Assessing the Effect of Missing Doses (Off-Days) of Daily Medication in Patients Stable on Pharmacotherapy for ADHD Receiving Atomoxetine or OROS Methylphenidate: A Parallel Matched Group Clinical Study (On/Off Study)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36754

Source
ToetsingOnline

Brief title
LYEN

Condition

- Other condition

Synonym
ADHD, Attention Deficit Hyperactivity Disorder

Health condition

Neurobiologische aandoeningen

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: ADHD, Atomoxetine, Attention-Deficit/Hyperactivity Disorder, OROS methylphenidate

Outcome measures

Primary outcome

The primary objective of the study is to assess the effect of missed doses of atomoxetine and OROS methylphenidate in ADHD patients who are stable on pharmacotherapy based on the patient*s daily behavior as assessed by the Daily Parent Report of Evening and Morning Behavior - Revised (DPREMB-R) scale from the parent perspective.

Secondary outcome

1. To compare the behavior of patients between on-days and off-days as measured by the

- DPREMB-R subscores (parent rated).

- Global Impression of Perceived Difficulties (GIPD) scale - patient version (GIPD-Pat): total score and individual items.

- Conners* Global Index - Teacher rating scale, total score.

2. To compare the effects of off-days between atomoxetine and OROS methylphenidate, as measured by

- DPREMB-R total score and subscores.

- GIPD-Pat total score and individual items.

- Conners* Global Index - Teacher rating scale, total score.

- GIPD-investigator version (GIPD-Inv), total score and individual items, at weekly visits.

- Attention-Deficit/Hyperactivity Disorder Rating Scale-Parent Version: Investigator Administered and Scored (ADHD-RS-IV Parent:Inv) total score and subscores at weekly visits.

- Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S) at weekly visits.

- Patient outcomes questions

3. To compare between atomoxetine and OROS methylphenidate the emotional aspects of the patient*s behavior at baseline and endpoint of the study, using

- Emotional Expression Scale for Children (EESC), total score (parent rated).

4. To describe the safety of the treatments during the study in patients with atomoxetine and OROS methylphenidate.

Study description

Background summary

There is insufficient evidence to suggest that missed dosages or so-called *drug holidays* significantly affect the ADHD treatment effect, or that a decreased exposure to medication is related to fewer Adverse Events. In addition, lack of compliance is still a factor in many pharmacotherapeutic treatments. Because of this it is important to investigate what the effect is of missed drug dosages in ADHD patients.

Study objective

The primary objective of the study is to assess the effect of missed doses of atomoxetine and OROS methylphenidate in ADHD patients who are stable on pharmacotherapy based on the patient*s daily behavior as assessed by the Daily Parent Report of Evening and Morning Behavior - Revised (DPREMB-R) scale from the parent perspective.

Study design

Multicenter, parallel matched group, and double-blind (with regard to missing doses), Phase IV study in approximately 130 outpatients with ADHD who are stable on atomoxetine (25, 40, 60, or 80 mg once daily) or OROS methylphenidate (18, 36, or 54 mg once daily). Patients will continue their established treatment during the entire study (approximately 6 weeks).

The intervention phase of the study consists of 3 periods. During the *run-in* period (a maximum of 7 days) patients will receive their usual daily medication. During the *On/Off* period (4 full weeks from Monday up to and including Sunday) the patients will subsequently experience 6 days on which they will receive placebo in stead of their regular medication. During the final *run-out* period (1-5 days) the patients will receive their usual daily medication again.

Intervention

During the screening phase patients taking their medication in the evening should switch to taking medication in the morning, without changing the dose.

During the intervention phase of the study 3 periods can be distinguished:
- During the *run-in* period (a maximum of 7 days) no intervention will take place, patients will take their usual medication and dose.
- During the *on-off* period (4 full weeks from Monday up to and including Sunday) the patients will take a placebo on six days in stead of their usual medication. There will be at most two days within one week on which patients will receive placebo in stead of their usual medication and these will never be two consecutive days.
- During the *run-out* period (1-5 days) there will be no intervention, patients will take their usual medication and dose.

Study burden and risks

During the study six visits are planned. The questions and questionnaires can be a burden to the patient, the parents and teachers. A urine pregnancy test will be performed for girls of child bearing potential.
The patient and/or the patient*s parents may decide to stop the study at any time during the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

[1] Patients must be male or female outpatients of at least 6 years of age, but must not have reached their 17th birthday at Visit 1.
[2] Patients must meet the DSM-IV-TR* diagnostic criteria for ADHD. For the purposes of this study the diagnosis of ADHD will be confirmed at Visit 1 by administering the K-SADS-PL.
[3] Patients must have an ADHD-RS total score of less than or equal to 20 at Visits 1 and 2.
[4] Patients must have a CGI-ADHD-I score of 1 (*very much better*) or 2 (*much better*) at Visits 1 and 2, compared to symptoms before initiation of their current treatment.
[5] Patients must have been taking either atomoxetine or OROS methylphenidate for the treatment of ADHD for at least 3 months and a maximum of 15 months prior to Visit 1.
[6] Patients must have been receiving the same dose of atomoxetine (allowed stable doses: 25, 40, 60, or 80 mg/day) or OROS methylphenidate (allowed stable doses: 18, 36, or 54

