Good Clinical Practice in the recognition and treatment of ADHD in adults with substance use dependence

Guideline for clinical practice

C. L. Crunelle
F. Matthys
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Vereniging voor Alcohol- en andere Drugproblemen vzw (VAD)
Forum voor Verslavingsgeneeskunde
Vrije Universiteit Brussel (VUB)

VAD VERENIGING VOOR ALCOHOL- EN ANDERE DRUGPROBLEMEN vzw

Vrije Universiteit Brussel

1. Introduction

1.1. Attention Deficit/Hyperactivity Disorder (ADHD)

ADHD is a neurobiological developmental disorder that start during childhood but often persists during adult life. ADHD is associated with significant impairment in psychosocial (Biederman, 2005) and comprised of three main characteristics:

- *Inattention*: i.e. difficulty to maintain attention (problems concentrating), making mistakes due to carelessness, being easily distracted, frequent absentmindedness, difficulty with organizing activities, difficulty in succeeding to finish something, forgetfulness, failure to follow instructions correctly and often loose things.
- *Hyperactivity:* i.e. moving excessively (with hands, feet, or the entire body) and difficulty in sitting still. In children, it is expressed in difficulty to play quietly, frequently climbing onto everything, running around continuously and a continuous urge to talk. In adults, it is rather denoted as an inner sense of restlessness, the inability to relax, difficulty sitting still and being constantly on the go.
- *Impulsivity*: is characterized as acting without thinking of the consequences, difficulty in postponing things or waiting one's turn, interrupting others, providing an answer before the question was finished, excitement- and thrill seeking.

During the past decennia, the criteria to diagnose ADHD changed regularly (Matthys et al., 2012). With DSM-III, the term "attention deficit disorder" (ADD) was mentioned for the first time, distinguishing between ADD with or without hyperactivity. In 1994, DSM-IV was published, including separate symptoms for inattention (nine in total) and for hyperactivity and impulsivity (nine symptoms). Additionally, it was acknowledged that ADHD may persist into adulthood (APA, 2000). If at least six of the nine symptoms are scored positive for at least six months, one can refer to attention deficit and hyperactivity / impulsivity, respectively. In this way, three types of ADHD can be distinguished: a predominantly inattentive type, a predominantly hyperactive-impulsive type, and a combined type.

In DSM-5 (2013), ADHD is part of the cluster "neurobiological developmental disorders" (APA, 2013). The nine symptoms of inattention and the nine symptoms of hyperactivity and impulsivity remained identical to the prior DSM version, but now additionally include specific examples for adolescents and adults (see Table 1). In children, at least six symptoms must be present for the diagnosis, while older adolescents and adults must present with five. An important change in DSM-5 includes the age at which the first symptoms must present (now: 12 years old). Symptoms must present in at least two domains (school, home, work,), but symptoms before the age of 12 are not required to have had a significant impact on school or social relationships. In addition, in DSM-5, a pervasive developmental disorder (PDD) is no reason for the exclusion of an ADHD diagnosis, as PDD is included in the neurodevelopmental disorders. As a result, Autism Spectrum Disorder does not exclude an ADHD diagnosis. Finally, ADHD subtypes are now presented as 'presentations' rather than 'subtypes', which better addresses that an individual may change presentations during their lifetime:

- A predominantly inattentive presentation;
- A predominantly hyperactive/impulsive presentation;
- A combined presentation.

DSM-5 Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development addressed by (1) or (2). Six or more of the symptoms have persisted for at least six months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities. The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), five or more symptoms are required.

(1) Inattention

(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
(b) Often has trouble holding attention on tasks or play activities.
(c) Often does not seem to listen when spoken to directly.
(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).
(e) Often has trouble organizing tasks and activities.
(f) Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
(g) Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
(h) Is often easily distracted.
(i) Is often forgetful in daily activities.

(2) Hyperactivity and Impulsivity

(a) Often fidgets with or taps hands or feet, or squirms in seat.
(b) Often leaves seat in situations when remaining seated is expected.
(c) Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
(d) Often unable to play or take part in leisure activities quietly.
(e) Is often "on the go" acting as if "driven by a motor".
(f) Often talks excessively.
(g) Often blurts out an answer before a question has been completed.
(h) Often has trouble waiting his/her turn.
(i) Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g. at home, school, or work; with friends or relatives; in other activities)

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic or occupational functioning

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal)

Table 1: DSM-5 criteria for ADHD

1.2. ADHD in adults

Contrary to what has long been thought, children with ADHD do not outgrow their disorder when they mature. However, the way in which the symptoms are expressed in the transition from child to adult can vary (Adler & Cohen, 2004; Culpepper & Mattingly, 2008).

In Belgium, it is estimated that 4.1% of adults have ADHD (Fayyad et al., 2007). ADHD is not always recognized in adults and, as a result, often remains untreated. One possible reason for this under diagnosis is that adults with ADHD were not diagnosed earlier in childhood. With rigorous structure and relatively little demands for the child, serious problems do not occur and the ADHD remains undetected. If changes in the expectations and responsibilities of the individual occur while growing up, the symptoms often become visible, and may necessitate treatment (Adler & Cohen, 2004). Another possibility is that ADHD is masked by the presence of other (comorbid) disorders. In adults with ADHD, mood and anxiety disorders occur up to four times more often (Kessler et al., 2006; Fayyad et el., 2007).

1.3. ADHD and substance use dependence

The term substance use dependence (SUD) is defined according to DSM-5, and includes substance abuse and dependence as a single disorder measured on a continuum from mild (2-3 symptoms present) until severe (6 or more symptoms present):

A1. Consuming more alcohol or other substance than originally planned.
A2. Worrying about stopping or consistently failed efforts to control one's use.
A3. Spending a large amount of time using drugs/alcohol, or doing whatever is needed to obtain them.
A4. Use of the substance results in failure to "fulfil major role obligations" such as at home, work, or school.
A5. "Craving" the substance (alcohol or drug)
A6. Continuing the use of a substance despite health problems caused or worsened by it.
A7. Continuing the use of a substance despite its having negative effects in relationships with others.
A8. Repeated use of the substance in a dangerous situation (for example, when having to operate heavy machinery, when driving a car).
A9. Giving up or reducing activities in a person's life because of the drug/alcohol use.
A10. Building up a tolerance to the alcohol or drug. Tolerance is defined by the DSM-5 as "either needing to use noticeably larger amounts over time to get the desired effect or noticing less of an effect over time after repeated use of the same amount."
A11. Experiencing withdrawal symptoms after stopping use. Withdrawal symptoms typically include, according to the DSM-5: "anxiety, irritability, fatigue, nausea/vomiting, hand tremor or seizure in the case of alcohol."

1.3.1. Comorbidity of ADHD and substance use dependence

ADHD and SUD are often co-occurring disorders (De Alwis et al., 2014; Estévez et al., 2015), most probably due to an overlap in the underlying neurobiological (dopaminergic) deficits of both diseases (Frodl, 2010; Ortal et al., 2015; van Wingen et al., 2013). ADHD influences the pathophysiology of SUD; how SUD develops, how the symptoms occur, and how effective treatment SUD response will be.

