International Naturalistic Cohort Study of ADHD and Substance Use Disorders (INCAS): clinical characteristics, treatment, and outcome

2019-08-08

RESEARCH PLAN

1. Background

Childhood attention deficit hyperactive disorder (ADHD) is associated with a high risk of substance use disorders (SUDs) (1-3). Not surprisingly, adult ADHD is highly prevalent in treatment seeking SUD patients. The International ADHD in SUD Prevalence Study (IASP) recently found a DSM-IV ADHD prevalence of 13.9 % in adult treatment seeking substance users, whereas 16 % fulfilled DSM-5 criteria for ADHD. In a recent meta-analysis, 23% of all treatment seeking SUD patients met diagnostic criteria for adult ADHD (4).

However, there is a lack of knowledge regarding the efficacy of treatments for combined ADHD/SUD. A series of randomized controlled trials with a standard dose of the psychostimulant methylphenidate, one of the most commonly used medications for adult ADHD, failed to show any significant main effects on the primary outcome variables selected, such as reduction of ADHD symptoms or reduction of alcohol or drug use (5). However, one randomized placebo-controlled study using atomoxetine for the treatment of patients with alcohol dependence and ADHD demonstrated encouraging results, with reductions in both ADHD symptoms and alcohol consumption (6). A more recent randomized placebo-controlled study using methylphenidate doses up to 180 mg/day showed significant reductions in both ADHD symptoms and drug consumption in amphetamine dependent criminal offenders with ADHD (7). The most recent study tested the effect of extended-release mixed amphetamine salts using doses between 60 to 80 mg along with cognitive behavioural therapy (CBT) and found improvements in both

ADHD symptoms and drug use in patients with cocaine dependence and comorbid ADHD(8). Finally, an ongoing study is testing the effectiveness of integrated CBT for SUD patients with adult ADHD (9). Whereas these clinical trials typically address the efficacy of a specified intervention in a selected population, they provide limited knowledge on the natural course of the disorders and on predictors of treatment efficacy in a routine clinical setting.

1.1 AIM

The aim of this study is to describe the treatments provided and the outcomes regarding ADHD symptoms and substance use in adult treatment seeking SUD patients with ADHD:

(1) to describe the treatment modalities provided to treatment seeking adult SUD patients with comorbid ADHD
(2) to describe differences in outcome for different treatment modalities (pharmacological psychological/psychosocial treatment)
(3) to identify predictors (such as gender, SUD and ADHD severity, comorbidity) for retention in treatment, ADHD symptoms, and substance use
(4) to investigate the safety profile of pharmacological treatment of ADHD in a naturalistic cohort of treatment seeking substance users with regard to adverse events (e.g. cardiovascular, psychiatric, misuse and diversion of medication)
(5) to derive hypotheses for future randomized trials
(6) to describe differences in treatment outcomes, predictors and baseline characteristics between treatment seeking adult SUD patients with and without comorbid ADHD

2 Design

This is a naturalistic multicentre observational cohort study in 1000 treatment seeking adult DSM-5 SUD patients with DSM-5 adult ADHD, and in 200 treatment seeking adult DSM-5 SUD patients without DSM-5 adult ADHD. Information is collected at baseline (treatment initiation), at four weeks, at three months, and at nine months after inclusion.

2.1 Research subjects

Patients will be consecutively recruited from the caseload of the participating addiction/psychiatric treatment centres. All patients with ADHD diagnosis starting a new treatment period at that

particular treatment centre are asked to participate. A patient who is assessed for ADHD at the start of the treatment period will be invited to join the study after the diagnostic procedure. For all patients included in the study ADHD diagnosis is confirmed using a checklist for DSM-5 symptoms (10). For the 200 individuals without ADHD, the inclusion criteria and study protocol is identical, with the exception that they do not fulfil the DSM-5 criteria of adult ADHD.

