A RANDOMIZED, CONTROLLED, EFFECTIVENESS TRIAL OF OROS-METHYLPHENIDATE COMPARED TO USUAL CARE WITH IMMEDIATE-RELEASE METHYLPHENIDATE IN ATTENTION DEFICIT- HYPERACTIVITY DISORDER

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ABSTRACT

Background
The thrice daily dosing regimen of immediate release methylphenidate (IR-MPH) for Attention Deficit/Hyperactivity Disorder (ADHD) requires in-school dosing, leading to issues surrounding dispensing and storage of controlled substances by school personnel and concerns over children's privacy and the embarrassment associated with taking medication in public at school. OROS-Methylphenidate (OROS-MPH) is a once-daily controlled-release formulation of methylphenidate (MPH) developed to overcome some of the limitations associated with IR-MPH and first-generation sustained-release formulations. Randomized, controlled trials (RCTs) that focus on treatment efficacy provide the best evidence for demonstrating whether an intervention works, but under ideal conditions one cannot discount the importance of efficacy study results. However, the most useful information to clinicians comes from an effectiveness study design.

Objectives
To evaluate the effectiveness and tolerability of OROS-MPH versus usual care with IR-MPH in children aged 6 to 12 years with ADHD.

Methods
This 8 week, multicentre, open-label study randomized 147 subjects to either once-daily OROS-MPH or usual care with IR-MPH. Subjects were titrated to a clinically effective dose of either study medication over 4 weeks and maintained on that dose for an additional 4 weeks. The SNAP-IV parent-rating scale was used to assess effectiveness.

Results
OROS-MPH showed statistically significant superiority to IR-MPH in remission rate based on the 18 ADHD symptoms ($p=0.0002$, $X^2=13.8$, $df=1$) and severity of ADHD and ODD symptoms ($p=0.004$, $F=8.4$, $df=1,127$), as well as on the following secondary assessments: IOWA Conners, Conners Parent Rating Scale (short version), Parent Stress Index, (short version); Visual Analogue Scale for social play; Clinical Global Impression-Severity, Clinical Global Impression-Improvement and Parent Satisfaction with treatment. OROS-MPH and IR-MPH were both well tolerated with a similar side effect profile.

Conclusions
Once-daily OROS-MPH is significantly more effective than usual care with IR-MPH based on multiple outcome measures including remission rate.

Key Words: *OROS® methylphenidate (OROS-MPH), immediate-release methylphenidate (IR-MPH), Attention-Deficit/Hyperactivity Disorder (ADHD), SNAP-IV parent-rating scale*

Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with significant educational and social impairment and an increased risk of accidents/injury.[1,2] The utilization and cost of health care resources for children with ADHD are significantly greater than those without this disorder.[3-5] These are two important reasons that provide the impetus to maximize the effectiveness of treatment for ADHD.

Stimulant medication is recommended as a first-line modality for treating ADHD.[6] In a long-term study conducted in ADHD children, sponsored by the National Institute of Mental Health, a systematic and structured medical management plan, including three times daily (TID) dosing of IR-MPH, proved to be superior to routine community care for the management of core symptoms.[7,8] Most clinicians are aware that a TID frequency is the most efficacious IR-MPH dosing regimen when treating ADHD. However, market research (IMS data 2001) demonstrates that the most common regimen prescribed is actually twice daily (BID). The TID and BID (usually morning and noon) regimen requires in-school dosing, leading to issues regarding time and effort of school personnel to store and dispense a controlled drug and concerns surrounding compromising children's privacy via the stigma and embarrassment associated with taking medication in public at school. These and other factors contribute to decreased compliance [9] and may explain why the actual daily dose of IR-MPH prescribed by the medical community is different from what has been published to be the most efficacious.[7,10]

OROS-MPH (Concerta®) is a once-daily controlled-release formulation of methylphenidate (MPH) developed to overcome some of the limitations associated with IR-MPH[11,12] and first-generation sustained-release formulations.[13,14] It uses osmotic pressure to deliver MPH at a controlled rate throughout the day, in an ascending pharmacokinetic profile designed to counteract acute tolerance.[15] This minimizes fluctuations of peak and trough plasma medication concentrations associated with multiple doses of IR-MPH.[9,16] Double-blind studies using the laboratory school protocol have demonstrated equivalent efficacy compared with TID IR-MPH.[9,17] These results were confirmed in a large clinical trial.[18]

Randomized controlled trials (RCTs) that focus on treatment efficacy provide the best evidence for demonstrating whether an intervention works, but under ideal conditions. While one cannot discount the importance of efficacy study results, the most useful information to clinicians comes from an effectiveness study design. March et al. recently provided a commentary on the importance of "practical clinical trials" that address how medications behave in real life clinic settings. Practical clinical trials are randomized, set in clinical practice and attempt to answer the question as to whether a treatment will do more good than harm under best practice clinical conditions.[19] The design of this trial (randomization to a new treatment or a usual treatment (control group)) attempted to reflect everyday practice by imposing fewer restrictions on how the treatment was delivered and monitoring of compliance.

