Homeopathy (2007) 96, 35–41
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doi:10.1016/j.homp.2006.11.004, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Randomised controlled trials of homeopathy in hyperactive children: treatment procedure leads to an unconventional study design

Experience with open-label homeopathic treatment preceding the Swiss ADHD placebo controlled, randomised, double-blind, cross-over trial

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Background: **Treatment of patients with attention deficit hyperactivity disorder (ADHD) with homeopathy is difficult. The Swiss randomised, placebo controlled, cross-over trial in ADHD patients (Swiss ADHD trial) was designed with an open-label screening phase prior to the randomised controlled phase. During the screening phase, the response of each child to successive homeopathic medications was observed until the optimal medication was identified. Only children who reached a predefined level of improvement participated in the randomised, cross-over phase. Although the randomised phase revealed a significant beneficial effect of homeopathy, the cross-over caused a strong carryover effect diminishing the apparent difference between placebo and verum treatment.**

Methods: **This retrospective analysis explores the screening phase data with respect to the risk of failure to demonstrate a specific effect of a randomised controlled trial (RCT) with randomisation at the start of the treatment.**

Results: **During the screening phase, 84% (70/83) of the children responded to treatment and reached eligibility for the randomised trial after a median time of 5 months (range 1–18), with a median of 3 different medications (range 1–9). Thirteen children (16%) did not reach eligibility. Five months after treatment start, the difference in Conners Global Index (CGI) rating between responders and non-responders became highly significant ($p = 0.0006$). Improvement in CGI was much greater following the identification of the optimal medication than in the preceding suboptimal treatment period ($p < 0.0001$).**

Conclusions: **Because of the necessity of identifying an optimal medication before response to treatment can be expected, randomisation at the start of treatment in an RCT of homeopathy in ADHD children has a high risk of failure to demonstrate a specific treatment effect, if the observation time is shorter than 12 months.** *Homeopathy* (2007) **96,** 35–41.

Keywords: ADHD; homeopathy; RCT; timing of randomisation; trial duration

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Received 21 September 2006; revised 2 November 2006; accepted 6 November 2006

Introduction

The attention deficit disorder is a combination of disturbed attention (visual, tactile, auditory and proprioceptive) and hyperactivity/impulsivity or passivity (ADHD/ADD). Diagnostic criteria for the disorder are six or more symptoms of either inattention, hyperactivity/impulsivity, or both.[1] ADHD is one of the most common disorders of childhood, occurring in 3–5% of children, with male to female ratios ranging from 3:1 to 9:1.[2] Common medical treatments include stimulants, such as methylphenidate (MPD, Ritalin®). Parents who do not want such medication for their child increasingly seek homeopathic alternatives.[3,4] Treating ADHD with homeopathy is a most demanding task. It often takes a long time to identify the specific medication that corresponds to the symptoms of the individual patient. Frequently parents find it very difficult to describe the symptoms of their child, a fact that is probably related to their extreme changeability. The initial phase of treatment is, therefore, often characterised by the use of different medications until the optimal treatment for each child is identified. For this reason a controlled study with randomisation at treatment start, was considered impossible for the Swiss ADHD trial. Instead we chose an approach in which children received an open-label treatment in a screening-phase until they had reached a predefined level of improvement. They then entered the parallel group, randomised, double-blind, placebo controlled cross-over trial. The double-blind part of the study consisted of two groups of children who received either verum for 6 weeks followed by placebo for 6 weeks, or placebo for 6 weeks followed by verum for 6 weeks. This procedure enabled us to find an appropriate treatment for each patient before they entered the double-blind study. Another advantage was that all patients were treated with verum during the trial, which facilitated patient recruitment. Prior to study start, the protocol was approved by the ethics committee of the Canton of Berne and Swissmedic, and written informed consent was obtained from the parents of each child.

The data from the randomised, double-blind phase of the trial have been published.[5] A significant difference between placebo and verum treatment was revealed, showing that the effects of homeopathy are specific and cannot be attributed to placebo. However, because all the children were treated with verum prior to enrolment into the cross-over trial, two problems were encountered. One was a strong carry-over effect: from the beginning of the open-label treatment to reaching randomisation eligibility the intensity of the ADHD symptoms, as indicated by the parent-rated Conners Global Index (CGI),[6] decreased by 11 points, while the relapse in the double-blind placebo period of the randomised controlled phase was only 4 points (ie a 'carryover' of 64% of the homeopathic treatment effect). The second problem was an unexpected rise in the CGI in the verum group during the first cross-over period. We attributed this to the parents' expectation that their child would receive placebo during this period. These two problems reduced the difference between placebo and verum, and hence the size of the apparent treatment effect; in a RCT with randomisation at treatment start and no open label run-in these problems would have been avoided.

