PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting
AUTHORS	Michalak, Arkadiusz; Chrzanowski, Jędrzej; Kuśmierczyk-Kozieł, Hanna; Klejman, Ewa; Błaziak, Katarzyna; Mianowska, Beata; Szadkowska, Agnieszka; Chobot, Agata; Jarosz-Chobot, Przemysława; Myśliwiec, Małgorzata; Makowska, Iwona; Kalenik, Anna; Zamarlik, Monika; Wolańczyk, Tomasz; Fendler, Wojciech; Butwicka, Agnieszka

VERSION 1 – REVIEW

REVIEWER	Francisco X Castellanos Nathan S Kline Institute for Psychiatric Research, Center of Brain Imaging and Neuromodulation
REVIEW RETURNED	11-Aug-2023

GENERAL COMMENTS	This protocol paper addresses the issue of stimulant treatment for pediatric patients with Type 1 diabetes mellitus (T1D) and co-occurring attention-deficit/hyperactivity disorder (ADHD). It describes a randomized cross-over open label (with blinded individuals collecting ratings) comparison of extended-release capsules of methylphenidate at doses of 18, 36, or 54 mg/day, versus lisdexamphetamine at doses of 30, 50 and 70 mg/day. Treatment will be for 6 months on each compound, with titration by unblinded clinicians who will obtain information from parents and patients, all of whom will be aware of the treatments. This is noted as a limitation, but it is not a major concern. Sample size has been determined based on an expected between treatment effect size of 0.33 SD units on the primary outcome (Conners 3 measures from parents). Accordingly, they plan to approach about 190 children, expecting 150 to enroll, and 135 to take part in the RCT after exclusions, so that they will have data from at least 90 completers. All that seems appropriate and feasible given their catchment of approximately 4000 children with T1D in the four centers which are collaborating in the study. The protocol is extremely well written and conceived. I have one concern, however, which is that the medications and doses being tested parallel a design that was established and funded by the manufacturer of lisdexamphetamine, Shire, as reported by Newcorn et al. (ref #45 in this protocol). Given that the Newcorn et al study was designed by Shire, and that the manuscript was written with substantial assistance credited to Shire or their contractors, I wonder about the possibility that the investigators,

	and/or the study sponsor, which is listed as the Medical University of Lodz, may have also received support from the manufacturer of lisdexamphetamine, such as in the form of providing medication without cost or at a discount. The protocol and consent forms explicitly state that the study is being conducted without commercial interests, but the design of the dose escalations raise questions. Specifically, extended-release methylphenidate capsules release somewhat less than the nominal contents, as the capsule is made of metal, and the osmotic release method does not fully expel all the contents. Thus, an 18 mg capsule is approximately equivalent to 15 mg delivered of immediate release; 36 mg is closer to 30 mg, and 54 mg is closer to 45 mg of methylphenidate in 3 doses of 15 mg each. In the Newcorn et al. study, the fixed dose titration showed superiority of lisdexamphetamine over methylphenidate, whereas the flexible dose titration did not. In this study, the dose titration is fixed, and the steps in the lisdexamphetamine arm are 20 mg increments, vs. 10 mg. increments in the Newcorn et al. study for all but the final increment. Again, makes me wonder if the study was designed to demonstrate superiority of lisdexamphetamine. Thus, I ask that the authors justify their dose titration scheme, and clarify whether they have any informal or undeclared connections with the manufacturers.

