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## International Consensus Statement on Screening, Diagnosis and Treatment of Substance Use Disorder Patients with Comorbid Attention Deficit/Hyperactivity Disorder

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## Abstract

Adult attention deficit/hyperactivity disorder (ADHD) often co-occurs with substance use disorders (SUD) and is associated with early onset and more severe development of SUD and with reduced treatment effectiveness. Screening tools allow for a good recognition of possible ADHD in adults with SUD and should be used routinely, followed by an ADHD diagnostic process initiated as soon as possible. Simultaneous and integrated treatment of ADHD and SUD, using a combination of pharmaco- and psychotherapy, is recommended. Long-acting methylphenidate, extended-release amphetamines, and atomoxetine with up-titration to higher dosages may be considered in patients unresponsive to standard doses. This paper includes evidence- and consensus-based recommendations developed to provide guidance in the screening, diagnosis and treatment of patients with ADHD-SUD comorbidity.

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## Keywords

Attention deficit/hyperactivity disorder; Substance use disorders; Diagnosis; Treatment; Consensus

## Introduction

#### Comorbidity of Attention Deficit/Hyperactivity Disorder and Substance Use Disorders

Attention deficit/hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder that can persist into adulthood [1]. ADHD is strongly associated with the development of substance use disorders (SUD), often at a very early age and with a faster transition from less severe to more serious SUD [2]. Patients with ADHD-SUD comorbidity show more complex and chronic patterns of substance use, including more poly-substance use, than adults with SUD without comorbid ADHD [1, 3]. They also present with greater psychiatric comorbidity, such as antisocial personality disorder, borderline personality disorder, anxiety disorders, bipolar disorders and/or post-traumatic stress disorders [4]. Despite being in treatment more often, adults with ADHD-SUD comorbidity have more difficulties remaining abstinent [5] and report a reduced quality of life with more professional, social and personal problems [6]. On a pharmacological level, several studies report lower effectiveness of standard-dose pharmacotherapy for the treatment of ADHD in patients with ADHD-SUD comorbidity [7].

In summary, ADHD-SUD comorbidity is associated with multiple problems and reduced effectiveness of standard treatments, making proper diagnosis and successful treatment in adults with ADHD and SUD a challenge.

#### Prevalence of ADHD and SUD

ADHD is associated with an increased risk of developing SUD later in life [8]. ADHD-SUD comorbidity is highly prevalent in addiction care: in a meta-analysis of 29 studies, 23.1% of patients with SUD also had adult ADHD [9]. The prevalence of ADHD depends on the type of substance of abuse, the setting (e.g., outpatient versus inpatient) and the diagnostic procedure (e.g., screening questionnaire versus structured clinical interview). In a large international study, 13.9% of treatment seeking SUD patients had a DSM-IV diagnosis of adult ADHD [10]. Age, gender, ethnicity and primary substance of abuse do not seem to systematically impact the prevalence rate of ADHD in SUD patients [10].

#### Aim and Objective of the Consensus Statement

This consensus statement was developed as a practical guide to assist professionals with the screening, diagnosis and treatment of adult patients with SUD and ADHD. The consensus statement is for patients and clinicians: general practitioners, psychiatrists, psychologists and other health professionals involved with alcohol and/or drug-dependent patients.

## Methods

PubMed, Cinahl and Psychinfo were searched for articles published January 1994 to December 2015 using the terms "drug abuse," "substance use," "addiction," "dependence" and "ADHD," limited to articles published in English, French and Dutch. Simultaneously, we searched for existing guidelines in Clinical Evidence, CEBAM, NHS Guideline finder, Cochrane library, NICE, National Guideline Clearinghouse and GIN database. All retrieved articles and relevant cross-references were reviewed.

A flowchart of the search of articles is presented in Figure 1. Publications were discarded if they did not include adults; if ADHD or SUD was not the primary diagnosis; if they were reviews prior to a meta-analysis; if they were personal opinion papers; and if they were study protocols. The statements in this consensus text are based primarily on scientific evidence from available publications (n = 212; online suppl. Material 1, see www.karger.com/doi/10.1159/000487767). When scientific evidence was lacking, a consensus was sought from the opinions of experts in the field, which is stated specifically in the main text when this was the case. To provide guidance on the strength of the evidence, the final recommendations summarized in Table 1 are assigned a rating based on the evidence quality score from the SIGN grading system. In the addendum to this main text, the full list of references that constitute the basis of this consensus statement can be found.

