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The International Collaboration on ADHD and Substance Abuse (ICASA): Mission, Results, and Future Activities

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Abstract
Background: The *International Collaboration on ADHD and Substance Abuse* (ICASA) is a network of 28 centers from 16 countries initiated to investigate the link between attention deficit-hyperactivity disorder (ADHD) and substance use disorder (SUD). In this article, we present the mission, the results of finished studies, and the current and future research projects of ICASA. Methods: During the past 10 years, 3 cross-sectional studies were conducted: two International ADHD in Substance use disorders Prevalence (IASP-1 and IASP-2) studies, directed at the screening, diagnosis, and the prevalence of adult ADHD in treatment-seeking patients with SUD, and the Continuous performance test for ADHD in SUD Patients (CASP) study, testing a novel continuous perfor-

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mance test in SUD patients with and without adult ADHD. Recently, the prospective International Naturalistic Cohort Study of ADHD and Substance Use Disorders (INCAS) was initiated, directed at treatment provision and treatment outcome in SUD patients with adult ADHD. ***Results:*** The IASP studies have shown that approximately 1 in 6 adult treatment-seeking SUD patients also have ADHD. In addition, those SUD patients with adult ADHD compared to SUD patients without ADHD report more childhood trauma exposure, slower infant development, greater problems controlling their temperament, and lower educational attainment. Comorbid patients also reported more risk-taking behavior, and a higher rate of other psychiatric disorders compared to SUD patients without ADHD. Screening, diagnosis, and treatment of this patient group are possible even before abstinence has been achieved. The results of the CASP study are reported separately in this special issue. ***Conclusions:*** The ICASA research to date has demonstrated a high prevalence of comorbid ADHD and SUD, associated with elevated rates of additional comorbidities and risk factors for adverse outcomes. More research is needed to find the best way to treat these patients, which is the main topic of the ongoing INCAS study.

Introduction

Attention deficit-hyperactivity disorder (ADHD) and substance use disorder (SUD) often co-occur and have great clinical relevance [1–4]. However, adult ADHD is still under debate in the literature, especially in the context of SUD [5]. As a result, ADHD is often overlooked and undertreated among adults with SUD. In order to improve the scientific basis for the screening, diagnosis, and treatment of ADHD-SUD comorbidity, the *International Collaboration on ADHD and Substance Abuse* (ICASA) was established as a foundation under Netherlands law in September 2010. Here, we describe the mission of the ICASA Foundation and summarize some of the findings of our first cross-sectional studies, including those from (1) the first International ADHD in Substance use disorders Prevalence (IASP-1) study, (2) the second International ADHD in Substance use disorders Prevalence (IASP-2) study, and (3) the Continuous performance test for ADHD in SUD Patients (CASP) study. In addition, we provide a short description of other ICASA Network publications and the study design of ICASA's first ongoing prospective study: the International Naturalistic Cohort Study of ADHD and Substance Use Disorders (INCAS).

ICASA Foundation's Mission

The ICASA Foundation's mission is "*to contribute to a substantial decrease in the proportion of ADHD patients developing an addiction/substance use disorder and to substantially improve the detection, diagnosis and treatment of patients having both ADHD and SUD*." ICASA strives to achieve this by performing and coordinating high-quality epidemiological clinical research. The ICASA organization consists of the ICASA board of 6 members, a research network currently consisting of 54 participants, representing over twenty addiction and mental health institutes from 16 different countries, and the ICASA research office, positioned at the Radboud University Medical Centre (Radboudumc) and the Nijmegen Institute for Scientist-Practitioners in Addiction in Nijmegen, The Netherlands. Further information on the ICASA Foundation can be found at www.adhdandsubstanceabuse.org.