2.1.1 Inclusion Criteria

- Men and women ≥18 years of age seeking treatment for SUD at any of the participating sites
- ADHD diagnosis according to DSM-5 (10, 11)
- SUD diagnosis (DSM-5 *moderate to severe*, ICD-10 *dependence*)(12)
- Informed consent

2.1.2 Exclusion Criteria

There are no formal exclusion criteria except incapability to complete the assessment.

2.2 Ethics

Each participating country will submit the study protocol for approval by their Institutional Review Board (IRB)/Ethical Review Board (ERB) according to the laws and regulations of that country.

2.2.1 Informed consent

All invited patients will receive oral and written information about the study, risks, benefits, and procedures, that the participation is voluntary, and that they may withdraw their participation at any time without any consequences to their treatment. Patients who agree to participate will be asked to sign an informed consent form, indicating that they fully understand the nature of the study and the consent form.

The informed consent must also state the aim of the study, the study procedure and that the participant can acquire additional information about the study at any time during the study.

Patients who do not comprehend written or verbal information because of intoxication will be asked about participation on a later occasion.

2.2.2 Risks and benefits

Patients seeking treatment might experience that their treatment may be negatively affected if they decline participation in the study. To avoid this, patients must receive unambiguous information, written and oral, about the option to decline participation without any impact on their treatment. Patients will receive treatment according to the regular clinical procedure of the respective center and any risks for the patients in connection to the study *per se* are deemed as small. On the contrary, the structured intake and follow-up procedures used may be considered beneficial for the patient. On a general level, patients with ADHD + SUD may benefit from the study as the goal is to assess factors beneficial or negative for treatment success.

2.3 Outcome measures

The study will investigate differences between treatment modalities with regard to:
1a.ADHD symptoms measured with adult the Adult ADHD Self-Report Scale (ASRS)(13) at 3 months follow-up.
1b. substance use measured with Time Line Follow-Back (TLFB) (14) defined as number of days with heavy alcohol use or days of illicit drug use the last 30 days at 3 months follow-up.
2a. ADHD symptoms measured with adult ASRS (13) at 9 months follow-up
2b. substance use measured with TLFB (14) defined as number of days with heavy alcohol use or days of illicit drug use the last 30 days at 9 months follow-up.

Heavy alcohol use is defined as more than 4 or more (women) or 5 or more (men) standard drinks per day. A standard drink is defines as 12 g ethanol.

2.3.1 Key secondary outcome measure

Retention to treatment
Retention to treatment is defined as time (number of days) to drop-out after inclusion. The drop-out date is defined as the last contact between the patient and the physician/clinical staff against advice of the staff (regardless of reason).

2.3.2 Secondary outcome measures

at follow-up 3 and 9 months

a) ADHD symptoms according to the Adult ADHD Self-Report Scale extended version
b) Employment
c) Use of emergency services: data collected through public records reported by the participant
d) Number of accidents as reported by the participant
e) Days with any alcohol use during the last 30 days

2.3.3 Predictors

The following baseline variables are investigated as potential predictors for outcome :

a) Substance use: substance, number of days with use, number of days of heavy use.
b) Route of administration: oral, nasal, inhalant, dermal, rectal, or injection
c) ADHD severity measured as the number of ADHD symptoms according to the ASRS/ASRS extended version
d) Current psychiatric diagnoses according to DSM-5
e) Functional impairment measured with CGI-S
f) Quality of life measured with EQ-5D
g) Feeling of self-efficacy
h) Employment status
i) Civil status
j) Age
k) Gender

(see attached questionnaires for details)

2.4 Data analysis

2.4.1 Sample size

In this non-interventional observational study the targeted sample size is not primarily based on statistical power, but rather to enable a solid description of the prospective clinical course in the specific patient population. In addition to the descriptive analyses regarding baseline factors related to the 3 months outcome will be assessed. As the power of these analyses will depend on many factors such as number of groups, distribution of patients between groups and missing data, it is

difficult to estimate the power needed. However, in the optimal case when there are only two groups of interest, with 300 patients per group and very few missing observations, there will be approximately 80 % power to detect a moderate effects size (Cohen's d approximately 0.5) at a 5 % significance level. In reality there will most likely be a less favorable distribution between groups and more missing data and thus a larger effect size will be needed in order to be detectable.