This consensus statement covers 2 main topics, (i) screening and diagnosis of ADHD and SUD and (ii) treatment of ADHD and SUD. This consensus statement was primarily developed from the perspective of adults with SUD and underlying ADHD, assessed in addiction services. The statements below are also valid for ADHD patients with SUD assessed in other mental health services.

Work on this consensus statement started with a Belgian guideline for the treatment of ADHD and SUD, supplemented by a Dutch guideline for the treatment of adults with ADHD and a Dutch Guideline on ADHD-SUD in adolescents [11–14]. No other guidelines were retrieved from our search. The first draft was developed by the Belgian and Dutch representatives of the International Collaboration on ADHD and Substance Abuse (ICASA: FM, CLC, WvdB, GvdG) and was circulated to ICASA members present at meetings in Stockholm (13 experts), Brussels (18 experts) and Budapest (21 experts), where it was discussed. The final statement was written by the Belgian ICASA members (CLC, FM) and adapted and approved by the other members.

## Consensus Statement for the Screening and Diagnosis of ADHD and SUD

#### Screening

ADHD has a significant impact on the development and course of SUD and early detection is of key importance for successful treatment. The high prevalence of ADHD in people with SUD, along with the fact that many patients will not spontaneously mention symptoms of ADHD and focus on their SUD problems, makes it important to always screen for the presence of ADHD. Several screening tools are available for use in adults with ADHD and Crunelle et al.

The Short Version of the Adult ADHD Self-Report Scale (ASRS-SV) screener is currently the most widely used and investigated screening tool in individuals with ADHD and comorbid SUD, with good sensitivity and specificity across studies (Table 1). Similarly, screening with Conners' Adult ADHD Rating Scale, Wender Utah Rating Scale, or Attention Deficit Scales for Adults also allows for a good recognition of possible ADHD (Table 1), but they take longer to complete. A positive screening result should always lead to further diagnostic assessments. Nevertheless, up to 20% of patients with ADHD are missed when using a single screener. Therefore, if time and budget allow this within the health care service, we recommend combining 2 screening result – should always receive an extended diagnostic assessment.

#### Difficulties and Concerns When Diagnosing Adult ADHD in Patients with SUD

The risk of both under-diagnosing and over-diagnosing ADHD in adult SUD populations is a point of concern. The strictness of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria, maintaining that ADHD had to occur independent of other disorders, could complicate the diagnosis of ADHD in adults with SUD and lead to under-diagnosis [15]. Also, adult patients with SUD often have more difficulties in remembering the early history of ADHD symptoms [15]. Therefore, ADHD can erroneously be overlooked in this population. Additionally, if an individual with SUD was not diagnosed with ADHD as a child, it is less likely that the behaviour as an adult will be linked to ADHD, because these are associated with intoxication, withdrawal or the (interpersonal) consequences of substance abuse [15]. As ADHD is mostly not the reason why patients with SUD seek treatment [16], it is the clinician's task to address and recognize ADHD in these patients. Finally, many consequences of ADHD (job loss, poor school performance) are also seen in patients with SUD, and they can be erroneously attributed to substance abuse. Adults with ADHD are often dealing with the symptoms for many years and have developed compensation strategies that limit the impact and/or mask the symptoms [17]. Less frequent, but important, is the problem of over-diagnosing ADHD in SUD patients, that is, when SUD symptoms are erroneously attributed to ADHD. It is important that ADHD symptoms also occur in settings, situations and stages of life without substance use. Over-diagnosing can also occur when the continuity of symptoms from childhood to adulthood is overlooked or when substance-induced symptoms or withdrawal symptoms are perceived as ADHD symptoms. Therefore, it is recommended that developmental history, psychiatric comorbidity and family history are all addressed. Finally, patients may exaggerate ADHD symptoms to obtain prescription stimulants for abuse or diversion. For all these reasons, a follow-up evaluation of ADHD symptoms during SUD treatment is recommended in order to reduce the risk of misdiagnosis [18].

Diagnosis should consist of the following necessary steps similar to those needed for the diagnosis of ADHD in an adult population without SUD: an examination of current ADHD symptoms, ADHD symptoms during childhood, family history of ADHD and SUD, school

and occupational history, marriage, physical signs and comorbidity [19]. It is important to include environmental and psychosocial factors in the broad sense of the term in the diagnostic process. These are factors that could have protective or risk-enhancing effects on the functioning of the individual. Moreover, to be diagnosed with ADHD according to DSM-5, some symptoms are required to have occurred before age 12. For confirmation, a collateral history can be taken with someone who knows the patient well (e.g., parents or siblings).