REVIEWER	Ronald Burian Ev. Krankenhaus "Königin Elisabeth Herzberge", Psychiatry, Pychotherapy and PSychosomatics
REVIEW RETURNED	11-Sep-2023

GENERAL COMMENTS	This is a very careful designed study and study protocol. As far I can see, the planned date for the study is not to be found in protocol, so please specify. Far more, I would like to recommend you to discuss why you did not plan a control group (e.g. placebo) as there are no previous studies about ADHD medication in this specific subpopulation of children with Diabetes (and ADHD). Second, please discuss why you use an open -label design. At last, in the protocol (f.i.)when you write about "Spnosor-funded devices...") you should mention that the "Sponsor" ist the University of Lodz- and not a Pharma Company.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Francisco X Castellanos, Nathan S Kline Institute for Psychiatric Research

Comments to the Author:

This protocol paper addresses the issue of stimulant treatment for pediatric patients with Type 1 diabetes mellitus (T1D) and co-occurring attention-deficit/hyperactivity disorder (ADHD). It describes a randomized cross-over open label (with blinded individuals collecting ratings) comparison of extended-release capsules of methylphenidate at doses of 18, 36, or 54 mg/day, versus lisdexamphetamine at doses of 30, 50 and 70 mg/day. Treatment will be for 6 months on each compound, with titration by unblinded clinicians who will obtain information from parents and patients, all of whom will be aware of the treatments. This is noted as a limitation, but it is not a major concern. Sample size has been determined based on an expected between treatment effect size of 0.33 SD units on the primary outcome (Conners 3 measures from parents). Accordingly, they plan to approach about 190 children, expecting 150 to enroll, and 135 to take part in the RCT after exclusions, so that they will have data from at least 90 completers. All that seems appropriate and feasible given their catchment of approximately 4000 children with T1D in the four centers which are collaborating in the study.

The protocol is extremely well written and conceived.

We would like to thank Professor Castellanos for devoting his time to read and review our work, and for very supportive comments. We also read the doubts/concerns raised by the reviewer, and noted they were very on point. We discussed them thoroughly within the team and provide a detailed answer below. We hope that the revised manuscript achieved the quality necessary for publication.

I have one concern, however, which is that the medications and doses being tested parallel a design that was established and funded by the manufacturer of lisdexamphetamine, Shire, as reported by Newcorn et al. (ref #45 in this protocol). Given that the Newcorn et al study was designed by Shire, and that the manuscript was written with substantial assistance credited to Shire or their contractors, I wonder about the possibility that the investigators, and/or the study sponsor, which is listed as the Medical University of Lodz, may have also received support from the manufacturer of lisdexamphetamine, such as in the form of providing medication without cost or at a discount. The protocol and consent forms explicitly state that the study is being conducted without commercial interests, but the design of the dose escalations raise questions. Specifically, extended-release methylphenidate capsules release somewhat less than the nominal contents, as the capsule is made of metal, and the osmotic release method does not fully expel all the contents. Thus, an 18 mg capsule is approximately equivalent to 15 mg delivered of immediate release; 36 mg is closer to 30 mg, and 54 mg is closer to 45 mg of methylphenidate in 3 doses of 15 mg each. In the Newcorn et al. study, the fixed dose titration showed superiority of lisdexamphetamine over methylphenidate, whereas the flexible dose titration did not. In this study, the dose titration is fixed, and the steps in the lisdexamphetamine arm are 20 mg increments, vs. 10 mg. increments in the Newcorn et al. study for all but the final increment. Again, makes me wonder if the study was designed to demonstrate superiority of lisdexamphetamine. Thus, I ask that the authors justify their dose titration scheme, and clarify whether they have any informal or undeclared connections with the manufacturers.

Thank you for this remark, as it is extremely important both for research, clinical and patient community that high-quality transparency is maintained in planning and reporting clinical trials of medical products. Indeed, the dose titration protocol was based on that reported by Newcorn et al. The study was used as a point of reference, as it pertains to a similar target population as our study, and utilized doses approved for the pediatric population in European countries (maximal dose for methylphenidate OROS is 54mg daily). This should create a common ground for discussing and comparing our study results.

Still, we would like to discuss our chosen titration scheme in more detail, as some points may not have been made clear in the protocol.
“(For LDX) All patients will receive a starting dose of 30 mg. (…) After a week, a teleconsultation will take place with a psychiatrist who will decide to modify or maintain the dose based on the assessment of its safety and effectiveness. Patients who have a sufficient effect of the drug or develop side effects (which do not result in the need to stop taking medications) will stay at the dose of 30 mg/day. The patients in whom the effect of the drug will be insufficient, and no side effects are observed, the dose will be increased by 20 mg individually depending on age and body weight, up to 50 mg/day.