Patients in addiction care with ADHD often started using drugs at an earlier age, exhibit more experimentation behaviour, and often use more psychoactive substances simultaneously (Carpentier et al., 2011). Additionally, they have an increased risk of traffic accidents (Schubiner et al., 2000), to undertake a suicide attempt, and they are more often hospitalized (Wilens et al.,

1997; Arias et al., 2008). Patients with ADHD and SUD also express a reduced quality of life (Carpentier et al., 2011) and more important professional, social and personal problems (Nogueira et al., 2014). In a qualitative study, patients with ADHD and SUD state to benefit from the use of psychoactive (often addictive) substances, but also express to be generally less happy with their lives and necessitating more treatment than patients with SUD but without ADHD (Kronenberg et al., 2015). Their main problem includes structuring of everyday life due to scheduling problems (Kronenberg et al., 2014).

ADHD is associated with an increased risk of developing a SUD later in life (Charach et al, 2011; Dalsgaard et al, 2014; Kousha et al, 2012; Levy et al, 2014; Wilens, 2011) and with a faster transition from less severe to more serious SUD (Wilens et al., 1997). Despite being in treatment more often, adults with ADHD and SUD have more difficulties remaining drug-free compared to SUD patients without ADHD (Wilens et al, 1998; Schubiner et al., 2000; Levin et al., 1998). In adult ADHD patients with SUD, ADHD symptoms often expressed more intensely (Levin et al., 2004) and more often in combination with other psychiatric disorders (behavioural problems, antisocial personality disorders, bipolar disorders and / or post-traumatic stress disorders) (Arias et al., 2008; Carpentier et al., 2011; Kousha et al., 2012; van Emmerik-van Oortmerssen et al., 2014). The SUD is often more complex and more chronic than in patients without ADHD (Young et al., 2015).

1.3.2. Prevalence of ADHD and SUD

A recent meta-analysis of 29 studies (6689 patients from 6 countries) shows that 23.1% of patients with SUD have an underlying ADHD (van Emmerick-van Oortmerssen et al., 2012). A large international study shows a prevalence rate of 13.9% (van Emmerick-van Oortmerssen et al., 2014). Age, gender and ethnicity do not impact the prevalence rate (van Emmerick-van Oortmerssen et al., 2012), although another study indicates a slightly increased prevalence in men (28%) compared to women (19%) (Schubiner et al., 2000). In a large recent international survey where 10 countries participated (including Belgium), it was shown that northern countries (Norway, Sweden) have higher prevalence rates (up to 31%) of patients with SUD and ADHD (Van de Glind et al., 2014). It was also shown that the prevalence was slightly lower when the diagnosis was made using the previous DSM-IV compared to DSM-5 criteria (Van de Glind et al., 2014).

2. Objectives and target audience

These guidelines are addressed to clinicians: general practitioners, doctors, psychiatrists, psychologists and paramedics who deal with individuals dependent on alcohol or other drugs in their daily practice or institution, both for ambulant or residential care.
These guidelines provide a useful and practical guide to diagnosing and treating adults (men and women aged 18 to 40 years) with ADHD and SUD. In addition, this document provides an overview of the available evidence and the gaps that exist with respect to this subject.

These guidelines aim to increase the expertise in the professional field regarding the diagnosis and treatment of ADHD in adults with SUD. If the recommendations are complied with, the continuity in the treatment of ADHD in referrals within (and outside) the addiction field will improve, patients will obtain more insight in their own problems and their chances of receiving effective treatment will increase.

2.1. Currently available guidelines on ADHD and SUD

In 2014, the Dutch Guideline on ADHD and substance use in adolescents was published (ISBN 978 94 92 121 134), for which our guideline published earlier in 2010 served as directive. This

guideline provides a comprehensive treatment protocol, a manual for caregivers, and a workbook for patients. This Dutch guideline states that it still needs to be further examined for effectiveness.

With caution, the here proposed guideline could also be used as a useful guide for the early screening of young adults with ADHD and SUD between 16 and 18 years old. At present, there is little literature available on the treatment of ADHD and SUD in young adults. Therefore, we recommend this guideline particularly regarding early screening.

A Dutch guideline for the treatment of adults with ADHD was established in 2015 by the Dutch Association for Psychiatry and available online (http://www.nvvp.net/stream/richtlijn-adhd-bij-volwassenen-fase-1-diagnostiek-en-medicamenteuze-behandeling-2015). Although it does not specify to adults with SUD, we mention this guideline as a comprehensive guide for the screening and treatment of ADHD in adults.

3. Main questions

Diagnosis

a. Which elements are important in order to make the diagnosis of ADHD in adults with addiction?
   a.1. When can the diagnostic procedure be started?
   a.2. Who is eligible to make the ADHD diagnosis?

b. Which specific aspects should be taken into account during the screening of ADHD in adults with SUD?
   b.1. Is it appropriate to screen adults with SUD systematically for ADHD and which instruments are preferred for screening?
   b.2. Which screening result should initiate more extensive diagnostic testing?

c. Which specific aspects should be taken into account when ascertaining current ADHD symptomatology and during the anamnestic process in the context of diagnosing ADHD in adults with SUD?

d. To what extent do personal characteristics of the patient play a role in the course of the diagnostic process and how this can be anticipated for during the diagnostic process?

e. Which specific aspects should be taken into account when performing additional research regarding the diagnosis of ADHD in adults with SUD?

Treatment

a. What includes proper treatment of ADHD in adults with SUD?

b. Which medication is effective in the treatment of ADHD in adults with SUD and what is the effect of this medication on the use of alcohol and other drugs?

c. How can we improve retention in adults with ADHD and SUD?

d. Which non-pharmacological interventions are effective for the treatment of adults with ADHD and SUD?

These guidelines include recommendations related to each of the above-mentioned main questions. A survey of the literature is presented by topic, comprising research as well as existing guidelines. The literature survey is followed by a summary including conclusions and formulated recommendations. These recommendations are based on existing evidence as well as on

specialists' opinions. When less extensive or unreliable information is available through literature, the more the recommendations reflect the experts' opinions.

4. Methodology

The guidelines were developed as much as possible based on a systematic review of the literature. When evidence was lacking, a consensus was sought by the opinions of experts in the field. The methodology as described by the Scottish Intercollegiate Guidelines Network was followed (SIGN, see http://www.sign.ac.uk).