Jacobs *et al*[7] have recently published the results of a randomised, placebo controlled, double-blind, pilot trial of homeopathic treatment in 43 children with ADHD. In contrast to our study, these patients were assigned to homeopathic medication or placebo at treatment start without an open label run-in. After a follow-up of 18 weeks, no significant differences between the two treatment arms were observed. Instead, a small but significant reduction in the parent-rated CGI between the non-treated state and the follow-up at 18 weeks was observed in both groups (verum—7.7%, placebo—12.9%): a non-specific effect of the intervention.[7]

Objectives

Jacobs[7] results led us to consider whether the data collected in the screening phase of our ADHD trial might help to explain the differences between the results of the two trials and thereby give some insight into the design of future studies in ADHD. The objectives of this retrospective exploratory analysis are to answer the following questions:

1. How long and how many different homeopathic medications did responding patients need until they reached randomisation eligibility? How many patients failed to reach randomisation eligibility, ie were non-responders?
2. What is the profile of the mean CGI values in responders and non-responders during the first 6 months of treatment? Is there a statistically significant difference in CGI course between responders and non-responders? If so, how long does it take for such a difference to appear, and how does this significance evolve during the first 6 months of treatment?
3. How do CGI values in responding patients change before and after identification of the optimal treatment?
4. How do patients pre-treated with stimulants (MPD) react to homeopathy?

These data should allow an estimation of the chances of success of a RCT with upfront randomisation and no open label active run-in.

Methods

Eligibility criteria for the screening phase

Children of both genders, aged between 6 and 16 years, with a confirmed diagnosis of ADHD diagnosis to the DSM-IV criteria[1] and known neuropsychological correlates, such as difficulty in learning and with memory, non-automated language and traditional frontal executive measures,[8,9] were eligible for the study. Further eligibility criteria were the need for treatment and the absence of any chronic physical, neurological or psychiatric disorder. The details of the diagnostic procedure are described in the previous publication.[5] Children conforming to all these criteria, including a parent-rated CGI of at least 14 points without any treatment, were referred to the homeopathic paediatrician for individual treatment.

Treatment during the screening phase

Patients began homeopathic treatment within one month of confirmation of the diagnosis. All patients received an individually prescribed homeopathic treatment daily according to the guidelines described by Hahnemann and Boenninghausen.[10,11] The homeopathic medications were administered as Q (LM) potencies as these result in a more stable treatment effect. To assist with the identification of the optimal medication and to cope with the special difficulties associated with the homeopathic treatment of ADHD, we used questionnaires which contain the most reliable symptoms of ADHD patients, including symptoms of perception which are sometimes not reported. In addition, polarity analysis, a new method of materia medica comparison,[12] helped to increase the precision of the prescriptions. Medication was adjusted until an optimal treatment was identified for each child; the child then received this medication for the duration of the study. Other treatment for ADHD was prohibited throughout the study: it was stopped either before or shortly after the start of homeopathic treatment; compliance was verified by periodic inquiry during assessments by the treating physician. The duration of the screening phase was unlimited.

Assessments during the screening phase

Every eligible child was seen only once by the homeopathic physician at the beginning of the screening phase to exclude influences other than the homeopathic medication. For the same reason, all assessments of the treatment were performed with the parents only, in the absence of the patient. Treatment progress was assessed at intervals of 4 weeks, including the CGI. No other counselling took place in these sessions.

Endpoints

The endpoint of the screening phase was to reach eligibility for the randomised, double-blind cross-over phase, defined as an improvement in the parent-rated CGI of 50% of the baseline value, or at least 9 points. The CGI is a 10-item rating scale containing the most important ADHD symptoms (ie temper outbursts/excitable, impulsive/overactive/cries often/inattentive/fidgeting/disturbs other children/easily frustrated/fails to finish things/moods change quickly. Rating: 0 = never, 1 = occasionally, 2 = often, 3 = very often).[6] The baseline value was the CGI in an untreated state before starting homeopathic medication. The CGI and subtests of WISC-III,[13] K-ABC,[14] VLMT[15] and TAP[16] were evaluated again after the child attained the eligibility criteria for the cross-over trial. To minimise learning effects, only a few of these tests were identical with those of the diagnostic evaluation.