2.4.2 Statistical methods

The statistical analyses will primarily be descriptive, in terms of descriptions of the population at baseline as well as at follow-up. The inferential statistical analyses will comprise (but not limited to) regression models (analysis of covariance and logistic regression depending on outcome measure) with the outcomes at follow-up as dependent variables and baseline variables as independent factors. Both univariate and multivariate models will be considered.

2.4.3 Missing data

As all missing data will lower the quality of the study efforts will be made to ensure that the number of missing evaluations will be kept to a minimum.

As for the descriptive analyses missing data will not be replaced, nor for the inferential statistical analyses. However, analyses will be performed regarding factors related to the probability of having missing values, as well as sensitivity analyses of the robustness of the results when imputing values when missing.

2.4.4 Sample description

The number of participants at each site will vary depending on the turnover of patients in that particular site. Each participating site will aim at enrolling a minimum of 50 patients with the actual number to be agreed on before that centre enters the trial.

Both males and females will be recruited; the female percentage is expected to be approximately 30%.

As adult ADHD occurs in all ethnic groups, a concerted effort will be made to include sites with patient populations that include individuals from various ethnic backgrounds (bearing in mind differences between participating countries), in order to ensure the generalizability of findings to the overall treatment population.

2.4.5 Treatment

Treatment modalities are defined as: a) Stimulants (short or long-acting methylphenidate, (lis)dexamphetamine, racemic amphetamine salts, b) atomoxetine, c) quanfacine, d)psychological treatment for ADHD (cognitive behaviour therapy CBT, skills-training; both individual or group) d) computerized cognitive training, neurofeedback, e) non ADHD-specific psychiatric pharmacotherapy, f) non ADHD-specific psychological treatment, and g) combinations of a-f

2.4.6 ADHD symptoms

ADHD symptom reduction will be assessed at follow up using the ASRS/ASRS extended version at follow-up. A score will be obtained from the ASRS/ASRS extended version at follow-up and will be compared to the baseline score. A treatment responder is defined as a person with ≥30% improvement of ARS scores.

2.4.7 Substance use

Substance use will be assessed using Time- Line-Follow-Back (TLFB) interview for the last 30 days. TLFB is performed at baseline, at 3 months and at 9 months.
Other information about substance of use (e.g. routes of entry) will be collected using a specially developed questionnaire (see attachment).

2.4.8 Other

Information about substance use treatment, employment or remand/incarceration or other sheltered environment will be collected using a specially developed questionnaire (See attachment New registration)

2.5 Study procedures and instruments

2.5.1 Personnel

A research coordinator at a local site is responsible for patient inclusion and local coordination of the study. A central research coordinator will assess the quality of the overall dataset generated by the participating treatment centers. Each site is responsible for the language translation of the research questionnaires according to WHO standards.

2.5.2 Structured screening

Before treatment starts, a set of baseline measurements are performed and information is collected from each participant by the clinician/research staff. A questionnaire (see attachment) is filled out for each participant on a study specific website or by using a paper questionnaire.
Patient characteristics include: age, gender, ADHD measures (subtype, symptom scores), substance use measures (type and severity of addiction, level of abstinence, age of first use), psychiatric comorbidities, prior and current medication use, and psychosocial measures (work, education, employment status, possible existing support systems).

2.5.3 Treatment

Clinical decisions on diagnosis and treatment is the responsibility of the patient's physician at each participating site, and is unrelated to the current protocol. It is assumed that each participant has been offered the best available treatment option taking into account patient preference and local guidelines. Monitoring of medication compliance, vital signs (heart rate and blood pressure), side effects and other clinical parameters is the responsibility of each participating site.