The *a priori* hypothesis was that OROS-MPH would result in significantly better remission rates and overall symptom control than usual care with IR-MPH with no additional safety concerns.

METHODS

Participants

Thirteen research centers across Canada recruited physically healthy, male and female outpatients, aged 6 - 12 years inclusive, with a documented Diagnostic Statistical Manual-Fourth Edition (DSM-IV) diagnosis of Attention-Deficit/Hyperactivity Disorder.[20] These criteria were confirmed by a clinical and structured interview (the Kiddie-Schedule for Affective Disorders and Schizophrenia -Present and Lifetime Version, K-SADS-PL, version 1.0). Subjects were medication naïve or currently on ADHD medication therapy; had a baseline Clinical Global Impression-Severity (CGI-S) score of 4 or greater (at least "moderate" severity); and had to demonstrate significant after-school/evening behavioural difficulties as assessed by the clinician via parent/child interviews. To approximate clinical practice settings, psychotropic medications to treat non-

ADHD disorders and psychological interventions were permitted as long as the treatment/intervention had been stable for a minimum of 4 weeks prior to entry and did not change nor newly commence during the trial.

Exclusion criteria included: known MPH non-responders, hypersensitivity, or adversely affected by methylphenidate; concomitant use of contraindicated medication likely to interfere with the safe administration of study medication; marked anxiety, tension, aggression/agitation; glaucoma; ongoing seizure disorder; psychotic disorder; diagnosis or family history of Tourette's disorder; bipolar disorder; suspected mental retardation or significant learning disorder; medication/alcohol abuse/dependence by either the child or parent; history of, or current eating disorder; severe gastrointestinal narrowing; inability to swallow study medications; and any serious/unstable medical illness.

Study Design

In this open-label, 8 week, parallel trial, children were randomized to OROS-MPH taken once daily in the morning or usual care with IR-MPH (prescribed as twice or thrice daily at the clinician's discretion). At study entry, patients on stimulant or non-stimulant medication to treat ADHD underwent a minimum 3-day washout.

Subjects assigned to OROS-MPH were initiated on 18 mg once daily. Over 4 weeks, the subjects were titrated by weekly increases, at the investigators' discretion; to the next dose level (27 mg, then 36 mg) to a maximum of 54 mg. Subjects assigned to IR-MPH were initiated at whatever dose the clinician felt was appropriate. Over 4 weeks each individual dose was titrated weekly by 5 mg or 10 mg increments, according to the manufacturer's recommendations and the investigator's clinical judgment, to a suggested maximum daily dose of 60 mg. The protocol required investigators to keep the child on this optimal dose for the last 4 weeks of the trial. Dose decreases were allowed if clinically significant side effects emerged.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions and approved by a research ethics board at each center. Written consent was obtained from the child if capable; written informed consent was obtained from their legally acceptable representative prior to enrolment.

There were four protocol-specified visits: screening, baseline, Week 4, and Week 8. Visits were scheduled monthly, but physicians could see their patients more often if desired. Caregivers were asked to retrieve medication from the pharmacy themselves and subjects remained in the study even if non-compliant with the medication regimen.

Effectiveness and Safety Measures

The primary effectiveness outcome instrument was the parent completed 26 item Swanson, Nolan and Pelham–Fourth Edition (SNAP-IV) rating scale [21] consisting of 18 ADHD items and 8 Oppositional Defiant Disorder (ODD) items. Each item is scored for severity on a 4-point scale (0-3, where 0=not at all and 3=very much).

Secondary effectiveness measures included:

- 10-item Inattention/Overactivity with Aggression (IOWA) Conners Parent Rating Scale, rated on a 4-point scale (0-3, 0=not at all, to 3=very much)[22,23]
- 27-item Conners Parent Rating Scale (short), scored on a 4-point scale (0-3, 0=not true at all, to 3=very much true)[24]
- 36-item Parent Stress Index (PSI) (short), rated on a 5-point scale (1-5, 1=strongly agree, to 5=strongly disagree)[25]
- Physician-rated Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I), rated on 7-point scales (1-7, 1=not ill, to 7=extremely severe on CGI-S, and 1=very much improved, to 7=very much worse on CGI-I)
- Parent/caregiver report of satisfaction with ADHD treatment rated on a 5-point scale (1-5, 1=completely dissatisfied, to 5=completely satisfied)
- 100 mm Visual Analog Scale (VAS) of homework and for social play ability scored by the parent/caregiver, where 0=no problem and 100=severely impaired

- Resource Use Questionnaire (RUQ) addressing support/medical services required, in the preceding four weeks

Safety assessments collected included adverse events, physical examination, vital signs, and body weight.