First International ADHD in Substance Use Disorders Prevalence Study

Background/Study Design

In order to learn more about the magnitude of the relationship between ADHD and SUD, a systematic review and meta-analysis was performed of existing prevalence studies. In their meta-analysis, van Emmerik-van Oortmerssen et al. [1] calculated that the average percentage of ADHD cases in SUD patients based on 29 included studies was 23.1%. As these results were based mainly on US studies using different sampling and assessment procedures, the ICASA network decided to conduct the *IASP-1 study*[6], a cross-sectional study including 3,578 treatment-seeking SUD patients from 47 sites in 10 countries (Norway, Sweden, The Netherlands, Belgium, France, Spain, Switzerland, Hungary, Australia, and the USA) using the Adult ADHD Self-Report Scale (ASRS) as a screener for ADHD, the Conners' Adult ADHD Diagnostic Interview for DSM-IV for the diagnosis of adult ADHD, the Mini-International Neuropsychiatric Interview (MINI-Plus) for the diagnosis of SUD and other DSM-IV Axis I disorders, and the Structured Clinical Interview for DSM-IV Axis II Disorders for the diagnosis of borderline personality disorder.

Main Findings

In this study, the prevalence of adult ADHD in treatment-seeking SUD patients ranged from 7.6% (CI 95%: 4.1–11.1) in the Hungarian sample to 32.6% (CI 95%:

26.4–38.8) in the Norwegian sample. Moreover, we observed higher prevalence rates for drug-dependent compared to alcohol-dependent patients, and higher prevalence rates in outpatient compared to inpatient samples [7]. In all participating sites, adult ADHD was more prevalent than the 2.5% ADHD prevalence in adults in the general population as presented by Simon et al. [8].

To establish the validity of the ASRS 6-item version, for adult ADHD in treatment-seeking SUD patients, van de Glind et al. [9] calculated sensitivity and specificity of the 6-item version of the ASRS with the CAADID as external criterion at intake and 1–2 weeks later with similar results at both time points (sensitivity = 0.84, 95% CI: 0.76–0.88; specificity = 0.66, 95% CI: 0.63–0.69). Since there is no specific instrument to diagnose ADHD in SUD patients, we assessed the validity of the ADHD module of the MINI-Plus in SUD patients, using the CAADID as external criterion (Ramos Quiroga, under review). Sensitivity of the MINI-Plus ADHD module was 74%, specificity was 91%, and Kappa was 0.60.

Taken together, these findings show that adult ADHD is highly prevalent in treatment-seeking SUD patients in the USA, Europe, and Australia, and patients can be effectively screened at intake, even during active substance use. Therefore, every patient in an addiction treatment center should be screened at intake for the presence of a comorbid diagnosis of adult ADHD.

Additional Findings

In their report on comorbidity in the IASP-1 study, Van Emmerik-van Oortmerssen et al. [10] showed that antisocial personality disorder, borderline personality disorder, and mood disorders were more prevalent in SUD patients with adult ADHD (SUD + ADHD) compared to SUD patients without adult ADHD (SUD-ADHD). Seventy-five percent of the SUD + ADHD patients had at least 1 additional comorbid disorder compared to 37% of SUD-ADHD patients. Furthermore, Wapp et al. [11] showed that SUD patients with BPD in the IASP-1 study had a significantly higher prevalence of comorbid adult ADHD (OR = 3.16), compared to SUD patients without BPD. Kaye et al. [5] reported that in the IASP-1 study, childhood ADHD persisted into adulthood in 72.8% of all cases. ADHD persistence was significantly associated with a family history of ADHD and the presence of conduct disorder and antisocial personality disorder.

Based on data from the IASP-1 study, Konstenius et al. [12] reported increased rates of ADHD (19.5%) in SUD patients with childhood trauma exposure (including sexual, physical, and emotional abuse; neglect; and family violence), compared to those without trauma (8.5%). In addition, Skutle et al. [13] showed that in the IASP-1 study, SUD with ADHD patients had a significantly slower infant development than SUD without ADHD patients, more problems controlling their temperament, and lower educational attainment.

Based on the Australian subsample of the IASP-1 study, Young et al. [14] provided evidence for increased drug dependence and chronicity in treatment-seeking SUD patients with a positive screen for ADHD. Based on the same Australian subsample, using additional questionnaires on risk-taking behavior, Kaye et al. [15] showed that ADHD symptom status was independently associated with a greater overall number of driving offences, a higher frequency of driving without a seatbelt, a greater likelihood of having driven without a valid license, more at-fault accidents, and having one's license disqualified at the time of interview.