#### Who Is Qualified to Make an ADHD Diagnosis?

An essential requirement for a correctly performed ADHD diagnosis is that the diagnostician must be knowledgeable and competent. The literature argues towards a targeted training on the dual-diagnosis of ADHD and SUD [20]. The expert group recommends that a physician or clinical psychologist can make the diagnosis of ADHD in SUD patients, provided he/she has received extensive training on the differential diagnosis of ADHD, has experience in addiction care, and has experience with adult ADHD populations.

#### When Should the Diagnostic Process Start?

The expert group suggests starting the diagnostic process as soon as possible: (i) when there are no serious withdrawal symptoms and (ii) when there is no serious intoxication. Clinical history taking, observation and screening can be started earlier. If feasible, one can include a period of abstinence, determined by the clinical experience of the diagnostician and taking into account the setting in which the patient is treated and the drug(s) abused. The preliminary diagnosis must be verified in the course of treatment, as the presentation of ADHD symptoms can change with successful SUD treatment. A good follow-up prevents over- or under-diagnosis and it is therefore essential to continue monitoring the patient.

#### Current ADHD Symptoms and Clinical History Taking in Adults with SUD

The diagnosis of ADHD should be part of a medical-psychiatric examination, and include a thorough investigation of current symptoms (using diagnostic instruments), (collateral) history taking (elements from childhood, family history, educational and occupational history, marriage, etc.) and additional examinations (for comorbidity and differential diagnosis).

Collateral history taking on current and childhood symptoms is essential to obtain information from another perspective. Memories are not always easy to recall, and involving family members (and significant others) may be helpful. Also, parents' memory is not always reliable [21]. In a population of adults with SUD, obtaining information regarding past experiences is even more difficult. The patient may be reluctant to share their contact information or the family may be unwilling to cooperate. In such cases, objective childhood data can be obtained through, for example, school reports and by paying particular attention to comments made by former teachers [19]. Symptoms associated with the patient's substance use may be erroneously identified as ADHD symptoms, and it is therefore recommended to focus on alcohol- and drug-free periods in the patient's life. Diagnostic interviews such as Conners' Adult ADHD Diagnostic Interview for the DSM-IV (CAADID) can be used to aid the diagnosis. The CAADID is often used as the gold standard for the diagnosis of adult ADHD in patients with SUD [22]. The Diagnostic Interview for ADHD in adults (DIVA) can be administered in the presence of the partner and relatives to simultaneously collect past history and collateral past history information but is not yet validated in adults with SUD. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) is a semi-structured interview that focuses on comorbid psychiatric diagnoses and is based on the DSM-IV criteria for axis 1 and II disorders, including ADHD [22]. In 80 patients with SUD (40 with and 40 without ADHD), the PRISM had a sensitivity of 80% and a specificity of 88% for the detection of ADHD, compared to CAADID [22].

#### Assessing (History of) Substance Abuse in Adult ADHD Patients

Personal interview is the best way to establish a history of substance abuse and the related disruptions in different life domains (social, schooling, work). This may be supplemented by a toxicological confirmation, for example, in urine, blood or hair samples.

Two generally accepted screening instruments are the Drug Abuse Screening Test and the Alcohol Use Disorders Identification Test. Both were investigated for their construct validity and reliability and results indicate they are acceptable screening instruments in adults with ADHD [23].

### Consensus Statement for the Treatment of ADHD and SUD

#### Treatment of ADHD in Adults with SUD

Proper treatment of ADHD in people with SUD comprises several components, including psycho-education, pharmacotherapy, individual and/or group cognitive and behavioral therapy, as well as peer support [24]. In adults with ADHD and SUD, research suggests the usefulness of combined pharmacotherapy and psychotherapy [25–26].

The treatment of ADHD should be integrated in the treatment of SUD and vice versa [26]. This is important because ADHD symptoms can interfere with SUD treatment and/or SUD can complicate the treatment of ADHD. It is advisable to first start SUD treatment, followed by ADHD treatment as soon as possible thereafter [27]. When the SUD is too severe, brief residential treatment may be appro priate. One should keep in mind that effective treatment of ADHD would usually not result in improvement of SUD, hence the importance of effectively treating both disorders.