Statistical Analyses

Based on a power analysis, a total of 130 randomized subjects (65 in each group) were required to detect a difference of 0.25 in SNAP-IV remission rates for those receiving OROS-MPH (0.5) versus those receiving IR-MPH (0.25), using a chi-square test and a 2-sided α of 0.05 and a power of 80%. Additional subjects were recruited to compensate for dropouts.

An independent statistician generated site randomization lists. Individual treatment assignments were sealed in opaque, sequentially numbered envelopes. The investigators prescribed IR-MPH or OROS-MPH as specified by the treatment assignment.

Baseline demographics and safety outcomes were summarized by treatment group for all randomized subjects who took at least 1 dose of study medication. Effectiveness analyses were performed on the intent-to-treat (ITT) sample, consisting of all randomized subjects who took at least one dose of trial medication and had at least one protocol-mandated post-baseline assessment. The endpoint was defined as last protocol mandated post-baseline observation carried forward (LOCF). Analyses were conducted at week 4, week 8 and endpoint.

The SNAP-IV rating scale was used to specify two primary effectiveness outcomes:

1. remission of symptoms at endpoint (remission was defined as a score of "0" or "1" on each of the first 18 ADHD items (referred to as SNAP-IV-18)); and,
2. change from baseline at study endpoint in the total rating scores on the 26-item (ADHD + ODD items) SNAP-IV (referred to as SNAP-IV-26).

Comparison of remission rates between treatment groups was performed by the Cochran-Mantel-Haenszel test for general association, after controlling for centre. Analysis of variance (ANOVA), with factors for treatment and centre, was used to analyze the change from baseline in total SNAP-IV-26 score. Treatment by centre interaction was added to the model as a secondary analysis. The interaction was not significant and was subsequently removed from the model. ANOVA methods were used for analysis of change from baseline in the VAS and the total scores of PSI, Conners, and the IOWA Conners Parent Rating Scale. Differences between treatments in parent-rated satisfaction with treatment, CGI-I, and the change from baseline in CGI-S were analyzed by the Van Elteren test.

Statistical tests on each of the two primary effectiveness outcomes at endpoint were evaluated at a 2-sided significance level of 2.5%, after Bonferroni correction for multiple comparisons. No adjustment for multiple comparisons was performed on the secondary effectiveness measures (each test evaluated at 5% level).

RESULTS

Subjects

During the period from March to December 2003, 147 subjects were randomized to treatment (73 to OROS-MPH arm, 74 to IR-MPH arm); 145 ubjects were included in the safety analysis (n=1 in each arm didn't receive study medication). The ITT effectiveness analysis consisted of 143 subjects: 70 in the OROS-MPH group (2 had no post baseline effectiveness assessment) and 73 in the IR-MPH group. The subjects in both groups were similar in terms of baseline characteristics (Table 1) and mean baseline scores for primary and all secondary effectiveness measures (Table 2). One hundred and twenty one (83%) subjects completed the 8-week trial. Twelve subjects (17%) in each group discontinued prematurely; adverse event (n=6 OROS, n= 2 IR-MPH), withdrew consent (n=2 OROS, n= 3 IR-MPH), lost to follow-up (n=1 OROS, n= 3 IR-MPH), protocol violators (1 patient per group), insufficient response (n=1 IR-MPH), and other reasons (2 patients per group).

TABLE 1 Participant characteristics

Characteristic	Once-Daily OROS-MPH (n=72)	Usual Care with IR=MPH (n=73)
Age at screening, years, mean ± SD (range)	9.0 ± 2.1 (6-12)	9.1 ± 1.8 (6-12)
Age at diagnosis, years, mean ± SD (range)	8.1 ± 2.1 (4-12)	8.4 ± 2.1 (3-12)
Diagnosis, n (%)		
ADHD, predominantly inattentive	13 (18%)	14 (19.1%)
ADHD, combined type	57 (79.2%)	58 (79.5%)
ADHD, predominantly H/I	2 (2.8%)	1 (1.4%)
Co-morbid Illnesses (currently active)		
Oppositional Defiant Disorder	31 (43.1%)	28 (38.4%)
Conduct Disorder	1 (1.4%)	0
Anxiety disorder	4 (5.5%)	2 (2.7%)
Gender, n (%)		
Male	61 (84.7%)	60 (82.2%)
Female	11 (15.3%)	13 (17.8%)
Race, n (%)		
Caucasian	63 (87.5%)	63 (86.3%)
Black	1 (1.4%)	4 (5.5%)
Asian	1 (1.4%)	0
Other	7 (9.7%)	6 (8.2%)