Other ICASA Network Publications

Reviews on ADHD and SUD

In their review of the literature, Slobodin and Crunelle [16] discuss the role of sociocultural aspects in the link between ADHD and SUD, including cultural factors such as perceptions of normal and abnormal behavior, behavioral norms, attitudes and knowledge about mental health problems, and factors related to the utilization of mental health services among certain populations. They conclude that a better understanding of the role of culture and context in the ADHD-SUD link may not only shed light on the large variation in the prevalence of ADHD in SUD patients across cultures but also assist in early detection of ADHD in SUD patients.

Slobodin et al. [17] also reviewed the literature about the role of different aspects of impulsivity (disinhibition, impulsive choice, and sensation seeking) as independent risk factors for SUD in patients with ADHD. They concluded that different impulsivity constructs operate independently and interact with each other to affect adult risk-taking behavior and SUD in patients with childhood ADHD [17].

Consensus Statement on Screening, Diagnosis, and Treatment of ADHD in SUD Adult Patients

To inform professionals working with patients suffering from SUD and (possible) adult ADHD, ICASA reviewed the existing scientific literature on screening, di-

agnosis, and treatment of SUD patients with adult ADHD and synthesized a consensus guide for clinical practice. In this consensus statement, Crunelle et al. [18] highlight the importance of screening for adult ADHD in all SUD populations and suggest how screening and diagnostic procedures can be carried out. Finally, the currently available evidence for treatment of ADHD in SUD patients was also summarized [18]. To serve more professionals, the consensus statement has now been translated into Dutch [19] and German [20], and we are working on a French and Swedish version.

Ongoing Projects

ICASA collected DNA in a subsample of the IASP-1 study and these DNA data are currently being analyzed. Furthermore, the IASP study was expanded to Puerto Rico and South Africa (IASP-2). Details on study design and some of the data from the IASP-2 study are presented in this special issue of European Addiction Research [21, 22]. In the CASP study, we collected data with a novel continuous performance test [23] in SUD patients with and without ADHD. Results from this study can be found in this special issue of European Addiction Research [24].

Finally, we intend to merge our data of IASP-1 and IASP-2 studies with other datasets in order to learn more about SUD patients with and without ADHD. An example is the pilot study by Regnart et al. [25], investigating the ASRS in a South African sample of treatment-seeking SUD patients. In this study, 43.3% of the SUD patients screened positive for ADHD, which is very similar to the 40.9% screen positives in the IASP-1 study [6].

New ICASA Study: INCAS

Background

There is a lack of evidence-based treatment options for SUD patients with comorbid ADHD due to limited research in this population [18]. Although some randomized controlled trials have investigated specific pharmacological treatments in selected populations, they provide limited data on the natural course of the disorders and predictors of treatment efficacy in routine clinical settings [2, 3].

Therefore, INCAS aims to investigate the treatment modalities provided to treatment-seeking SUD patients with comorbid ADHD, and to identify predictors for successful treatment outcomes, as measured by retention, substance use, and ADHD symptoms. In addition, the tolerability and safety profile of different pharmacological treatments will be recorded.

Study Design

This prospective international cohort study has a naturalistic observational design, with a recruitment target of 600 treatment-seeking adult SUD patients with comorbid adult ADHD. Patients are currently (May 2020) recruited at 23 different sites in Belgium, Germany, Hungary, The Netherlands, Spain, Sweden, Switzerland, and the USA, whereas recruitment will start soon in Australia and France. Data are collected from patient files, interviews, and self-rating scales at inclusion, after 4 weeks, 3 months, and 9 months.

Each participating treatment center invites consecutive patients with ADHD and comorbid SUD to participate in the study. The planned recruitment period is from July 2017–June 2021.

Methods

The primary outcomes are retention, ADHD symptoms, and substance use at 3 months' follow-up. At 4 weeks, 3 months, and 9 months, ADHD symptoms are measured by the ASRS and substance use as number of days with heavy alcohol use and/or days with illicit drug use during the last 30 days before assessment using the Timeline Followback method. In addition, overall functioning will be assessed with the Clinical Global Impression Severity/Improvement scale and the EuroQol-5D.