#### Pharmacotherapy

Studies show that medication is moderately effective in reducing ADHD symptoms in patients with ADHD-SUD comorbidity (mean standardized effect size 0.40–0.50). On the other hand, medication has more positive effects when combined with psychotherapy, while ADHD pharmaco-therapy by itself is generally not effective in reducing the use of substances and is associated with a higher frequency of adverse effects and treatment discontinuation [7, 27].

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Non-randomized studies showed some promise for the improvement of both ADHD and SUD, but the more recent double blind and placebo-controlled trials were less positive. Open trials in ADHD-SUD patients provided some evidence for the effectiveness of bupropion to reduce ADHD symptoms, but this is contradicted in a small controlled study showing no effect over placebo in the treatment of ADHD with SUD [28]. In several studies, ADHD symptoms seemed to show improvement across all groups, indicating that there is an important placebo effect associated with either expectation and/or the effect of the psychotherapy provided in all treatment conditions.

Controlled randomized trials with short- and long-acting standard doses of methylphenidate either show to neither improve ADHD and SUD symptoms or to improve ADHD symptoms but not drug use [28–31]. However, caution should be taken with the interpretation of negative results, because some of these studies showed promise with regard to SUD outcomes in secondary analyses [31–33]. Two studies with higher doses of methylphenidate (up to 180 mg/day) showed a decrease in ADHD symptoms and a decrease in the reinforcing effects and the use of cocaine and amphetamines (and other drugs) in adult stimulant-dependent ADHD patients [34–35]. Also, robust doses of extended-release mixed amphetamine (60 and 80 mg/day) showed substantial reductions in both ADHD and drug use in cocaine-dependent patients with ADHD [35]. Pemoline had a significant effect on ADHD symptoms, but not on drug use [33]. Atomoxetine resulted in a significant reduction on ADHD symptoms, and was associated with a decrease in alcohol craving and consumption [32].

#### Safety of Pharmacological ADHD Treatment in Adults with Comorbid SUD

Prescribing stimulants to individuals with SUD remains controversial and many clinicians are reluctant to prescribe proper ADHD treatment in individuals with SUD. While stimulants can be effective in treating those with ADHD and SUD, particularly at higher doses [34–35], there is the clear risk of misuse and diversion of stimulants and this cannot be overstated. It is also important to recognize that this risk may differ by patient characteristics. Two groups that are at substantial risk include adolescents and young adults [36], although adults are not immune from misusing or abusing their medication. Importantly, long-acting formulations, particularly osmotic-release oral system formulations of methylphenidate (OROS-MPH) and lisdexam-phetamine, have considerably lower rates of misuse and diversion compared to immediate-release preparations [37].

Adverse events are not increased in ADHD patients with SUD compared to when giving stimulants to ADHD patients without SUD [38]. The literature does not mention severe complications or increases in substance abuse with prescribing central stimulants in this patient population [27]. However, a dose-dependent interaction between disulfiram and methylphenidate resulting in psychotic episodes has been described [39]. Finally, the use of stimulant treatment for ADHD does not precipitate the onset of SUD in adults without previous SUD [40]. In SUD patients, treatment of ADHD can be useful to reduce ADHD symptoms without worsening the SUD [41] and should not be avoided.

Regarding prevention of SUD, stimulant treatment of children with ADHD may have some protective effects on the development of SUD if children receive stimulant treatment from a young age and for a long enough time [42].

Taken together, clinicians need to be circumspect when prescribing stimulants, particularly among high-risk populations. However, abuse and diversion can be reduced by close monitoring, use of longer acting formulations, and engaging in a discussion with patients on the importance of safeguarding their medication. As with any prescription of controlled substances, the clinician must weigh the risk of abuse/diversion versus the medication's potential therapeutic benefit. After careful deliberation of these factors, the prescriber must use his/her clinical judgement regarding whether it is reasonable to initiate or to continue stimulant pharmacotherapy.

#### **Treatment Retention**

Treatment retention is an important difficulty in the treatment of SUD, particularly in SUD patients with ADHD [5]. Patients often regard ADHD treatment as a sign of recognition of their problems, potentially increasing treatment retention. Under-diagnosing ADHD in SUD patients may result in problems with compliance and SUD treatment retention. Medication that takes effect only after a few weeks (e.g., atomoxetine) may also be a reason for continued substance use and drop out.