ADHD= Attention-Deficit/Hyperactivity Disorder, H/I= Hyperactivity/Impulsivity

TABLE 2 Summary statistics and analyses of effectiveness measures

Effectiveness Measure	Mean Baseline Score and Mean Change from Baseline Score (±SD)			ANOVA of Changes from Baseline Score	
	Once-Daily OROS-MPH	Usual Care with IR-MPH		Est. Trt. Diff. (±SE)	P-Value
SNAP-IV 26-item (ADHD + ODD items) Scale:					
Baseline	51.5 ± 13.1	51.5 ± 12.4			
Week 4	-24.1 ± 16.8	-18.1 ± 16.5		-6.0 ± 2.7	0.031 *
Week 8	-26.4± 18.3	-17.9 ± 15.3		-8.4 ± 3.0	0.006 *
Study endpoint	-25.5 ± 18.7	-17.5 ± 15.2		-8.3 ± 2.9	0.004 *
SNAP-IV 18-item (ADHD items) Scale:					
Baseline	38.0 ± 9.6	38.8 ± 9.6			
Week 4	-18.4 ± 13.1	-14.8 ± 12.3		-3.6 ± 2.1	0.08
Week 8	-20.2 ±13.7	-14.5 ± 11.4		-5.7 ± 2.2	0.01*
Study endpoint	-19.6 ± 13.9	-14.3 ±11.6		-5.5 ± 2.1	0.01*
IOWA Conners Parent Rating Scale, Total:					
Baseline	20.2 ± 6.1	19.9 ± 5.5			
Week 4	-8.6 ± 7.4	-6.3 ± 6.2		-2.3 ± 1.1	0.044
Week 8	-10.3 ± 8.1	-6.1 ± 5.8		-4.0 ± 1.3	0.002 *
Study endpoint	-9.4 ± 8.5	-6.0 ± 5.9		-3.5 ± 1.2	0.006 *
IOWA Conners Parent Rating Scale, Inattention/Overactivity Sub-scale:					
Baseline	10.9 ± 3.0	11.2 ± 2.7			
Week 4	-4.8 ± 4.0	-4.2 ± 3.5		-0.7 ± 0.6	0.27
Week 8	-5.9 ± 4.4	-4.0 ± 3.1		-1.8 ± 0.7	0.009*
Study endpoint	-5.4 ± 4.5	-3.9 ± 3.2		-1.6 ± 0.7	0.01*
Conners Parent Rating Scale:					
Baseline	55.8 ± 14.1	55.5 ± 11.8			
Week 4	-25.7 ± 19.2	-18.8 ± 15.6		-7.1 ± 2.9	0.015 *
Week 8	-30.0 ± 20.5	-19.2 ± 15.7		-10.1 ± 3.1	0.002 *
Study endpoint	-27.5 ± 21.9	-19.2 ± 15.6		-8.7 ± 3.1	0.006 *

TABLE 2 Summary statistics and analyses of effectiveness measures (cont.)

Parent Stress Index, Short Form:					
Baseline	117.9 ± 22.2	116.8 ± 19.4			
Study endpoint	+14.0 ± 19.2	+6.1 ± 14.8		7.8 ± 2.9	0.008 *
Visual analog scale (mm): homework					
Baseline	67.0 ± 24.8	67.2 ± 23.6			
Week 4	-33.1 ± 28.3	-19.7 ± 33.5		-13.5 ± 7.2	0.066
Week 8	-36.2 ± 31.1	-26.5 ± 27.9		-9.7 ± 7.9	0.223
Study endpoint	-31.8 ± 29.6	-23.0 ± 33.8		-8.9 ± 7.1	0.218
Visual analog scale (mm): social play					
Baseline	44.6 ± 27.6	42.7 ± 29.9			
Week 4	-13.7 ± 30.3	-6.0 ± 30.9		-7.5 ± 5.3	0.159
Week 8	-20.1 ± 28.8	-8.6 ± 26.6		-12.8 ± 5.0	0.011 *
Study endpoint	-17.9 ± 30.4	-7.5 ± 27.0		-11.1 ± 4.9	0.026 *
Effectiveness Measure	**Once-Daily OROS-MPH**	**Usual Care with IR-MPH**		***P-Value**	
CGI-I: mean rating ± SD					
Week 4	2.4 ± 1.3	2.7 ± 1.4		0.123	
Week 8	1.8 ± 1.1	2.5 ± 1.3		0.0002 **	
Study endpoint	2.0 ± 1.2	2.6 ± 1.4		0.0008 **	
CGI-S: mean change from baseline rating ± SD					
Baseline~	5.1 ± 0.9	5.1 ± 0.8			
Week 4	-1.9 ± 1.4	-1.4 ± 1.5		0.034 *	
Week 8	-2.4 ± 1.1	-1.7 ± 1.5		0.0001 **	
Study endpoint	-2.2 ± 1.2	-1.6 ± 1.4		0.0005 **	
Parent satisfaction with current ADHD medication: mean rating ± SD					
Baseline^	3.2 ±1.1	3.3 ± 1.3		0.531	
Week 4	4.1 ± 1.0	3.6 ± 1.3		0.024*	
Week 8	4.1 ± 1.2	3.4 ± 1.3		0.001*	
Study endpoint	4.0 ± 1.3	3.4 ± 1.3		0.003*	