mg/day) as monotherapy in a single daily dose during the 4 weeks prior to Visit 1.
[7] Patients must be able to swallow capsules.
[8] Patients must be of normal intelligence as assessed by the investigator (that is, without a general impairment of intelligence and likely, in the investigator*s judgment, to achieve a score of 80 on an intelligence quotient [IQ] test). The administration of a formal IQ test is not an entry requirement for this study. Specific learning disabilities are not considered general impairments of intelligence.
[9] Patients and parents must have an educational level and degree of understanding sufficient to communicate suitably with the investigator and study coordinator.
[10] Patients and parents must have been judged by the investigator to be reliable to keep appointments for clinic visits and all tests and examinations required by the protocol.
[11] For females of child-bearing potential only: Test negative for pregnancy at the time of entry (Visit 1) based on a urine pregnancy test. If local law, an ethical review board (ERB) and/or regulatory bodies have different requirements then these requirements take precedence.
[12] Parents of patients must have signed an informed consent document (ICD) and assent should have been obtained from the patient (when appropriate).

Exclusion criteria

[1] Patients who weigh less than 20 kg or more than 70 kg at study entry.
[2] Patients who have a documented history of bipolar disorder, any history of psychosis or pervasive development disorder (autistic spectrum disorder). If the investigator believes that such a diagnosis has previously been made in error, he/she should contact Lilly and discuss the case history with the Lilly physician responsible for the study prior to allowing the patient to enter the study.
[3] Patients with a history of any seizure disorder (other than febrile seizures) or patients who have taken (or are currently taking) anticonvulsants for seizure control.
[4] Patients at serious suicidal risk as assessed by the investigator (this evaluation must include the items a, b, c, d, and e of K-SADS-PL*s depression module, and there can not be a score of 3 in any of these items).
[5] Patients with a history of severe allergies to more than one class of medications or have had multiple adverse drug reactions.
[6] Patients who have glaucoma.
[7] Patients with a history of alcohol or drug abuse within the past 3 months prior to Visit 1 (excessive or compulsive use as judged by the investigator), or who are currently using alcohol, drugs of abuse, or any prescribed or over-the-counter medication in a manner which the investigator considers indicative of abuse.
[8] Patients with acute or unstable medical conditions, including (but not limited to) inadequately controlled diabetes, hepatic insufficiency (specifically any degree of jaundice), uncorrected hypothyroidism or hyperthyroidism, acute systemic infection, renal insufficiency , gastroenterological, respiratory, endocrine, neurological, immune, or hematological disease should be excluded.
[9] Patients with cardiovascular disease or other conditions that could be aggravated by an increased heart rate or increased blood pressure.

[10] Patients who have a medical condition that would markedly increase sympathetic nervous system activity (for example, catecholamine-secreting neural tumor), or who are taking a medication on a daily basis (for example, albuterol, inhalation aerosols, pseudophedrine) having sympathomimetic activity are excluded. Such medications can be taken on an as-needed basis.
[11] Patients who at any time during the study are likely to need psychotropic medications apart from the drugs under study.
[12] Patients who have used a monoamine oxidase inhibitor during the 14 days prior to Visit 1.
[13] Patients with hypertension which is clinically significant in the opinion of the investigator or who are currently taking an antihypertensive agent for blood pressure control.
[14] Patients who are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an off-label use of an investigational drug or device (other than the study drug used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
[15] Have previously withdrawn from this study or any other study investigating atomoxetine or OROS methylphenidate.
[16] Pregnant or breastfeeding females are excluded from the study.
[17] Sexually active females who do not use a medically acceptable method of contraception are also excluded from the study. For this study, medically acceptable methods of contraception include barrier methods (condom or diaphragm with spermicidal agent) or oral contraception. The rhythm method (abstinence during predicted times of ovulation with unprotected intercourse at other times) or coitus interruptus prior to ejaculation by the male partner are not acceptable means of contraception.
[18] Patients who at any time during the study are likely to begin a structured psychotherapy program aimed at ADHD symptoms are excluded. Structured psychotherapy initiated at least 4 weeks prior to Visit 1 is acceptable; however, after study participation started, only ad hoc supportive or educational therapy is permitted.
[19] Patients whose families anticipate a move outside the geographic range of the investigative site within the anticipated duration of the study.
[20] Patients who will have long-term school holidays (more than 14 days or affecting more than 2 calendar weeks [Monday to Sunday]) within the anticipated duration of the study or starting any anticipated holiday in the last week of the on/off period (Week 4).
[21] Patients not participating in an educational system, i.e. not having a teacher.
[22] Patients who are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
[23] Patients who are Lilly employees.
[24] Patients who are unwilling or unable to participate in recording responses to questionnaires using technology provided by the sponsor.
[25] Patients who have pre-existing identified growth or sexual maturation retardation.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-06-2010
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Strattera
Generic name:	Atomoxetine Hydrochloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	10-08-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO

Date:	16-06-2010
Application type:	First submission

Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	03-09-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	28-01-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	02-02-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	29-03-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	04-05-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-011426-33-NL
CCMO	NL28677.003.09