a time frame of 3 weeks. This increased time frame lead to inclusion of other compounded capsules with adjunct medication (e.g. melatonin, risperidon, olanzapin, lithium) and did not lead to the detection of any additional N-of-1 trial meeting the criteria.

An N-of-1 trial can be a useful tool in deciding whether a stimulant treatment is a suitable treatment for the individual patient [15-18,20]. Moreover, we think that a well-conducted N-of-1 trial is more ethically acceptable than the usual trial of therapy because an N-of-1 trial is a systematic, double-blind and placebo-controlled evaluation. This is especially the case as a significant proportion of the 20-30% non-responders are expected to experience adverse effects [5]. The advantage of an N-of-1 trial over the usual titration is that youth, parents and physicians are blinded, which enhances the objective rating of behavior changes. Also youth and parents are more actively involved in the decision-making process. It has been shown that parents were more satisfied with their child’s treatment after participating in an N-of-1 trial than after a normal trial of therapy, although rates of compliance did not differ after 6-week and 3-month follow-up [15]. We think the use of an N-of-1 trial before stimulant treatment should be encouraged in clinical practice. More uniformity in the protocols used would make it easier for physicians to encompass the N-of-1
Use of N-of-1 trials in their daily practice. More uniformity in N-of-1 protocols is also helpful in making ready-for-use statistical tests easily available to the physician.

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