SD=standard deviation, SE=standard error of the estimated difference, ANOVA=analysis of variance, Est.Trf.Diff.=estimated treatment difference, ^Satisfaction with pre-study ADHD medication prior to wash-out, ~Mean rating ±SD at baseline, ***** p<0.05, ******p<0.001

Study Medications

At endpoint, the mean daily dose of OROS-MPH was 37.8±11.9 mg (1.17±0.52 mg/kg; range 18-54 mg), namely, a mean IR-overcoat bolus dose of 8.31 mg and a mean reservoir dose of 29.48 mg. The distribution of subjects by daily dose was 10% on 18 mg (4 mg overcoat + 14 mg reservoir), 19% on 27 mg (6 mg + 21 mg reservoir), 42% on 36 mg (8 mg overcoat + 28 mg reservoir), and 29% on 54 mg (12 mg + 42 mg reservoir). At endpoint, the mean daily dose of IR-MPH was 33.3±13.2 mg (1.03±0.46 mg/kg; range 10 -70 mg), with 61% on TID (mean 1.08±0.46 mg/kg), and 38% on BID regimens (mean 0.98±0.46 mg/kg). The distribution of subjects by total daily dose was 24% on 10 – 20 mg, 38% on 25 – 35 mg, 28% on 40 – 50 mg, and 10% on 55-70 mg. The mean durations of treatment were: 54.1±16.5 days for OROS-MPH vs. 53.6±12.2 days for IR-MPH subjects.

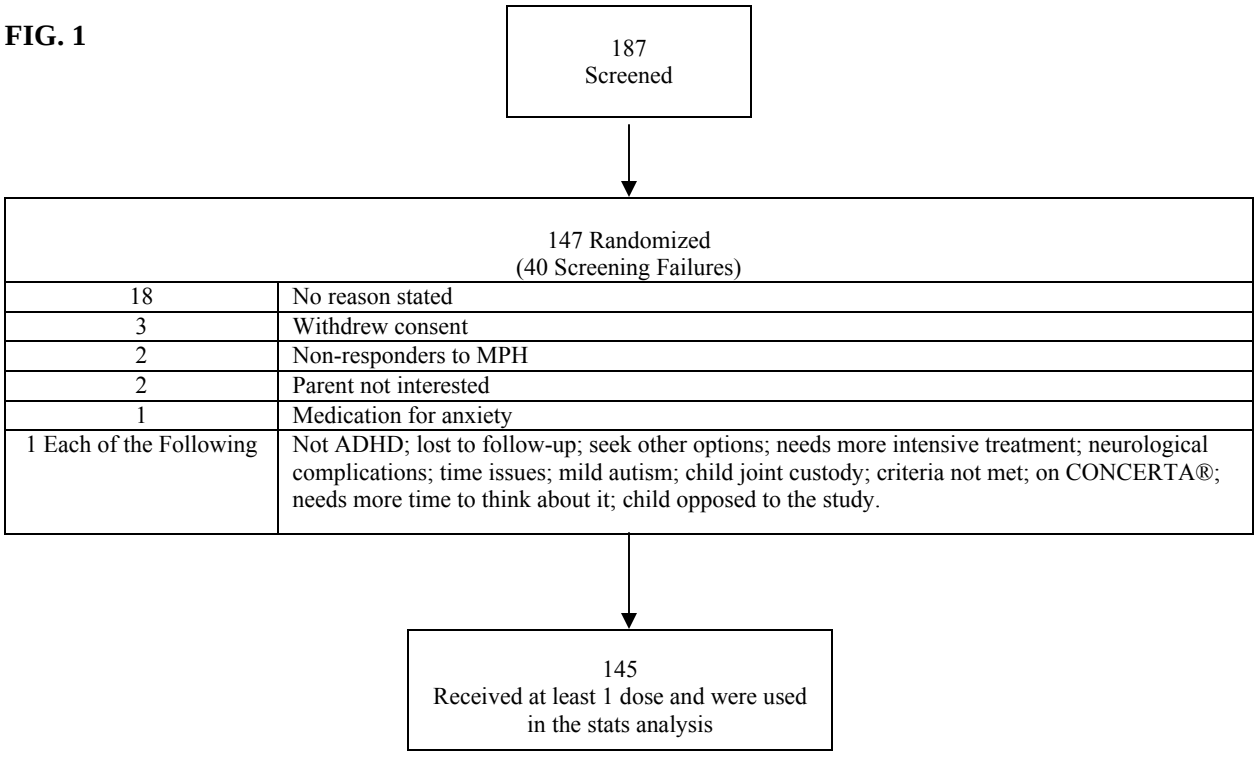
The percentage of subjects who missed any dose during the trial was much higher with IR-MPH (84%) than OROS-MPH (56%). The mean total number of missed doses was low overall for OROS (1.9±3.6) and for IR-MPH (10.4±11.2).