Information on provided treatment, such as psychological and pharmacological treatments, including stimulant dosing, will be assessed continuously. At baseline and follow-up visits, the following predictors of treatment provision and treatment outcome are assessed through information collected via interviews and patient files: sociodemographic data (housing, employment, level of education, etc.), age, gender, previous treatments, other psychiatric comorbidities, adverse events (in relation to ADHD medications), and misuse/diversion of prescriptive drugs (see Table 1).

Conclusions

ICASA is an active group of clinicians and clinical researchers that conducted important cross-sectional studies on adult ADHD in treatment-seeking SUD patients (IASP-1, IASP-2, and CASP). Currently, ICASA is executing its first prospective study on treatment provision

Table 1. Overview of administrated self-rating scales in the INCAS study

Instrument	Items	Administrated at
Expanded ASRS	36	Baseline, 3 and 9 months
EQ-5D	5	Baseline, 3 and 9 months
Self-efficacy	3	Baseline, 3 and 9 months
Fagerstrom test for nicotine dependence	6	Baseline, 3 and 9 months
Assessment of craving	3	Baseline, 3 and 9 months
Sensitivity to punishment and sensitivity to reward questionnaire	17	Baseline and 3 months
Difficulties in emotion regulation-16	16	Baseline, 3 and 9 months
Religious salience	3	Baseline, 3 and 9 months
Questionnaire on anger and agression	8	Baseline

INCAS, International Naturalistic Cohort Study of ADHD and Substance Use Disorders; ASRS, Adult ADHD Self-Report Scale; EQ-5D, EuroQol-5D.

and treatment outcome in treatment-seeking SUD patients with adult ADHD (INCAS).

So far, our review/meta-analysis [1] and the results of the IASP-1 study [5–7, 9, 10, 12–15] show that approximately 1 in 6 SUD patients meet criteria for adult ADHD. The results also show that compared to SUD patients without ADHD, these patients report more childhood trauma exposure [12], slower infant development, greater problems controlling their temperament, and lower educational attainment. Moreover, this group of patients shows more risk-taking behavior [15] and higher rates of other psychiatric disorders, including antisocial personality disorder, major depression, borderline personality disorder, and hypomanic episode [10]. Finally, our international consensus statement underscores that screening, diagnosis, and treatment of this patient group is well possible [18].

Various aspects regarding the etiology, risk profile, neurobiology, genetics, development, screening, diagnosis, and treatment of ADHD-SUD comorbidity need ongoing attention of both clinicians in the field and researchers in the scientific community. Our prospective cohort study, INCAS, addresses some of these topics and will provide unique data on the natural course of the disorders and on predictors of treatment efficacy in a routine clinical setting. ICASA brings together professionals with wide-ranging expertise in the fields of ADHD and SUD and is, therefore, ideally positioned to provide answers to at least some of the remaining questions.

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Disclosure Statement

Van de Glind G. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Brynte C. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Ramos-Quiroga J.A. was on the speakers' bureau and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Sinogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice, and Rubió in the last 5 years. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió. Skutle A. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Kaye S. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Konstenius M. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Levin F.R. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Matthys F. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Demetrovics Z. acknowledges the support of the Hungarian National Research, Development and Innovation Office (Grant numbers KKP126835). Moggi F. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Schellekens A. reports no conflict of interest. Crunelle C. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Dom G. declares that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Van den Brink W. received speaker's fees and was a consultant for Lundbeck, Eli Lilly, Indivior, Pfizer, Mundipharma, D&A Pharma, Bioproject, Novartis, Takeda, Angelini, and Opiant Pharmaceuticals in the last 5 years. Franck J. is currently the PI for a clinical trial of Vivitrol.

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Author Contributions

This paper summarizes the work of the International Collaboration on ADHD and Substance Abuse (ICASA) network and presents future projects. All authors have contributed equally to the writing of this overview. All authors have significantly contributed to the referred publications of ICASA network and/or ongoing research projects. For a detailed description, the reader is referred to the original publications, which are summarized in this paper.

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