2.6 Instruments

2.6.1 Screening

- A brief structured interview for inclusion/exclusion criteria.
- If the patient agrees to participate, and after making sure that the patient has understood the information, an informed consent form is signed.

2.6.2 Inclusion

Inclusion must occur within 30 days of screening. Each participant is given a unique identification code to allow follow-up. The code lists are stored separately from the collected data.

On the day of inclusion, the following baseline data is collected:

- ASRS/ASRS extended version (comprising ASRS 18-item version + additional 18 items) to measure ADHD symptoms
- A questionnaire on key variables such as demographics, substance use, prior treatment, and additional psychiatric diagnoses is filled out by clinician/research staff (see attachment)
- TLFB
- EQ 5D (15)
- Clinical Global Impression Severity (CGI-S) (16)

- Self-efficacy (17)

2.6.3 Follow-up

Follow-up measurement is performed by telephone, or in person at 3 and 9 months (+/- 4 wks) from the inclusion. The 4 weeks follow-up is performed via patient files. Patient files are also be used for outcomes such as retention to treatment. All follow-ups will include measures of substance use (as defined above), ADHD symptoms, treatment retention, and participation in structured psychoeducation or psychotherapy, and medication use. (See attachment 2 and 3)

2.6.4 4-week follow-up

- Patient files are used to check treatment continuation/discontinuation

2.6.5 3-months follow-up

- Structured Interview, telephone or in person (see attachment)
- ASRS 18-item/ASRS extended version to measure ADHD symptoms (10-15 min)
- TLFB
- CGI
- EQ-5D
- Self-efficacy
- Patient files are used to check treatment continuation/discontinuation and types of treatment received

2.6.6 9-months follow-up

- Structured Interview, telephone or in person (see attachment)
- ASRS 18-item/ASRS extended version to measure ADHD symptoms (10-15 min)
- TLFB
- CGI
- EQ-5D
- Self-efficacy
- Patient files are used to check treatment continuation/discontinuation and types of treatment received

2.6.7 Description of instruments

2.6.7.1 TLFB

The TLFB assesses the following areas of substance use: cocaine, amphetamine, alcohol, cannabis, opiates, and an option for other substances (e.g. ecstasy, hallucinogens, inhalants, and sedative hypnotics / anxiolytics). The TLFB tracks the use of each substance for the preceding 30 days. Data extracted from TLFB is inserted into the CRF which then constitutes the source data.

2.6.7.2 CGI

The CGI-I is a 7-point scale rated as progressively improved from baseline (rated from 3 to 1 with increasing improvement), no change from baseline (rated 4) or progressive worsening (rated from 5 to 7).

2.6.7.3 EQ5D

EQ-5D is a standardized instrument for use as a measure of health outcome.

2.6.7.4 Self-efficacy

Three questions on self-efficacy: relevance, motivation, and confidence (17) found predictive of remaining abstinent.

2.6.7.5 For each site optional scales:

- *Fagerstrom Test for Nicotine Dependence* (see attachment). Optionally added at baseline, 3 months follow-up and 9 months follow-up.
- *Assesment of Craving* (see attachment). Optionally added at baseline and all follow-up visits.
- *Questionnaire on Anger and Aggression* (see attachment). Optionally added at baseline.
- *Sensitivity to Punishment and Sensitivity to Reward Questionnaire* (see attachment). Optionally added at baseline and 3 months follow-up.
- *Difficulties in Emotional Regulation* (see attachment). Optionally added at baseline, 3 months follow-up and 9 months follow-up.
- *Religious salience* (see attachment). Optionally added at baseline and all follow-up visits.