In patients with ADHD, severity of SUD – rather than the mere presence of ADHD – is a predictive factor for treatment outcome [43]. Adult ADHD-SUD patients treated with methylphenidate have better retention in treatment than ADHD patients who receive placebo [44]. Higher doses of methylphenidate are also associated with better long-term treatment adherence [45].

#### **Non-Pharmacological Interventions**

There are few studies on non-pharmacological treatment of patients with both ADHD and SUD. Clinicians should consider therapy with a focus on overlapping symptoms as part of a multimodal treatment approach including psychotherapy and medication [25–26, 46]. Data collection of the first randomized controlled trial comparing integrated cognitive behavioral therapy (ICBT) with standard CBT for patients with both SUD and ADHD has been finalized and 2 case reports are available, while results are expected in 2018 [47]. In a qualitative study, patients with ADHD and SUD mention their wish for a coaching attitude [48]. A dialectic behavioral therapy-based skills training for adults with ADHD and SUD is also described, with varying results regarding efficacy [49]. A Belgian guideline that presents a practical approach for the non-pharmacological treatment of adult ADHD in patients with SUD was published [50]. Other non-pharmacological interventions, such as individual coaching, structured skills training, dialectic behavioural therapy and mindfulness-based therapy are not yet investigated in the context of ADHD-SUD comorbidity.

## Discussion

Given the high prevalence of ADHD in SUD patients, all patients in addiction care should be screened for the presence of adult ADHD. The ASRS, the Wender Utah Rating Scale and the Conners' Adult ADHD Rating Scale have been sufficiently validated as screeners. If the screening result is positive or if ADHD is clinically suspected, a physician or clinical psychologist with specialist training on the differential diagnosis of ADHD and experience in addiction care should initiate a more extensive diagnostic examination. The use of questionnaires and semi-structured interviews can be useful for diagnosis. To date, no semi-structured ADHD interview has been sufficiently validated in a population with ADHD and SUD. Diagnostic examination should be complemented with observation and (collateral) history taking, including a good follow-up to reduce the risk of over- or under-diagnosis. Partner and siblings can provide information on the patient's former and current symptoms, but also school records and comments by former teachers can be useful. An extensive description of the patient's current and past substance use can best be determined by focusing on drug- and alcohol-free periods in the patient's life.

This consensus statement refers to the diagnosis and treatment of ADHD among treatmentseeking SUD patients. However, more than one third of these patients are also affected by other comorbidities [4], which mostly have been clinically diagnosed or even systematically evaluated even before ADHD is considered. For example, van Emmerik-van Oortmerssen et al. [4] showed that having an ADHD diagnosis as a SUD patient doubles the likelihood of having an additional psychiatric diagnosis to more than 75%, making ADHD a highly relevant risk factor for additional comorbidities. Therefore, detecting and treating ADHD is the focus of this consensus statement.

Treatment of ADHD patients with SUD remains a challenge. Controlled trials show moderate improvements in ADHD symptoms upon pharmacological ADHD treatment in ADHD-SUD patients. However, pharmacotherapy should not be avoided and should be critically encouraged in patients with ADHD and SUD with a preference for high doses of long-acting stimulants in ADHD patients with stimulant use disorders or atomoxetine in patients with alcohol use disorder. Treatment of ADHD can be useful to reduce ADHD symptoms without worsening the SUD. One should consider treating both ADHD and SUD with their own medication simul taneously, that is, for patients with ADHD and an alcohol use disorder, one may consider treatment with atomoxetine and with naltrexone, nalmafene, acomprosate or topiramate. A multimodal integrated approach, combining pharmacotherapy (for ADHD and SUD) with a non-pharmacological intervention that targets both the ADHD and SUD, such as an integrated CBT, is warranted but further research is needed. Table 2 summarizes the key diagnostic and treatment recommendations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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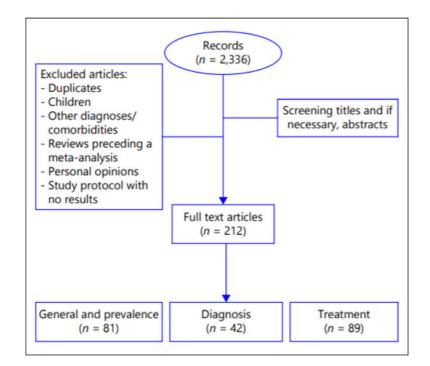
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Flowchart showing the search results.