The next teleconsultations (and possible dose modifications) will take place after 3 and 5 weeks of observation. Each time, possible side effects will be assessed, and the effectiveness of the dose will be verified. Patients who achieve a sufficient effect of the drug will stay with the current dose. Patients who experience side effects will have a dose reduction of 20 mg (down to a minimum dose of 30 mg/day). In patients whose effect of the drug is insufficient, and no side effects are observed, the dose will be increased by 20 mg compared to the usual dose (up to a maximum dose of 70 mg/day).”

Thus, our chosen scheme corresponds to the “flexible titration” rather then to “forced titration” as decribed by Newcorn et al. study. Lowering of the drug dose is allowed in case of intolerance or subjective feeling of “overmedication” reported by the patient. Moreover, after the first 3 months of established treatment, lowering the dose by one step is permitted down to minimum 30mg/day. However, we agree that the dose optimization plan is not without limitations. For example, if not for budget limitations, it would be preferable to start with lower DX dose and allow for more intermediate dosages. Our personal clinical experience is that some younger patients (eg 8-9 year-olds) may benefit from an initial LDX 20mg and longer titration to diminish the risk of side effects.

However, that would heavily increase the cost of drugs as multiple potential dosages should be secured for each patient. Moreover, such a decision would extend the dose optimization process. Therefore, because of economic reasons, we decided to keep the dose optimization plan short and relatively simple.

We agree that the issue of drug release efficacy is an important one and can change the true effective dosages of MPH and LDX being compared. However, this also applies to routine care conditions and might contribute to clinical differences between corresponding MPH and LDX doses. As the primary endpoint of this study is comparing optimized treatment regimens with both drugs with intention of choosing best therapy in the pediatric population with T1D and ADHD, we accept this risk and will discuss it when reporting the results of the trial.

To reflect our discussion, we added a relevant bullet point to the study`s strengths/limitations summary.

As for conflicts of interest, we would like to confirm that, as previously stated, this is purely a non-commercial clinical trial. It is in full funded by a Polish government via Medical Research Agency. We intend to purchase both tested drugs independently via an independent supplier, at full cost. We did contact the manufacturer (Takeda) to inquire about the availability of Elvanse, which turned out to be currently limited and resulted in a delay of trial starting date. If necessary, we can provide an official statement from Takeda that they did not have any role in study design or funding.

The conflict-of-interest statement was updated to include the critical of above-mentioned details.

Also, none of the authors have any explicit or implicit conflicts of interest to disclose, including lecturer`s fees. The trials` principal investigator (AB),a child and adolescent psychiatrist in Region Stockholm until august 2023 utilized lisdexamphetamine in her regular clinical practice in Sweden provided by public health care provider Child and Adolescent Psychiatry the Region Stockholm. Pediatric health care in Sweden, including mental health services and ADHD treatment, is fully tax-funded and free of charge for patients and their families (including visits to child psychiatrists and medications) registered as permanent residents in Sweden. Any contact between public servants and industry is strictly restricted by the Swedish low. All clinical decision making regarding the choice of first- , second- and third-line ADHD medication is based on detailed Regional and National Guidelines.

Reviewer: 2
Dr. Ronald Burian, Ev. Krankenhaus "Königin Elisabeth Herzberge"
Comments to the Author:
This is a very careful designed study and study protocol.

We would like to thank Dr Burian for the effort devoted to the review of our work and the encouraging feedback. We carefully read all comments and answered them point by point below. We hope that after revision the manuscript meets the quality requirements of peer review and the journal.

As far I can see, the planned date for the study is not to be found in protocol, so please specify.

We included a small paragraph specifying the study`s planned timeline in the manuscript, and updated relevant information in the study registry.