Based on an initial screening of the literature in 2009, focus groups were organized: with physicians, other caregivers and with patients. The purpose of these focus groups was to involve different areas of expertise related to ADH and SUD for the development of these guidelines. Based on the results of these focus groups, together with the steering committee (see further), a search strategy (keywords, useful databases, etc.) was developed resulting in a systematic review of evidence-based research. A first draft of the guidelines (September 2009) was submitted to the experts of the Forum for Addiction Medicine and other professionals in the field. Following the adaptations based on the expert meeting, the guideline was evaluated in twelve alcohol and drug abuse treatment centres for six months. This test phase was then evaluated, after which the guidelines were revised (September 2010). In December 2015, the literature search was updated, and the guideline was rewritten comprehensively and evaluated again (February 2016). The authors of the current revision are Dr. Crunelle and Prof. Dr. Matthys.

a. Search strategy

The available literature published between January 1994 and April 2009 was searched for in the databases PubMed, Cinahl en Psychinfo using the following terms: "drug use OR drug abuse OR drug misuse OR substance abuse OR substance misuse OR addiction OR dependence OR methylphenidate OR self-medication OR detoxification OR anamnesis OR alcohol OR atomoxetine OR amphetamines OR cocaine OR comorbidity OR gender OR craving OR screening OR diagnosis OR treatment OR coping OR personality disorder OR mourning OR therapy OR motivation OR education OR adults OR opiates OR abstinence OR culture) (AND ADHD) (AND adults)". The search strategy was limited in time to 1994 because the context and nature of problematic substance use and ADHD before 1994 differed too much from the present situation. Both English-language and Dutch-language publications were included. Parallel, a search was conducted for existing guidelines in the databases Clinical Evidence, CEBAM, NHS Guideline finder, The Cochrane library, NICE. For the update of this Guideline, we additionally searched in the databases of the National Guideline Clearinghouse and the GIN database.

This literature search was extended to December 2015 for the update (see attachment 4).

In an initial phase, all publications resulting from the search strategy were categorized by research question. Then, abstracts were screened to select relevant studies. Only publications regarding ADHD and SUD in adults were selected. When no literature was available regarding a specific research question, the search was widened. Two independent reviewers assessed all publications on content and quality. Dr. Cleo Crunelle and Prof. Dr. Frieda Matthys performed the updated literature search. Dr. Crunelle performed the first search as specified earlier, which led to 91 retained manuscripts. Based on titles and abstract content, these were assessed independently by Dr. Crunelle and Prof. Dr. Matthys. Of these 91 manuscripts, those not including adults with ADHD and SUD, focusing on children with ADHD, where ADHD or SUD was not the primary diagnosis, reviews prior to an available meta-analysis, personal author opinions with no research scope, and study protocols without research results, were discarded. A total of 63 manuscripts were retained.

Based on the above-mentioned exclusion-and inclusion criteria, there were no discrepancies on the decision of which manuscripts were to be retained.

The selected studies were subsequently evaluated on quality. The SIGN methodology was used to determine:

1. Whether the content of each publication corresponds to the specified clinical questions;
2. If there is sufficient methodological and clinical consistency between the corroborating evidence and the essential points and
3. Whether these points are acceptable and applicable in a Belgian setting.

To determine the level of evidence of the retained manuscript, the study design, selection bias and potential confounders were assessed. The independence of the investigators and how the randomization of the study population was done were also examined. Evidence tables were created in which the studies used as the basis for the recommendations were summarized. For the update of 2016, Dr. Crunelle and Prof. Dr. Matthys determined the level of evidence, and the evidence tables were adjusted to include the additional evidence for the 2016 update.

When scientific evidence was lacking, a consensus was sought from the opinions of experts in the field (expert meetings, focus groups and consensus meeting - see 4.d and 4.f). The recommendations were assigned a rating based on the evidence quality. Attachment 5 provides and overview of the items on which the literatures study was based.

For the update in 2016, an expert meeting was held for SUD clinicians and paramedics who were involved in the development of this guideline: Dr. F. Matthys, Dr. C. Crunelle, Dr. E. Debusscher, Dr. P. Joostens, Dr. A. Van Den Heuvel, Dr. J. Boiy, Dr.C. Matheï, Dr. A. Vermassen, Mrs. N. Claes, Mr. H. Jenaer, Mr. G. Lauwers, Mr. M. Panis. The recommendations were reformulated based on the complementary literature, and the recommendations were, where necessary, adapted together with the experts in the field. Dr. Tremery (psychiatrist) provided her adaptations and comments at a later time. The update of this guideline was not re-evaluated by external experts. Given the excessive burden on the field and the limited changes in the updated recommendations, no new focus groups were held.

A new update will be presented within 5 years.

There was no funding for this update.

b. Literature overview

Where possible, the guideline relies on evidence-based studies, including meta-analyses, systematic literature reviews and randomized controlled trials. If such publications were not available, observational studies were also evaluated. No guidelines for adults with ADHD and SUD were found in the literature.

The studies used in the formulation of the recommendations were subdivided into function of the study design and quality of the study. Then, the recommendations were assigned a rating according to the quality of the evidence on which they are based, using the SIGN grading system (SIGN, 2001).

Level of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability for a causal relationship
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion
Level of recommendation	
A	At least one meta-analysis, 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	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 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+

c. Steering committee

To optimally control the quality of the guideline development process from the field, the project was followed for its entire duration by a steering committee consisting of:

- Prof. Dr. Bert Aertgeerts (general practitioner, director CEBAM, KU Leuven, current director ACHG, Leuven)
- Dr. Cleo Crunelle (postdoctoral researcher, UZ Brussel) (2015-2016)
- Dr. Peter Joostens (psychiatrist, OPZC, Rekem, currently PZ Broeders Alexianen, Tienen)
- Prof. Dr. Frieda Matthys (psychiatrist, Free Clinic, Antwerpen; AZ St.Maarten, Mechelen, currently UZ Brussel, Vrije Universiteit Brussel)
- David Möbius (criminologist, executive studie & onderzoek VAD, Brussel) (2008-2010)
- Prof. Dr. Bernard Sabbe (professor of psychiatry, CAPRI, Universiteit Antwerpen)
- Dr. Steven Stes (psychiatrist, UPC KU Leuven, campus Kortenberg)
- Prof. Dr. Bie Tremmery, departement neurowetenschappen, kinder- en jeugdpsychiatrie, Kuleuven.
- Dr. Annemie Vermassen (addiction physician, ADIC, Antwerpen, currently AZ Stuivenberg, Antwerpen)

This steering group met every two months during the project, and monitored the quality of the guideline development process. Prof. Matthys received earlier honoraria from Lundbeck, Eli Lilly, and Novartis, of Takeda Pharmaceuticals, and Janssen Pharmaceutics. Prof. Bernard Sabbe received honoraria and research grants from Janssen Pharmaceutics. Peter Joostens received earlier honoraria from Novartis and gave lectures for Lundbeck and Janssen Pharmaceutics. These potential conflicts of interest did not influence the writing and reviewing of this guideline. All other steering committee members acknowledge no conflicts of interest. In addition, an advisory committee set up by the Federal Public Health Service monitored the guideline development process. The first guideline has been developed with support from the federal government. The government has in no way influenced the contents of this guideline.

For the review of the update of this guideline, members of the steering committee were invited as part of the present expert committee. The following members of the steering committee were present for the update: Dr. F. Matthys, Dr. C. Crunelle, Dr. P. Joostens, Dr. A. Vermassen.

d. Focus groups

Focus groups were organized to supplement the findings from the literature with experience from the field. The purpose of these focus groups was to involve experts from different fields and professions from both categorical outpatient and residential addiction care (psychiatrists, nurses, psychologists, EPSI, etc.) in the development of the guidelines. The focus group participants were recruited from the Forum for Addiction Medicine of the Association of Alcohol and Other Drug Problems (VAD). This forum is composed of physicians (MDs, GPs and psychiatrists) employed mainly in the addiction field. Physicians were additionally asked to invite other professionals dealing with ADHD within their organizations. Since the participants in the focus groups were a selection of interested and specially trained professionals, the obtained information is not considered to reflect the view and attitude of the entire Flemish addiction care sector. However, the experiences from the field are seen as an important addition to questions and problems the literature could not answer.