Statistical analysis

The sample size was calculated for the CGI, the primary endpoint in the randomised cross-over phase.[5] Data collected during the screening phase, including data from patients who were not enrolled in the subsequent cross-over phase, were used in this exploratory analysis. CGI ratings at different time points are presented using descriptive statistics. At each time point (1, 2, 3, 4, 5 or 6 months), the CGI rating was compared between responders and non-responders using analysis of covariance including CGI rating at baseline as covariate. The Bonferroni correction was applied to adjust for multiple testing at the six time points. For patients reaching randomisation eligibility and leaving the screening phase prior to 6 months, missing values at later time points (3 observations at month 3, 13 observations at month 4, 19 observations at month 5, and 28 observations at month 6) are imputed using the last-value-carried-forward method before performing statistical tests. As a sensitivity analysis, the tests were repeated with no imputation, ie using all available data at each time point. The correlation between number of medications and time to reach randomisation eligibility for the responders is described by the Pearson correlation coefficient. Fishers exact test was applied to contingency tables for associations between responder group and MPD pre-treatment.

The time to reach randomisation eligibility was estimated (median and 95% confidence intervals [95% CI]) for all patients using the Kaplan–Meier (K–M) method. Data from non-responding patients were censored at the time of study drop-out. The number of medications and time to reach randomisation eligibility for patients with and without previous MPD treatment were also estimated using the K–M method. The log-rank test was used to compare the two patient groups. For responders, the within-patient difference in CGI change rate (points/month) between the suboptimal and the optimal treatment phases was analysed by the signed rank test. For patients who immediately entered the optimal treatment phase, their

CGI change rate was set to zero for the suboptimal treatment phase. For non-responders, the CGI change rate in the suboptimal treatment phase was analysed also by the signed rank test. All tests were two-sided.

Results

Of the 83 patients who entered the screening phase 74 (89%) were boys, and 9 (11%) girls. The median age of the patients was 9.2 years (range 6.1–15.3). Eighteen patients (22%) had previously received stimulant treatment and 28 children (34%) were raised by a single parent (Table 1).

The Kaplan–Meier curve shows the relationship between treatment duration and the proportion of patients reaching eligibility for the randomised controlled phase (Fig. 1). Seventy patients (70/83 = 84%) were responders, ie attained the eligibility criteria of the cross-over phase. Seventy percent of the responding patients (49/70) had reached the eligibility criteria within 6 months, 87% (61/70) within 9 months and 99% (69/70) within 1 year of treatment start.

Responders took a median time of 5 months (range 1–18) and a median number of 3 different homeopathic medications (range 1–9) until they reached randomisation eligibility (Table 2). Thirteen patients (16%) were non-responders and dropped out of the screening phase. In this group the median duration of treatment until dropout was 8 months (range 2–17), with a median of 6 homeopathic medications (range 1–9). In responding patients, a strong correlation between time to reach eligibility for the randomised controlled phase and number of different medications is evident (Pearson correlation coefficient = 0.86).

Table 3 presents the absolute and percent relative change from baseline in mean CGI in responders, non-responders and all patients after 4, 5 and 6 months of homeopathic treatment. Whereas the absolute mean CGI of responding patients was decreased at month 4 and continued to fall up to month 6, that of the non-responding patients had fallen slightly at month 4 but had increased towards the pre-treatment value at month 6.

The profiles of mean CGI values during the first 6 months of treatment (including imputed values for early responders) for responders and non-responders are plotted in Fig. 2. The corresponding group-effect *p*-values with adjustment for multiple testing are also plotted. The between-group difference tended to become more and more obvious with time and reached statistical significance at months 5 and 6 (*p*-values: 0.0366 at month 3, 0.1818 at month 4 and 0.0006 at months 5 and 6). The sensitivity analysis without imputation gave very similar results.

The changes in CGI observed during the suboptimal and optimal treatment periods are presented in Table 4.