Primary Effectiveness Outcomes

At endpoint, remission (SNAP-IV-18) was achieved by 44% of OROS-MPH subjects compared with 16% of IR MPH subjects ($p=0.0002$, $X^2=13.77$, $df=1$) (Figure 1). Remission rates were higher in the OROS-MPH group (33%) than in the IR-MPH treated group (14%) at week 4 ($p=0.01$, $X^2=6.48$, $df=1$) and at week 8 (47% vs. 16%, $p=0.0003$, $X^2=13.27$, $df=1$).

A post hoc remission analysis compared OROS-MPH to BID and TID IR-MPH respectively. 61% of IR-MPH patients were dosed thrice daily. There was a statistically significant treatment difference in favour of OROS-MPH subjects meeting remission criteria at week 8 (47%-OROS-MPH, 23% TID IR-MPH, $p=0.02$) and at endpoint (44% OROS-MPH, 24% TID IR-MPH, $p< 0.05$) but not at week 4 (33% OROS-MPH, 22% TID IR-MPH, $p=0.27$). Statistically significant treatment differences were noted at every time point in favour of OROS-MPH patients compared to BID IR-MPH (week 4: 33% OROS-MPH, 4% bid IR-MPH, $p<0.003$; Week 8 and endpoint: 47% and 44% OROS-MPH, 4% bid IR-MPH, $p=0.0001$).

FIG. 1



Secondary Effectiveness Outcomes

Results of the secondary effectiveness analyses are reported in Table 2. ANOVA of the change in total SNAP-IV-26 score at endpoint revealed a main effect of treatment in favour of OROS-MPH (49% improvement) compared to IR-MPH (34%) (p=0.004, F=8.39, df=1,127) (Table 2). ANOVA of the mean change in the SNAP-IV-26 score revealed a significant treatment effect in favour of OROS at week 4 (-6.0 point difference), week 8 (-8.4 point difference), and endpoint (-8.3 point difference). The increase in remission rate and reduction in total SNAP-IV scores continued to improve in the OROS-MPH group between weeks 4 and 8 but no further change beyond week 4 was observed for IR-MPH. The effect size for mean change on the SNAP-IV-26 score was 0.38 at week 4, 0.51 at week 8, and 0.50 at endpoint. Statistically significant differences at endpoint in favour of OROS-MPH were found on the IOWA Conners, Conners Parent Rating Scale (short), CGI-I, CGI-S, VAS social play, and the PSI (short). Thirty-five (50%) of OROS-MPH parents vs. fifteen (21%) IR-MPH parents were "completely satisfied" with current treatment (p=0.003, X^2=8.94, df=1). The VAS for homework completion and the resource utilization questionnaire did not show a statistically significant difference between groups. The study was conducted during the summer months, and homework observations were present in less than 60% of the subjects (38/70 = 54.3% in the OROS-MPH group and 42/73 = 57.5% in the IR-MPH group). Post-hoc power analysis indicated that sample size was insufficient to detect a between group effect if there was one.

On the CGI-I, 57 (83%) OROS-MPH subjects vs. 45 (62%) IR-MPH subjects were rated as "Very much improved" or "Much improved" at endpoint and 53 (77%) OROS-MPH patients vs. 36 (49%) IR-MPH patients were rated as "mild", "very mild" or "not ill" on the CGI-S.