Focus groups were organized covering three themes:

- *General aspects regarding the presence of ADHD in adults with SUD (February 19, 2009)*
  During this session, participants were divided in two groups (13 physicians and six caregivers) to discuss general statements regarding ADHD and SUD. The topics included: general aspects of diagnosis and treatment of ADHD in adults with SUD, necessary competences of the physician / professional and guideline development. The purpose of this first meeting was to determine topics and related propositions for the next two, more in-depth, focus groups.

- *Diagnosis of ADHD in adults with SUD (March 12, 2009).*
  Here, two groups of participants (11 physicians and 7 other professionals) discussed statements regarding the diagnosis of ADHD in adults with SUD. The topics included: screening, diagnostic criteria, patient population, problems and difficulties, and the training and expertise needed to make a correct diagnosis

- *Treatment of ADHD in adults with SUD (March 26, 2009).*
  Two groups of participants (12 physicians and 6 other professionals) discussed statements regarding the treatment of ADHD in adults with SUD. The following topics were covered: treatment goals, treatment options, pharmacotherapy, non-pharmacological treatment, comorbidity, competences and specific problems related to treatment settings.

To increase the validity and reliability of the guidelines following international standards (Franck et al., 2008), a focus group was organized including patients/clients. This focus group, in which seven patients participated, took place on March 26, 2009. The topics discussed were: general aspects, diagnosis and treatment.

Based on focus group results, the literature review and the expert group feedback, a draft version of the guidelines was prepared and tested. Following this guideline test phase (see e. Test phase), the quantitative data from the registration forms were supplemented by qualitative findings from participants in the test phase. To obtain this qualitative data, a new focus group was organized after completion of the test phase (24 September 2010 - 10 participants). During this focus group, the recommendations were reviewed and comments were noted based on practical experience of physicians and caregivers during the test phase. The guidelines were put into their final form based on the outcome of this focus group.

Finally, a focus group was organized for psychiatrists who never diagnose ADHD (November 29, 2010). Their views and concerns were used to identify barriers for implementation.

All focus groups were tape-recorded, transcribed and feedback was given to the steering committee.

Following the literate update in December 2015, the guideline was adapted in terms of content and level of evidence and submitted to a consensus meeting (February 5, 2016).

e. Test phase

The practical feasibility, acceptability and utility of the implementation of the guidelines for physicians, therapists and patients were evaluated by means of a six-month test phase in twelve alcohol and drug abuse treatment centres (December 2009 - May 2010), including:

- Centra voor Alcohol en andere Drugproblemen - CAD Limburg (Hasselt)
- Katarsis (Genk)
- Openbaar Psychiatrisch Zorgcentrum (OPZC - Rekem)
- ADIC (Antwerpen)
- Free Clinic (Antwerpen)
- AZ St. Maarten (Mechelen)
- PZ St.-Camillus (St.-Denijs Westrem)
- PC St. Jan Baptist (Zelzate)
- UPC KULeuven, campus Kortenberg
- PC Broeders Alexianen (Tienen)
- De Spiegel (Lovenjoel)
- De Spiegel, Ambulante Drugzorg (Asse)

On December 17, 2009, the representatives (psychiatrists and psychologists) of the twelve institutions registered for the test phase were invited to the opening meeting of this test phase. AT this point, the content of the guideline and the practical functioning of the test phase were described. The necessary documents [guideline, summary, decision tree, questionnaires, registration form, informed consent] were handed over. At regular intervals, the participating centres were contacted to monitor and coordinate the implementation of this test phase. The ethics committees of the respective centres approved the test phase.

During the test phase, the responsible physicians of the participating centres were asked to apply the guideline to all new patients who would qualify. The physician for each new patient filled in a registration form, such that the guidelines could eventually be evaluated regarding their practical feasibility, acceptability and utility. After the test phase and after processing the evaluation results, they were re-evaluated by means of focus groups (see *c. focus groups*).

The final version of the guideline was approved by the Belgian Centre for Evidence Based Medicine (CEBAM).

f. Consensus meetings

Two consensus meetings were organized separate from the focus groups -including (external) ADHD and SUD experts- in order to examine the intrinsic value of the guideline for compatibility with experience from the field. The first meeting (September 23, 2009 with six participants) was held to establish the test version of the guideline. A second meeting (October 22, 2010 with six participants) took place after the processing of quantitative (registration forms) and qualitative (focus group) data derived from the test phase. During these meetings, all recommendations were checked and discussed one by one. In this way, the participants reached a consensus on the formulation of guideline for the diagnosis and treatment of ADHD in adults with SUD.
A third consensus meeting was held for the update of the guideline (February 5, 2016; nine participants).

g. Implementation

During the projects pilot phase, the amount of participating centres was limited to those mentioned earlier. After approval of the guideline, we proceeded with the general implementation of the guideline throughout addiction care centres in Flanders.

Two training sessions were given (including 14 and 16 participants) to caregivers in addiction centres who were willing to coach their teams. Given the busy research activities in this area, there was a need for a continuous update of the information and a demand for revision of the guideline.

Promoting and limitation factors in the implementation:

- During the development of the guideline, the implementation was taken into account in several ways: members from all relevant professional and patient groups were represented in the steering committee; the members of the working group were officially delegated on behalf of their scientific associations; in the text preceding the official recommendations, possible impediments to their deployment in practice (e.g., the cost of medication) were given attention. In this way the process of developing the guideline enhanced its implementation.
- A summary of the conclusions and corresponding recommendations was drafted. This simple summary was widely distributed in printed form (as an attachment to the guideline) and can also be downloaded as a separate PDF file (www.vad.be).
- The digitalization of the guideline and accompanying attachments ensures easy access to the available literature and files on which the guideline is based.
- The guideline is included in the VAD educational program. Training courses are offered to physicians and caregivers, thereby paying attention to the specific expectations of participants.
- The guideline will be presented at several national congresses. The guideline is available in Dutch and English, and we are currently working on an international guideline.
- The centres taking part in the test phase have already shown effects of their participation in the development of the guideline. Gaps in diagnostic and therapeutic skills were identified, existing strategies were reviewed and plans to raise awareness of structural interventions (training, time, development modules, etc.) were conceived.
- The scepticism of some psychiatrists (and other professionals) about the diagnosis of ADHD will be met by organizing training opportunities. A focus group was held on November 29, 2010 for psychiatrists who never diagnose ADHD. Their concerns and different views will be incorporated into the training. There may be a lack of expertise in various aspects of the diagnosis and treatment of ADHD. Before the introduction of the guideline, professionals in the field often had their own traditions of working with ADHD. These needs will be met by organizing training opportunities. Moreover, there is the necessary space in the guideline to allow the clinical experience of the psychiatrist, therapist, etc. to carry its weight. For example, it was decided not to favour certain diagnostic tools, but to allow the clinicians to determine the most suitable instruments. This was also an endeavour to remove the fears of the professionals of losing their autonomy in making certain decisions.
- The guideline is developed for use in both outpatient and residential settings. Differences between these two settings were discussed extensively during both the expert meetings and the consensus meetings.