Table 1 Baseline data

	$N = 83$
Gender (girls/boys)	9/74 (11%/89%)
Mean age, years (range)	9.2 (6.1–15.3)
Social situation (intact family/single parent)	55/28 (66%/34%)
Prior stimulant treatment	18 (22%)

Table 2 Time to eligibility, time to drop-out and number of medications

	Responders	*Non-Responders*
Number (% total, $N = 83$)	70 (84%)	13 (16%)
Time to eligibility (months)		
Median (range)	5 (1–18)	
Time to drop-out (months)		
Median (range)		8 (2–17)
Number of medications		
Median (range)	3 (1–9)	6 (1–9)

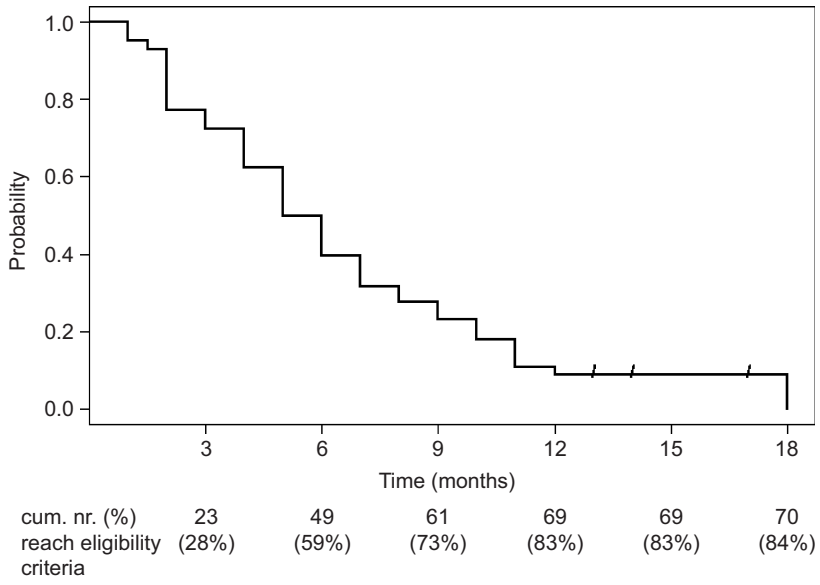

Fig. 1 Kaplan–Meier curve of time to reach eligibility criteria. Non-responders (drop-outs) were censored at the time of drop-out.

Table 3 Changes in absolute and percent relative CGI*

Patients Treatment	*Responders N = 70 Verum*		*Non-responders N = 13 Verum*		*All patients N = 83 Verum*	
	*MeanCGI**	*% Difference*	*MeanCGI**	*% Difference*	*MeanCGI**	*% Difference*
Baseline	19.03		20.23		19.22	
Month 4	13.10	−31.2	16.30	−19.4	13.60	−29.2
Month 5	11.88	−37.6	16.67	−17.6	12.65	−34.2
Month 6	11.70	−38.5	18.00	−11.0	12.90	−32.9

*CGI = Parent rated Connor's Global Index.

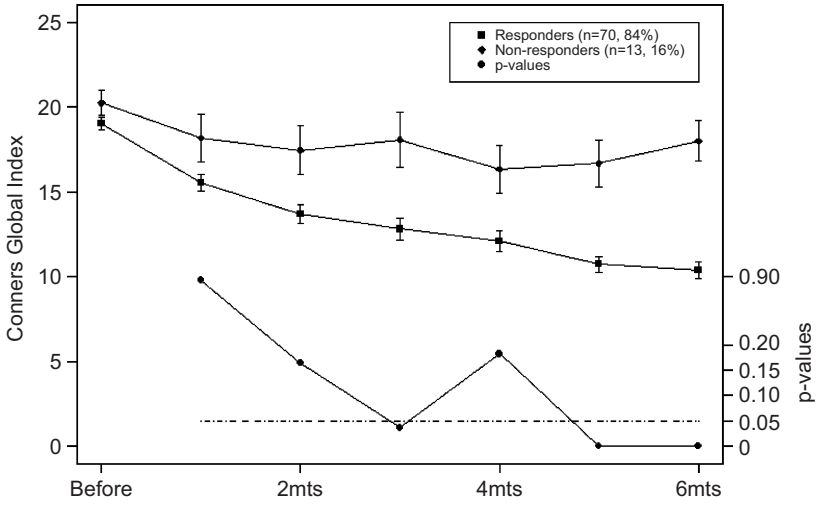

Fig. 2 The two upper curves are profiles of mean CGI-values during the first 6 months of homeopathic treatment for responders and non-responders, respectively. The vertical bars indicate ± standard error. The bottom curve is profile of *p*-values of the response group effect from the ANCOVA analysis, including CGI value at baseline as covariate. The *p*-values were adjusted for multiple testing using the Bonferroni method. For responders who reached randomisation eligibility and left the screening phase before 6 months, missing CGI values at later time points were imputed using the last-value-carry-forward method.