Far more, I would like to recommend you to discuss why you did not plan a control group (e.g. placebo) as there are no previous studies about ADHD medication in this specific subpopulation of children with Diabetes (and ADHD). Second, please discuss why you use an open -label design.

Thank you for this comment. Indeed, the chosen design deserves a more detailed explanation. The decision to forgo a placebo group has mainly an ethical motivation. There is ample evidence that stimulants are an essential part of ADHD therapy, and that they confer considerable benefits to the patients. There are little arguments suggesting that children with ADHD and type 1 diabetes would be in this regard any different from general population. In fact, clinical observations clearly show that the severity of unmedicated ADHD symptoms heavily impairs general quality of life and diabetes management. Therefore, we viewed it as unethical to recruit pediatric participants without offering any active treatment.

However, some comparison to no-treatment conditions will be possible in the current design. Due to ADHD being heavily underdiagnosed in Polish pediatric population, we expect a considerable part of the study group to be treatment-naive at inclusion, which will enable us to perform a paired comparison between baseline and end of treatment for each drug.

Secondly, an open-label design was chosen for two reasons. First, blinding the patients would necessitate over-encapsulation of both MPH and LDX original capsules (as in the study reported by Newcorn et al, DOI: 10.1007/s40263-017-0468-2). However, we view such operation as not feasible in our study setting, as: 1) bigger additional capsule might be difficult to swallow for smaller children, 2) additional capsule could be easily broken to reveal the visually distinct studied drug. Second, even if visual blinding could be effectively maintained, the studied drugs differ in terms of their time of action and could be easily differentiated based on the ADHD symptoms change. Therefore, we decided to keep the study open-labeled and devote the allocated funding (capped by the funding agency) to other measures to assure the study`s quality. Still, to preserve research quality, we intend to blind the study assessor who will be measuring the study`s primary endpoints to minimize bias connected to the investigators` expectations.

The whole reasoning behind those two design choices exceeded the allowed world-count of the manuscript, however, we included its key points in relevant section of the manuscript (see tracked changes).

At last, in the protocol (f.i.)when you write about "Sponsor-funded devices...") you should mention that the "Sponsor" ist the University of Lodz- and not a Pharma Company.

Thank you for this remark. We clarified this throughout the manuscript, emphasizing that devices are provided by the University (which acts as Sponsor of the study). We also reviewed the whole protocol (attachment) and clarified appropriate wordings.

VERSION 2 – REVIEW

REVIEWER	Francisco X Castellanos Nathan S Kline Institute for Psychiatric Research, Center of Brain Imaging and Neuromodulation
REVIEW RETURNED	23-Oct-2023

GENERAL COMMENTS	I appreciate the authors' forthright responses. A couple of minor points: in the abstract, the authors refer to the study as a 2nd phase trial; elsewhere they use the standard nomenclature of "a phase 2 trial." Consistency is desirable to avoid confusing readers. In line 158, I recommend: "The project consulted with and was supported by a national patient organization..." In line 340, "to their leading physicians' recommendations" should be "to their attending physicians' recommendations..." I concur that the study is likely to yield clinically valuable insights into a pressing clinical problem.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Francisco X Castellanos, Nathan S Kline Institute for Psychiatric Research

Comments to the Author:

I appreciate the authors' forthright responses.

Re: We are grateful for the encouraging comments and further suggestions. We revised the manuscript accordingly.

A couple of minor points: in the abstract, the authors refer to the study as a 2nd phase trial; elsewhere they use the standard nomenclature of "a phase 2 trial." Consistency is desirable to avoid confusing readers.

Re: We corrected the phrasing for consistency.

In line 158, I recommend: "The project consulted with and was supported by a national patient organization..."

Re: We corrected this line appropriately.

In line 340, "to their leading physicians' recommendations" should be "to their attending physicians' recommendations..."

Re: We corrected this line appropriately.

I concur that the study is likely to yield clinically valuable insights into a pressing clinical problem.

Re: We appreciate the positive comments and hope that the study results will prove valuable for care providers working with children with type 1 diabetes and concurrent ADHD.