The impact of compliance with the guideline will primarily result in improved continuity in the treatment of ADHD in referrals within (and outside) the addiction sector. As a result, the likelihood of patients receiving adequate treatment will increase while gaining more insight into their own problems. Criteria to assess the implementation of the guideline are based on the recommendations from this guideline. The procedures followed by physicians, psychiatrists and psychologists dealing with adults with SUD in their everyday practice or SUD specialists working within an outpatient and/or residential setting with respect to the diagnosis and treatment of ADHD in adults with SUD should meet the following criteria:

- Every new client of 18 years or older with SUD is screened for ADHD when drug use is stabilized.
- Upon positive ADHD screening results, an extensive diagnostic evaluation will be performed.
- In addition to the use of questionnaires and semi-structured interviews, comprehensive history taking will be conducted. This takes into account the personal characteristics of the client. Psychiatric comorbidity should be identified, as well as a comprehensive assessment of current and former substance use.
- Treating ADHD in SUD patients will start when the SUD is stabilized. This way, tackling the substance abuse and any other mental disorders or difficulties will be incorporated into the treatment.
- The treatment comprises a combination of medication (preferably atomoxetine) in combination with psychotherapy (psycho-education, individual coaching, peer support, cognitive behavioural therapy and skills training).

5. The diagnosis of ADHD in adults with SUD

5.1. The role of diagnosis

Diagnostics is broadly defined as the process to describe the problem areas in functioning in detail, at the same time comprehensively portraying the development in many different areas. It also includes an inventory of environmental variables that affects functioning. Diagnosis is thus not focused on tracing specific problems, but the process is aimed towards the full range of development, the identification of problem areas and detecting factors that affect functioning (GGZ, 2005).

Described below, diagnosis is described as determining ADHD-related characteristics, which is only part of the whole diagnostic process. Indeed, in the diagnostic phase it is important to make use of information from various situations in which the person is at home, at work and in the study location. It is, after all, only when behaviour shows ADHD characteristics in various situations that one can speak of ADHD.

5.2. Problems and concerns related to the diagnostic process

5.2.1. Psychiatric comorbidity

ADHD is associated with more complex and chronic dependence problems (Young et al., 2015) and psychiatric comorbidities (i.e., conduct disorder, antisocial personality disorder, bipolar disorder and post-traumatic stress disorder) in comparison to a population with SUD but without ADHD (Arias et al., 2008). A study by Wilens and colleagues (2005) in 46 methadone users with ADHD indicates that about 49% suffered from depressive moods and that 60% had trouble keeping their temper under control (Kalbag & Levin, 2005). Compared to non-depressed patients with ADHD and SUD, depressed patients often have more severe SUD problems before and during treatment, which necessitates a combined treatment for depression (Warden et al., 2012). An international study in 1205 patients with SUD showed that psychiatric comorbidity occurred more frequently in adults with comorbid ADHD than in patients with SUD without ADHD (van Emmerick-van Oortmerssen et al., 2014). 75% of patients with ADHD and SUD have at least one additional co-morbid disorder compared to 37% of patients with SUD but without ADHD (van Emmerick-van Oortmerssen et al., 2014). Certain patterns of comorbidity were found to be depending on the ADHD presentation: major depression was mainly present in ADHD patients with inattentive / combined ADHD presentation, while (hypo)manic episodes and antisocial personality disorders were observed mainly in the hyperactive-impulsive ADHD presentation (van Emmerick-van Oortmerssen et al., 2014).

Given the high level of comorbidity it is advisable to include this in the diagnostic assessment (Matthys et al., 2013).

5.2.2. Under- en over-diagnosis

The strictness of the DSM-criteria can complicate the diagnosis of ADHD in adults, which can lead to under diagnosis of ADHD in the adult population (Levin & Upadhyaya, 2007):

- For the diagnosis in populations of substance users as well as in the general population, the DSM-criterion maintaining that ADHD has to occur independent of other disorders may be a source of confusion. It is often wrongly assumed that if anxiety disorders, depression or other psychiatric disorders are present, no ADHD diagnosis van be made. If ADHD occurs along with other Axis I disorders, both should be taken into account (Kalbag & Levin, 2005).

- Since the DSM-symptoms were originally developed for children, the lack of age-specific symptoms can lead to under diagnosis of adults with ADHD (Levin & Upadhyaya, 2007).
- Patients SUD and ADHD often have more difficulty than adults without SUD to remember early history of ADHD symptoms necessary for the diagnostic process (Levin & Upadhyaya, 2007).
- There is a lack of interest in the diagnosis of ADHD in adults with SUD. Indeed, if an individual with SUD was not diagnosed with ADHD as a child, it is unlikely that the behaviour that he or she demonstrates will be linked to ADHD (Levin & Upadhyaya, 2007).
- Many consequences of ADHD (job loss, poor school performance, etc.) are also associated with SUD. All too often, in individuals with SUD who were not before diagnosed with ADHD, it is assumed that all their problems are due to substance abuse. Moreover, adults with ADHD have often been dealing with these symptoms for years and they have developed compensatory strategies, which have allowed them to manage to limit the impact of these symptoms (Kalbag & Levin, 2005; Adler & Cohen, 2004). Therefore, the clinician should pay attention to this, taking into account the fact that these coping strategies may mask certain symptoms whereby deterioration in the condition of the patient is not always noticeable. This means that the degree of compensation should always be taken into account when recording the severity of the symptoms (Culpepper & Mattingly, 2008).

In addition to underdiagnosis of ADHD, it is also possible that symptoms are attributed wrongly to ADHD. In this case, we speak of overdiagnosis. For example, individuals with bipolar disorders and/or depression display a number of similar symptoms to individuals with ADHD. Moreover, it is important that the ADHD symptoms occur in different settings and situations. Overdiagnosis also occurs when the continuity of symptoms from childhood to adulthood is overlooked or when substance inducing symptoms or withdrawal symptoms are perceived as pure ADHD symptoms. Therefore, it is highly recommended that developmental history, psychiatric comorbidity and family history of the patient be addressed adequately in the diagnostic process (Kalbag & Levin, 2005).

Another risk of overdiagnosis lies in the fact that patients may exaggerate their ADHD symptoms, in order to influence and gain an advantage from diagnosis. A few examples include students receiving extra time to take examinations or obtaining stimulant medications. This should be taken into account in the diagnostic process, always keeping in mind what a particular patient may gain from the diagnosis of ADHD and asking pointed questions to keep this risk to a minimum (Upadhyaya, 2007).