Safety Outcomes

Adverse events were reported for 82% of subjects in both the OROS and IR-MPH groups (Table 3). Adverse events were similar between the two groups and most events were assessed to be either mild or moderate in severity. No serious adverse events were reported in either treatment group.

TABLE 3 Number (%) of subjects reporting adverse events (n=145)

Adverse Event Type	Once Daily OROS-MPH (n=72)	Usual Care with IR-MPH (n=73)
Any event	59 (82%)	60 (82%)
Any possibly medication related event	46 (64%)	38 (52%)
Most common events (≥10% in any group)		
Decreased Appetite	17 (24%)	23 (32%)
Headache	14 (19%)	12 (16%)
Insomnia	12 (17%)	10 (14%)
Abdominal pain	10 (14%)	9 (12%)
Nervousness	9 (13%)	9 (12%)
Emotional lability *	9 (13%)	2 (3%)
Agitation	8 (11%)	5 (7%)
Fatigue	7 (10%)	2 (3%)
Flu-like symptoms	7 (10%)	7 (10%)
Sleep disorder	3 (4%)	7 (10%)

*actual recorded events described as: belligerence, overtalkative, talking less, whiney, argumentative, shorter furse, increased impulsiveness, behaviour problems/disorder, chatters, disorganized, interruptive, 2 verbatims (behaviour problems;reactive) were coded as severe;11 verbatims were coded as mild and the rest moderate

DISCUSSION

Remission of symptoms is an important foundation to educational and social re-integration and improved functioning. The child who experiences complete and sustained remission from ADHD symptoms may have the best opportunity to benefit from other non-pharmacological evidence-based treatment programs to improve long term outcomes. We used a rigorous definition of remission based on the requirement of a score of 0 or 1 ("no" or "very mild" severity) on every item of the 18 item ADHD subscale of the SNAP-IV 26 scale based on the parent's perception of their child (with no inclusion of teacher rated scales). With this strict definition of complete remission, OROS-MPH subjects displayed over twice the rate of complete remission than the IR-MPH group at 4 weeks (33%/14% = 2.36), at 8 weeks (47%/16% = 2.94), and at endpoint (44%/16% = 2.75).

Parents of children with ADHD exhibit more stress, have less self-esteem, and are at greater risk for depression, marital discord, increased alcohol consumption, and other types of personal distress.[26-28] The presence and severity of the child's ADHD is also a significant predictor of heightened parental stress.[29,30] Our results reveal a significantly greater decrease in parental stress in the OROS-MPH than in the IR-MPH group. This pattern of superiority of OROS over the IR-MPH condition also held for other secondary measures, including an increase in parent satisfaction with treatment and improved child socialization. Taken together, these changes may provide a family atmosphere of optimism and hope, allowing for constructive and collaborative interactions between the child and family members which augers well for the social reintegration of the child within their community of peers.

Given that compliance with thrice daily dosing is poor for all medications[31], we can expect medication treatment compliance in ADHD children and their families, who already exhibit symptoms of disorganization and forgetfulness, to be as low as 50%.[32,33] This was reflected in the observation with our trial, which revealed more IR-MPH (84%) patients missed at least one dose compared with the OROS-MPH group (56%). Since families participating in clinical trials tend to be more organized and willing to adhere to medication regimens, we speculate that compliance with IR-MPH might be worse in a clinician's usual practice, than in this trial setting, leading to an even more marked difference in effectiveness between OROS-MPH and IR-MPH.

Compliance may also affect the way clinicians prescribe medication. Concerns about the stigma and embarrassment of children taking medication at school or in after school programs, or the refusal or forgetfulness of caretakers in administering medication during the day may lead to missed doses. A post-hoc remission analysis evaluated OROS-MPH compared to BID and TID IR-MPH separately. Results revealed that OROS-MPH was superior to IR-MPH in remitting patients at both dosing frequencies [44% (OROS-MPH) vs. 4% (BID IR MPH), p=0.0001; 44% (OROS-MPH) vs. 24% (TID IR MPH), $p<0.05$].