#### Table 1

#### Tools for screening ADHD in individuals with comorbid SUD

ADHD screening tool	ASRS-SV	WURS	CAARS	ADSA
Number of items	6	61	26*	54
Time to fill in	<2 min	<15 min	<8 min	<12 min
Considered in populations with SUD (yes/no)	Yes	Yes	Yes	Yes
Sensitivity, range	67–100% <sup>a_f</sup>	80–93% <sup>e,f</sup>	94% <sup>f</sup>	58–71% <i>g</i>
Specificity, range	66–82% <sup>a_f</sup>	60–70% <sup>e,f</sup>	86% <sup>f</sup>	94–82% <i>g</i>
Sensitivity if combined	+WURS:	+ASRS: 57–92% <i>e</i> , <i>f</i>	+ASRS: 67% <sup><i>f</i></sup>	
	57–92% <sup>e,f</sup>		+WURS: 87% <sup><i>f</i></sup>	
	+CAARS: $67\%^{f}$			
Specificity if combined	+WURS: 91% <sup><i>f</i></sup>	+ASRS: 91% <sup><i>f</i></sup>	+ASRS: 92% <sup><i>f</i></sup>	
	+CAARS: $92\%^{f}$		+WURS: 90% <i>f</i>	

Overview of available screening tools for diagnosing ADHD in adults with comorbid substance use dependence (SUD).

ASRS-SV, Adults ADHD Self-Report Scale Short Version; WURS, Wender Utah Rating Scale; CAARS, Conners' Adult ADHD Rating Scale; ADSA, Attention Deficit Scales for Adults.

<sup>r</sup>Also available in a long (66 items) and screening (12 items) version.

<sup>*a*</sup>van de Glind et al. [51].

<sup>b</sup>Chiasson et al. [52]. <sup>c</sup>Reyes et al. [53].

<sup>d</sup>Konstenius et al. [54].

<sup>e</sup>Daigre et al. [55].

*f* Dakwar et al. [56].

<sup>g</sup>West et al. [57].

#### Table 2

#### Summary of key points from the consensus statement

	Level of evidence*	Recommendation level*
Diagnosis		
The ASRS is the most extensively tested screener and performs well as a screening tool for ADHD in adults with SUD, but some other instruments have also shown promise (e.g., WURS).	2+	С
The diagnostic process should be started as soon as possible, keeping in mind that the diagnostic process is a continuous one. A good follow-up prevents over- or under-diagnosis of ADHD in patients with SUD.	3	D
A physician or clinical psychologist can make the diagnosis of ADHD provided that he/she has received extensive training on the differential diagnosis of ADHD, has experience in addiction care, and has experience with adult ADHD populations.	4	D
Clinicians should consider the diagnosis of ADHD unspecified and consider ADHD treatment when adult ADHD symptoms are present with sufficient severity.	4	D
If possible, involve the patients' parents, partner and/or relatives to assess former and current symptomatology and assess functional impairments. Additional information can be gathered from school records and comments added by former teachers.	3	С
The diagnostic process should include current and past substance use (frequency and quantity of use, social context).	3	С
Focus on drug- and alcohol-free periods in the patient's life during (collateral) history taking.	3	D
Treatment		
Consider adequate medical treatment of both ADHD and SUD.	2	С
Always consider a combination of psychotherapy and pharmacotherapy.	2	D
Integrate the ADHD and other psychiatric comorbidity treatment with SUD treatment as soon as possible.	2	С
Psychotherapy, preferentially targeting the combination of ADHD and SUD, should be considered.	3	С
Long-acting methylphenidate, extended-release amphetamines, and atomoxetine are effective in the treatment of comorbid ADHD and SUD, and up-titration to higher dosages may be considered in some patients. The abuse potential is limited with long-acting agents.	3	С
Caution and careful clinical management is needed to prevent abuse and diversion of prescribed stimulants.	3	С

Overview of the summary points from the consensus statement on the screening, diagnosis, and treatment of adult ADHD in individuals with comorbid SUD.

The recommendations are assigned a rating according to the quality of the evidence on which they are based, using the SIGN grading system based on level of evidence ranging from 1++ (meta-analyses or systemic reviews of RCTs) to 4 (expert opinion; SIGN, 2001). A, at least one metaanalysis, systematic review, or RCT rated as 1++, and directly applicable to the target population or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results; B, body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+; C, A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++; D, evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+.