On the other hand, symptoms related to SUD (including withdrawal symptoms) of the patient may be erroneously identified as ADHD symptoms, which can lead to overdiagnosis of ADHD in an SUD population (Levin & Upadhyaya, 2007). Therefore, during history taking, it is recommended to focus on drug-free and alcohol-free moments in the life of the patient (Sullivan & Rudnik-Levin, 2001). A follow-up evaluation of ADHD symptoms during SUD treatment is also recommended in order to reduce the risk of misdiagnosis (Fatseas et al., 2012).

5.3. Steps in the diagnostic process

Several instruments can be used to determine whether or not a patient with SUD has an underlying ADHD. It is generally accepted that a good diagnosis consists of a number of necessary steps that are more or less similar to the diagnosis of ADHD in an adult population without SUD: an examination of the current symptomatology, elements from childhood, family history, school and occupational history, marriage, physical signs and comorbidity (Adler & Cohen, 2004). It is important to include environmental factors in the broad sense of the term in the diagnosis. These are factors that could have protective or risk-enhancing effects on the functioning of the individual. Moreover, a necessary condition to be diagnosed with ADHD as an adult is that some symptoms already occurred before age twelve. It is therefore important that, in addition to the history of the patient, a collateral history be taken with someone who knows the patient well (e.g., parents or

siblings) to verify whether the ADHD symptoms were present during childhood. Specific to the diagnosis in a population of SUD individuals is that some aspects of the normal diagnostic procedure of ADHD in adults are added and elaborated in order to reduce to a minimum problems related to overdiagnosis or underdiagnosis of ADHD in patients with SUD (Upadhyaya, 2007). Thus, for example, an important addition to the diagnosis in this population would be screening of the (current) SUD.

5.4. Who makes the diagnosis and when?

An essential part for a correctly performed ADHD diagnosis is that the diagnostician is knowledgeable and competent. The literature argues towards a targeted training on the dual-diagnosis of ADHD and SUD (Martinez-Raga et al., 2013). From the expert group, the following recommendations were formulated:

The diagnosis of ADHD can be made by every physician provided that he/she:

- ✓ has received extensive training on the differential diagnosis of ADHD;
- ✓ has experience in addiction care;
- ✓ has experience with adults ADHD populations.

Although no specific evidence-based recommendations are available regarding when to begin the diagnostic process in individuals with SUD, the literature mentions the need for a sufficiently long period of abstinence in order to make an accurate and valid diagnosis (Wilens, 2004). Other sources state that the patients must be at least approachable. The reason for this is that symptoms and problems of the disorder are determined over the lifetime of the patients, and not only in the current time. The history taking process plays an important role here (Van de Glind et al., 2004). A screener can already be used at intake, because the screener shows similar sensitivity and specificity at intake compared with a period of 2 weeks after admission (Van de Glind et al., 2013).

The expert group of the ADHD-SUD project noted that a distinction should be made between patients in a residential and outpatient setting. After the test phase, and based on the experiences from the field during this test period, the recommendation was reformulated as follows:

Assessing current symptomatology and the (differential) diagnosis can be started after a sufficiently long period of abstinence. This period of abstinence is determined by the clinical experience of the diagnostician taking into account the setting in which the patient is treated and with the drug being abused. The expert committee suggests the following criteria must be met to start the diagnostic process:

- There are no withdrawal symptoms
- There is no intoxication
- The patient is sufficiently stabilized

Case history study, observation, and screening can be started earlier. The preliminary diagnosis must be verified in the course of treatment as the ADHD presentation can change in the course of SUD treatment. It is therefore essential to continue to monitor the patient (Martinez-Raga et al., 2013).

Which elements are important in order to make the diagnosis of ADHD in adults with addiction?

- *When can the diagnostic procedure be started?*
- *Who is eligible to make the ADHD diagnosis?*

Conclusions:

Level of evidence 3	The diagnostic process is a continuous process. A good follow-up is needed to reduce problems related to ADHD over- or under-diagnosis in patients with SUD (Fatseas et al., 2012).
Level of evidence 3	A proper diagnosis comprises a number of necessary steps: ascertaining the current symptomatology, elements from childhood, family history, educational and occupational history, marriage, physical signs and comorbidity (Upadhyaya, 2007; Adler & Cohen, 2004).
Level of evidence 3	There is no research on when is the best time to begin the diagnostic process in individuals with SUD problems (Wilens, 2004).
Level of evidence 4	For the proper diagnosis of ADHD in adults with SUD it is essential that care providers be knowledgeable and competent (Van de Glind et al., 2004). The literature argues towards a targeted training regarding the dual-diagnosis of ADHD and SUD (Martinez-Raga et al., 2013).

Recommendations

Level of recommendation D	Do not base the diagnosis only on questionnaires. Results from a comprehensive (collateral) anamnesis and additional diagnostics (including substance abuse) should also be recorded. This means that the following steps should be taken to proceed to the diagnosis of ADHD in adults with SUD:
	- Screening
	- Diagnosis:
	  ○ Present symptomatology
	  ○ (Collateral) anamnesis
	  ○ Additional examination and differential diagnosis
	  ○ Follow-up to confirm or adapt the preliminary diagnosis

Level of recommendation D	Evaluating the current symptomatology and differential diagnosis can be started after a sufficient period of stabilization of substance use. The length of the stabilization period is determined by the clinical experience of the diagnostician, taking into account the setting in which the patient is being treated and the abused substance. (Collateral) anamnesis, observation and screening can be started earlier.
Level of recommendation D	The diagnosis of ADHD can be made by every physician provided that he/she: ➢ has received extensive training on the differential diagnosis of ADHD; ➢ has experience in addiction care; ➢ has experience with adults ADHD populations.
Level of recommendation D	When the questionnaires are filled out by the patient in the presence of a caregiver, this can be useful as an observation moment.

5.5. Screening

Screening is important for the identification of ADHD characteristics in individuals for which an in-depth diagnostic investigation would be useful, and should thus occur prior to the actual diagnosis. Screening is of importance for the following reasons:

- ADHD has a significant impact on the development of SUD (West et al., 2007). Early detection of ADHD in a population of SUD individuals is of key importance for successful treatment of these disorders (Kalbag and Levin, 2004).
- The high prevalence of ADHD in people with SUD, along with the fact that many clients will make no mention of the core symptoms of ADHD but mainly focus on their SUD problems, makes it important to screen for the occurrence of ADHD.

The use of extensive diagnostic tools at an early stage of diagnosis can lead to a heavy burden for the patient. Essential components of a good screening tool include a short decay time, the ability to exclude of a high proportion of false positives and a good validity and reliability (Wild et al., 2007).

5.5.1. Screening instruments

A number of tools that can be used to give an indication of the presence of ADHD in adults with SUD are presented below. The following screeners are covered:

- Six-item Adult ADHD Self-Report Scale Screener (ASRS-screener)
- Conner's Adult ADHD Rating Scales screener (CAARS-short version)
- Zelfrapportage vragenlijst over aandachtsproblemen en hyperactiviteit

Six-item Adult ADHD Self-Report Scale (ASRS) Screener
This screening instrument consists of 6 of the 18 items from the ASRS, an official self-report instrument developed by the World Health Organization. The items were selected on the basis of a stepwise logistic regression to optimize the agreement with the clinical classification. The ASRS screener has the advantage of a rapid take in clients at intake: it is easy to use and can be filled in in a short time (less than 2 minutes) with accurate results.