2.7 Handling of Case Record Forms (CRF)

All data collected during the study will be documented in a web-based CRF, unique for each subject. In case the local site uses a paper and pen form, the site is responsible of inserting the data into the web-based CRF. The content of the electronic CRF is defined as source data. Each site will have access to their CRFs. The data manager at Karolinska Institutet has access to the all sites´ CRFs. After the data collection, the data will be exported into a statistical database, evaluated and stored in accordance with the Swedish Personal Data Act (PUL). Each site is responsible for ensuring that personal data is handled according to each site's IRB approval.

2.8 Monitoring of the study and Quality Assurance

The study will be carried out in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (18).
The data entry is monitored by the central project coordinator on a monthly basis using the web-based CRF. Each participating site is responsible for their external data monitoring and quality assurance. Signed monitor reports from each site will be submitted to the central coordinators office for quality assurance and archiving.
Each site is responsible for keeping study documents in accordance with the legislation and regulations of that specific country. Archives must be kept so that documents can be examined by the responsible authorities.

Any changes and corrections of documents will be logged in the CRF system.

References

1. Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. Journal of the American Academy of Child and Adolescent Psychiatry. 2011;50(1):9-21. Epub 2010/12/16.
2. Groenman AP, Oosterlaan J, Rommelse N, Franke B, Roeyers H, Oades RD, et al. Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. Addiction. 2013;108(8):1503-11. Epub 2013/03/20.
3. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev. 2011;31(3):328-41. Epub 2011/03/09.
4. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, Smit F, Crunelle CL, Swets M, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. Drug and alcohol dependence. 2012;122(1-2):11-9. Epub 2012/01/03.
5. Wilens TE, Morrison NR. Substance-use disorders in adolescents and adults with ADHD: focus on treatment. Neuropsychiatry. 2012;2(4):301-12.
6. Wilens TE, Adler LA, Weiss MD, Michelson D, Ramsey JL, Moore RJ, et al. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. Drug and alcohol dependence. 2008;96(1-2):145-54. Epub 2008/04/12.
7. Konstenius M, Jayaram-Lindström N, Guterstam J, Beck O, Philips B, Franck J. Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. Addiction. 2014;109(3):440-9.
8. Levin FR, Mariani JJ, Specker S, et al. Extended-release mixed amphetamine salts vs placebo for comorbid adult attention-deficit/hyperactivity disorder and cocaine use disorder: A randomized clinical trial. JAMA psychiatry. 2015;72(6):593-602.
9. van Emmerik-van Oortmerssen K, Vedel E, Koeter MW, de Bruijn K, Dekker JJ, van den Brink W, et al. Investigating the efficacy of integrated cognitive behavioral therapy for adult treatment seeking substance use disorder patients with comorbid ADHD: study protocol of a randomized controlled trial. BMC psychiatry. 2013;13:132. Epub 2013/05/15.
10. APA. Diagnostic and statistical manual of mental disorders
The American Psychiatric Association. 2013;5th ed.
11. APA. Diagnostic and Statistical Manual of Mental Disorders. 4 th edition. Text Revision edition. Washington, DC: The American Psychiatric Association; 2000.
12. Organization WH. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva: : World Health Organization; 1992.
13. Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med. 2005;35(2):245-56. Epub 2005/04/22.
14. Sobell LC, Toneatto T, Sobell MB, Leo GI, Johnson L. Alcohol abusers' perceptions of the accuracy of their self-reports of drinking: implications for treatment. Addictive behaviors. 1992;17(5):507-11. Epub 1992/09/01.
15. . Available from: http://www.euroqol.org/about-eq-5d/publications/user-guide.html

16. W G. ECDEU Assessment Manual for Psychopharmacology-Revised (DHHS Publ No ADM 91-338). . 1976 Contract No.: .

17. Ludwig F, Tadayon-Manssuri E, Strik W, Moggi F. Self-efficacy as a predictor of outcome after residential treatment programs for alcohol dependence: simply ask the patient one question! Alcoholism, clinical and experimental research. 2013;37(4):663-7. Epub 2012/10/19.
18. World Medical Organization. Declaration of Helsinki. British Medical Journal. 1996;313(7070):1448 -9.