Table 4 Changes in CGI during optimal and suboptimal homeopathic treatment in responding patients

Responding patients N = 70	*Suboptimal treatment*	*Optimal treatment*	*Optimal-suboptimal*	*p-value*
Duration (months)	4	1		
Median (range)	(0–15)	(1–3)		
CGI change* rate (points/month)	−0.53	−4.50	−3.55	<0.0001[a]
Median (range)	(−7–2)	(−14–(−1))	(−14–2.5)	

*Larger negative values refer to greater improvement
[a]Signed rank test

During the optimal treatment period which led to eligibility for the randomised controlled phase, responding patients had a median rate of change in CGI of −4.50 points per month (range −14 to −1) compared with a rate of change of −0.53 points per month (range −7–2) during the preceding suboptimal treatment period ($p<0.0001$). Once the optimal medication was identified, eligibility for the randomised controlled phase was reached quickly (median 1 month, range 1–3). Non-responding patients, for whom an optimal medication was not identified, had a median improvement of only −0.57 CGI points per month (range −4–0.5), a rate of change similar to that observed in the responding patients during the suboptimal treatment period (data not shown).

The time and number of medications necessary to reach eligibility required by the children who had previously been treated with MPD compared with those with no pre-treatment are shown in Table 5. Although the proportion of responders in the pre-treated patients was not statistically different from that in those without pre-treatment ($p = 0.09$), the K–M estimate of the median time to reach eligibility for patients without pre-treatment was 5 (95% CI, 4–6) months compared with 6 (95% CI, 5–18) months for patients with pre-treatment ($p = 0.023$, Fig. 3); the corresponding estimate of the median number of medications for patients without pre-treatment was 4 (95% CI, 3–5) compared with 5 (95% CI, 3–9) in patients with pre-treatment ($p = 0.031$, Fig. 4).

Table 5 Kaplan–Meier estimate of time and number of medications to reach eligibility in patients with and without pre-treatment with MPD

	*With MPD**	Without MPD*	*p value*
Total sample $N = 83$	18 (21.7%)	65 (78.3%)	
Number of responders ($N = 70$)	12 (10.8%)	58 (89.2%)	0.09
Kaplan-Meier median (95% CI)**			
Time to eligibility (months)	6 (5–18)	5 (4–6)	0.023
Number of medications	5 (3–9)	4 (3–5)	0.031

*MPD = methylphenidate.
**Total population, including responders and non-responders.

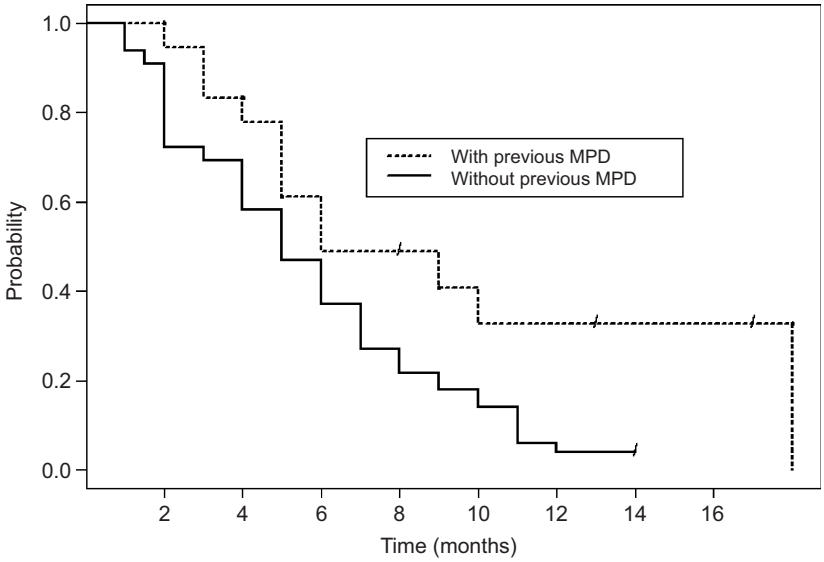

Fig. 3 Kaplan–Meier curves of time to reach eligibility criteria. Non-responders (drop-outs) were censored at the time of drop-out.