The ASRS screener was validated for the specific target group of adults with SUD (Van de Glind et al, 2014.), with a sensitivity of 84% (95% CI: 76% - 0.88%) and a specificity of 66% (95 % CI: 63% - 0.69%) in a group of 1138 adults with SUD (13% with ADHD). The ASRS was proven sensitive to screen for ADHD in adults with SUD, with few missed cases of ADHD if receiving a negative screening. In addition, the validity of the ASRS was high (short version with 6-items), both when the ASRS was taken immediately upon admission, or some time (two weeks) later (Van de Glind et al., 2014). A smaller study in 138 patients with ADHD and SUD, however, reports a low specificity using the ASRS, with only a confirmed diagnosis of ADHD in 20% of the cases (Chiasson et al., 2012). Other studies provide a good sensitivity (83.3 - 100%) and specificity (66.1 - 68.6%) for the ASRS in ADHD patients with SUD (Konstenius et al., 2015; Roncero et al., 2015; Daigre et al., 2015). The specificity of the ASRS is highest in patients with alcohol dependence (76%) compared to other drug (56%) (van de Glind et al., 2013). The sensitivity can be increased up to 92.3% when another screener like the WURS is co-administered (Daigre et al., 2015).

This screening tool is to be considered as a good starting point in the recognition of ADHD symptoms but it cannot be used as a substitute for extensive diagnostic testing (Kessler et al., 2005; Adler et al., 2009). A validated Dutch version of this tool can be obtained at no cost through http://www.hcp.med.harvard.edu/ncs/asrs.php.

He questions relate to the situation of the *past 6 months*:
(never (0); rarely (+1); sometimes (+2); often (+3); very often (+4))

1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?
3. How often do you have problems remembering appointments or obligations?
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?

Each item is given a score ranging between 0-4 (total number of points for the six questions: 0-24), where 12 points is considered as the cut-off for an increased likelihood of the occurrence of ADHD in adults with SUD (Ramos-Quiroga et al., 2009; Van de Glind et al., 2014).

Conner's Adult ADHD Rating Scales
The Conner's Adult ADHD Rating Scales (CAARS) is available in three versions: a long (66 items), a short (26 items) and a screening instrument (12 items). Research into a number of psychometric properties of the CAARS (26 items) in a population of treatment-seeking SUD patients shows that the instrument may be useful for the screening of ADHD symptoms in SUD individuals (Cleland et al., 2006). In 102 cocaine-dependent patients (25 with ADHD), the CAARS (26 items) had a sensitivity of 80.0% and a high positive predictive value of 74.1%. Combining the CAARS (26 items) and the WURS within this population increased the sensitivity up to 96.0% (Dakwar et al., 2012). The CAARS is only available in English and must be purchased, although a Dutch version of the CAARS seems available (Saviouk et al., 2011; Derks et al., 2014).

Zelfrapportage vragenlijst over aandachtsproblemen en hyperactiviteit
Kooij and colleagues (2005) developed a Dutch self-report questionnaire for ADHD in adults, based on the DSM-IV-TR criteria for ADHD. The list consists of 46 items, with the first 23 items that assess adult behaviour over the past six months. The other 23 items retrospectively assess the patient's behaviour as a child. The 46 items are divided into two subscales: a scale which shows the current attention deficit and a scale for the current hyperactive / impulsive behaviour. All items should be answered by the subject using a 4-point Likert scale ranging from 0 (never or rarely) to 3 (very common). The patient can complete this in about ten minutes. Besides the actual screening tool, a corresponding list of scoring rules was developed which clearly states how the clinician needs to interpret these scores. Scoring the list takes approximately two minutes (Van de Glind et al., 2004). The reliability, convergent and divergent validity, as well as the prediction of the clinical diagnosis of ADHD based on the self-report questionnaire was studied in 120 adults with ADHD, their partners and their parents. The questionnaire proved sufficiently reliable and valid, and the clinical diagnosis was well predicted (Kooij et al., 2008). The instrument is, however, not studied in a population of adults with ADHD and SUD. A Flemish version was developed and validated, and the Self Reporting Questionnaire for attention problems and hyperactivity (ZVAH) is available for young adults between 16 and 25 years (Baeyens et al., 2012).

5.5.2. After screening

If the screening result indicates a possible presence of ADHD, an expert in ADHD or a psychiatrist should initiate a more extensive examination. Diagnosis solely based on the results of screening instruments can easily lead to overdiagnosis (Upadhyaya, 2007). In this examination, all aspects of ADHD should be addressed, both during childhood and in the present. The presence of ADHD and related disorders should be looked for in the family as well. An interview should also be conducted with a parent, brother or sister, to obtain more information about the childhood. This is done to

prevent that a false clinical picture is formed due to the individuals' own over- or underestimation of their symptoms.

Which specific aspects should be taken into account during the screening of ADHD in adults with SUD?

- Is it appropriate to screen adults with SUD systematically for ADHD and which instruments are preferred for screening?

- Which screening result should initiate more extensive diagnostic testing?

Conclusions:

Level of evidence 2+	The screening is best performed using a validated questionnaire based on DSM-5 criteria for ADHD.
Level of evidence 3	Screening provides a first indication of the possible presence of ADHD at intake (Van de Glind et al., 2004; Van de Glind et al., 2014). Only basing the diagnosis on the results of screening instruments can lead to overdiagnosis (Upadhyaya, 2007)

Recommendations:

Level of recommendation C	Considering the high prevalence of ADHD in individuals with SUD, it is important to screen patients in addiction care for the occurrence of ADHD.
Level of recommendation D	The ASRS screener is the preferred screening tool in adults with ADHD and SUD (Van de Glind et al., 2014).
Level of recommendation D	If the screening results show that there is a risk of ADHD, a more extensive examination should be initiated.

5.6. Making the actual diagnosis

The diagnosis of ADHD should be part of a medical-psychiatric examination. For the specific diagnosis of ADHD the following steps should be taken:

- A thorough investigation of the current symptomatology (using diagnostic instruments);
- (Collateral) history taking (elements from childhood, family history, educational and occupational history, marriage, etc.);
- Additional examination (for comorbidity and differential diagnosis) (Adler & Cohen, 2004).