Although the current data suggest the possibility that dose regimen and non-compliance were important factors in the lower effectiveness of IR-MPH; one cannot conclusively rule out the negative effects of rapidly fluctuating pharmacokinetic and pharmacodynamic peaks and troughs, within the same day, on both symptoms and adverse events, thus potentially affecting clinical outcome directly and not simply explained as a result of poor medication compliance. Our findings add empirical support to the recent preference for long duration stimulants recommended in the current International Consensus Statement on ADHD and Disruptive Behaviour Disorders.[34]

To assist with the interpretation of our results, we compared our data to a sub-analysis of the MTA dataset, where "near normalization" was defined based on a combined parent-teacher SNAP-IV-18 mean score of ≤ 1.[35] A similar sub-analysis for our parent rated SNAP-IV-18 demonstrated statistically significant "near normalization" at endpoint for OROS-MPH (55%) compared to IR-MPH (31%) (p=0.006, $X^2=7.70$, df=1). These results are consistent with the rigorous application of a thrice daily medication protocol demonstrating 37% of children achieving "near normalization" vs. 28% of community care children as highlighted in the 24 month MTA study.[35]

Previous research has demonstrated that community physicians are resistant to implementing a medication algorithm.[36] This may

mean that use of once daily medication formulations could improve the effectiveness of stimulant use in the community to more closely resemble the efficacy rates found in clinical trials. Physicians who elect to prescribe once daily OROS-MPH should make the family aware of the higher cost of once daily formulations compared to generic thrice and twice daily formulations.

This current trial demonstrates treatment with OROS-MPH, when compared with usual care with IR-MPH, results in a greater percentage of cases that achieve remission of ADHD symptoms as well as a greater change (improvement) in average rating on the parent-completed SNAP-IV-26 scale. The current trial selected children with problematic after school behaviour. These results in conjunction with the double blind efficacy trials measuring effect during school hours[9,17,18] offer a potential spectrum of effect beyond school hours. We anticipate that these enhanced benefits of treatment with medication in childhood will result in improved functioning into adolescence and adulthood. We are testing the first phase of this hypothesis in a 6-month extension study, which is currently ongoing. Long-term studies of children with enhanced symptomatic remission will be required to ascertain if the expected beneficial changes in adulthood are manifested, and decrease the risk of potential long-term consequences such as excessive smoking and drinking.

Limitations

This trial was not blinded. A double blind, double-dummy design would have negated the objective of providing data on effectiveness in everyday clinical practice. A design based on randomizing physicians (who would then prescribe only one treatment condition) and using a separate placebo control for IR-MPH and OROS, would be a possible alternative, but this would require a sample size twice as large and would have exposed half of the subjects to placebo conditions for two months, which may not be justified or accepted by Internal Review Boards (IRBs).

Parent bias could lead to preference for a new treatment option such as OROS-MPH. This bias may have been less likely in physicians who had been using IR-MPH for years, had not previously used OROS-MPH, and were sceptical that any difference could exist between dissimilar delivery systems of an identical active ingredient. The robust differences between the groups among different raters, and on a wide variety of different outcome measures, suggests the findings are unlikely to be explained by a "halo effect" alone.

This trial did not quantify the stigma associated with school administration of medication, and any benefits to the child who seeks peer acceptance by missing doses. To our knowledge, these factors have not been addressed in published studies, but in future studies the addition of such child-centered measures would be an important and valuable addition.

One of the most obvious limitations is the lack of teacher ratings. Although children spend a great deal of time in school and the DSM-IV definition of ADHD requires evidence of difficulty in school as well as home settings, our a priori hypothesis focused solely on the evaluation of after–school behaviour which rendered teacher ratings not applicable in our study construct.

Clinical Implications

Our study documented the extent of symptomatic remission, reduction in parental stress, and improved socialization associated with standard treatment regimens that have been in place for decades versus the new regimens based on once daily administration that now predominate in clinical practice. The results of this study should be viewed as an important initial step, which in conjunction with relevant other treatment interventions, demonstrate how a new long acting formulation may offer the young person with ADHD and their family a way to improve overall functioning and achieve normalization. This may decrease the risk of long-term consequences such as substance abuse, personal/familial distress, and self-injury due to accidents, which are important clinical goals that have not been fully evaluated.

OROS-MPH offers a smooth delivery of medication without the peaks and troughs of IR-MPH, which is suspected of leading to a "roller-coaster" effect on behaviour during the day. This effectiveness study was not designed to evaluate this possibility directly, but does confirm clinical impressions that a long duration stimulant is significantly more effective than twice or thrice daily dosing with IR-MPH.

Despite some limitations, this study demonstrates that research into effectiveness is possible and can produce valuable empirical

information about practical issues associated with the changing environment (i.e. introduction of new formulations and treatment paradigms) concerning the use of stimulant medication. For the practicing physician, symptomatic remission means the patient no longer meets the DSM-IV diagnostic criteria for ADHD.

The findings of this study provide evidence that symptomatic remission is possible, and show that this high standard is a reasonable treatment goal for ADHD.

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