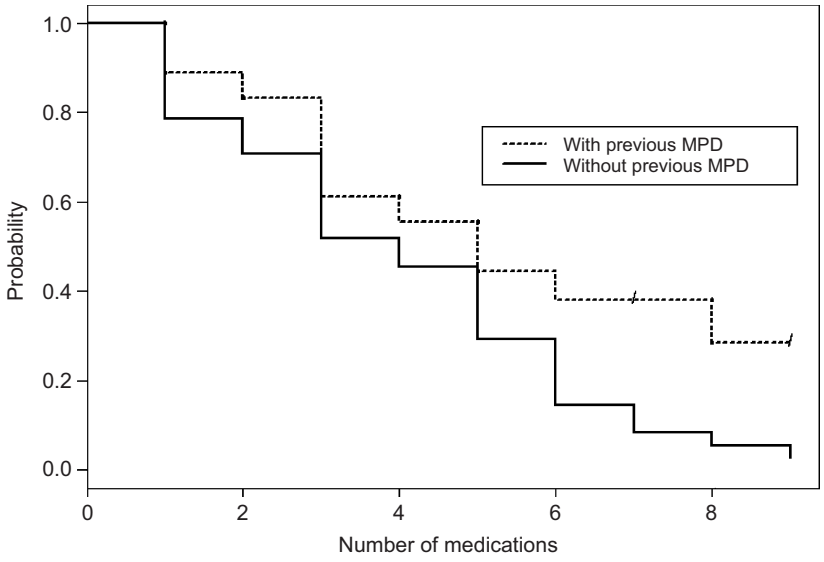

Fig. 4 Kaplan–Meier curves of number of medications to reach eligibility criteria. Non-responders (drop-outs) were censored at time of drop-out.

Discussion

Even with an optimised homeopathic treatment of patients with ADHD,[12] considerable effort is still required to reach a substantial reduction in CGI-rating. The difficulties of homeopathic treatment of ADHD patients are mainly due to inaccuracy in the reporting of symptoms by parents, family problems and external influences, such as school and social pressure, on the child and family. The need for a fast amelioration of symptoms due to this pressure is often stressful, and conflicts with the usual slow amelioration

induced by homeopathic treatment. The data presented here were collected from patients taking part in the non-randomised, open-label, screening phase prior to the double-blind, cross-over phase of the Swiss ADHD trial.[5]

The 70 patients (84%) who reached an improvement of 50% or 9 points in parent-rated CGI needed a median time of 5 months (responders), while 13 (16%), did not improve significantly and dropped out of treatment after a median time of 8 months (non-responders). Of the responders, only 70% attained the eligibility criteria for the double-blind cross-over phase within 6 months of treatment start after a median of three medications. The struggle to achieve eligibility can best be demonstrated by the necessity of a median of six different medications (range 1–9) to reach the eligibility criteria for the 30% of responders who took longer than six months. Despite these difficulties we could show that the difference in the CGI-values between responders and non-responders becomes highly significant and stable after 5 months of treatment ($p = 0.0006$).

Homeopathy assumes that only medications which optimally cover the characteristic symptoms of an individual patient cause clinically relevant improvement. In our study we found a highly significant difference in effect between optimal and suboptimal medications ($p < 0.0001$). A comparison of the effects of suboptimal medications with the placebo effects in the study of Jacobs[7] reveals that they are similar, while the effects of optimal homeopathic medications exceed those of suboptimal ones by a factor of eight. This suggests that an optimal medication has a specific effect and emphasises the necessity to identify the optimal homeopathic medication for individual patients before comparing these patients with a placebo group in a RCT.

Finally, clinical impression suggests that patients pre-treated with stimulants are more difficult to treat with homeopathy and may be an obstacle in a double-blind clinical trial. Our data confirm this impression; compared with children with no stimulant pre-treatment, the pre-treated children needed a longer time (median 6 vs 5 months, $p = 0.023$) and needed more different medications (median 5 vs 4, $p = 0.031$) to achieve randomisation eligibility.

Conclusion

Our data suggest that, as a result of the need to identify an optimal medication before a response to treatment can be observed, a RCT in ADHD children comparing placebo with homeopathy with randomisation at treatment start has a high risk of failure to show a specific effect, especially if it is of short duration; suboptimal treatment, with increased rates of late or non-response, may be a major pitfall. In order to demonstrate a clinically relevant treatment effect of homeopathy in ADHD children, such a RCT should have a total observation time of at least 12 months to allow the time necessary to identify the optimal medication for each child and thereby enable a true comparison with placebo. The precise knowledge of the study team's treatment data is an indispensable prerequisite for the planning of any homeopathic double-blind trial.

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