5.6.1. Current symptomatology

Similar as for the screening, a questionnaire based on the 18 diagnostic criteria in DSM can be used for a more comprehensive assessment of the current symptomatology. In what follows, instruments, which qualify for this, are presented. Since only few of these instruments were validated in a population of adults with SUD, instruments were also included that have not (yet) been tested in this population but are widely accepted and validated for determining current ADHD symptoms in an adult population without SUD. Because of the limited availability of Dutch validated instruments, we also include English instruments and instruments only available in commercial versions. The following instruments are covered:

- Wender Utah Rating Scale (WURS)
- Adult Self-Report Scale (ASRS – full version)
- Barkley's Current Symptoms Scale-Self-Report
- Attention Deficit Scales for Adults (ADSA)

Other instruments are available, including the Brown Attention Deficit Disorder Scale (BADDS), a 40-item scale that addresses symptoms of attention deficit but not hyperactivity and impulsivity. While its use has been accepted in adults (Kooij et al., 2008), its converging validity (comparing the patient score with a partner score) is rather low. In addition, the BADDS is not sensitive or specific enough to be used for differential diagnosis (Solante et al., 2004), and its use is limited. The CAARS instrument is also available to assess ADHD symptoms during the diagnostic process (the CAARS was discussed earlier (see 'screening') and is therefore not added to the list above). Research shows that results of the BADDS are correlated with results of self-report instruments such as the CAARS and the WURS (Rodriguez & Simon-Dack, 2013). The final choice of the diagnostic instrument to be used depends primarily on the available time and the preference of the diagnostician.

Wender Utah Rating Scale (WURS)

This rating scale consists of 64 items assessing retrospective symptoms from childhood as well as current hyperactivity, attention deficit and other symptoms (Ward et al., 1993; McCann et al., 2000).

The scale is based on the "Utah Criteria for ADHD in Adults":

1. In childhood, there were both poor concentration and hyperactivity;
2. In addition, childhood was characterized by behavioural problems at school, impulsivity, excitability and fits of temper (at least one of these four);
3. In adulthood, there are persistent problems with concentration and hyperactivity, and at least two of the following five symptoms: weak affect, irascibility, stress intolerance, impulsivity and disorganization.

The use of this instrument for assessing retrospective childhood ADHD symptoms in adulthood has been described in smokers (Fond et al., 2015), in cocaine-dependent individuals (Dakwar et al., 2012; Pérez de Los Cobos et al., 2012), in alcohol-dependent individuals and in polydrug users (Ohlmeier et al., 2008). The WURS has a sensitivity of 87.5 % for the assessment of ADHD symptoms in cocaine-dependent individuals (Dakwar et al., 2012).

Adult Self-Report Scale (ASRS)
This is an official instrument of the World Health Organization, consisting of 18 items based on the DSM criteria. It is the longer version of the previously discussed *six-item Adult ADHD Self-Report Scale Screener*. Research on the ASRS' psychometric properties demonstrates that the ASRS is a valid and reliable scale to diagnose ADHD in adults (Adler et al., 2006). A validated Dutch version can be obtained at no cost from http://www.hcp.med.harvard.edu/ncs/asrs.php.

The ASRS is validated in adults with ADHD and SUD (see 'screening instruments – ASRS') and can additionally be used for a quantitative scoring of ADHD symptoms in adults with SUD, e.g., for clinical research (Crunelle et al., 2013).

Barkley's Current Symptoms Scale-Self-Report
This scale assesses the frequency of the 18 DSM symptoms. The odd items focus on symptoms of attention deficit and the even items on symptoms of hyperactivity and impulsivity; using a scale from 0 (never or rarely) to 3 (very often). Eight additional questions address the possible presence of a comorbid oppositional defiant disorder (Barkley, 2009). This instrument is (for the time being) only available in English and as a commercial version.

Attention Deficit Scales for Adults (ADSA)
A study on the use of the ADSA in a population of substance users provides some support that the ADSA is a reliable and valid instrument to determine which clients with SUD might benefit of a more thorough diagnostic examination for ADHD. Additionally, ADSA results correlate well with those of the DSM-IV criteria for ADHD (West et al., 2007; West et al., 2003). This instrument is (for the time being) only available in English and in a commercial version.

- ➔ All these instruments form the basis of good diagnostic practice, but it is not recommended to use them as the sole basis for diagnosis. This would yield too many false positive or false negative results. In addition to the results obtained on these scales, other factors should be taken into account to reach a correct diagnosis: results from comprehensive (collateral) history taking and additional diagnosis.

5.6.2. (Collateral) history taking

Collateral history taking on current and former symptomatology is essential to obtain objective information. However, as mentioned earlier, it may be difficult to determine whether the ADHD symptoms that an adult faces were already present in childhood and, if so, whether these were not due to other disorders during childhood (learning disabilities, depression, etc.). Memories are not always easy to recall, and involving family members may be helpful. In a population of adults with SUD, obtaining retrospective information regarding past experiences seems even more difficult. The patient may be reluctant to give contact information or the family is unwilling to cooperate with the diagnostic procedure. In these cases, objective childhood data can be obtained through e.g., school reports, by paying particular attention to comments made by former teachers (Kalbag & Levin, 2005).

Involvement the patient's partner and parents in the diagnostic process is important. Research by Kooij and colleagues (2008) suggests that adults with ADHD are the best informants to recognize their own symptoms (better than other informants such as parents, partners, etc.) but that they often tend to underestimate severity. The symptoms have often become so normal to them that they frequently feel that it is not all that bad. The question of the objectivity of one's own memories comes up here as well. Reports from parents and partners can cast a different light on that same behaviour. If available, report cards, test results and conduct reports can also be useful (Adler & Cohen, 2004; Weiss & Murray, 2003). The expert group in this project also stressed the importance of involving the parents (or in their absence other siblings, grandparents, etc.) in collecting objective information, particularly from the patient's first twelve years of life. However, a longitudinal study shows that parents' memory is not always as reliable, and one should be careful when interpreting parent's memory as well (Moffit, 2015).

Adults with ADHD have often developed compensation strategies to managed and limit the impact of their ADHD symptoms (Kalbag & Levin, 2005; Adler & Cohen, 2004). The clinician should pay attention to this and take into account that some of these coping strategies may mask certain symptoms, such that ADHD symptoms are underestimated. The degree of compensation should always be taken into account when recording the severity of symptoms (Culpepper & Mattingly, 2008).

Symptoms associated with the patient's substance use (including withdrawal symptoms) may be erroneously identified as ADHD symptoms, which can lead to an overdiagnosis of ADHD in individuals with SUD (Levin & Upadhyaya, 2007). Therefore, it is recommended to focus on drug-free and alcohol-free moments in the patient's life (Levin et al., 1999; Sullivan & Rudnik-Levin, 2001) during (collateral) history taking. Also, symptoms from other disorders can be wrongly attributed to ADHD. This could for example include the overlap between symptoms of ADHD and those of bipolar and/or depressive disorders (Kalbag & Levin, 2005). Overdiagnosis can also occur when patients exaggerate their symptoms in order to obtain certain benefits (Upadhyaya, 2007). The use of substances at home or within the family is also important (Bukstein, 2008).

Diagnostic interviews

Conner's' Adult ADHD Diagnostic Interview for the DSM-IV (CAADID)
CAADID is a structured interview that can be used as an aid in the diagnosis of ADHD in adults. It consists of two parts: a survey of the developmental history (including comorbidity) and a diagnostic interview to assess DSM-criteria for ADHD. The CAADID is used as the golden standard for the diagnosis of ADHD adults with SUD, and as a tool to compare other diagnostic instruments (Ramos-Quiroga et al., 2015) and to validate the available screeners (see earlier) (van de Glind et al., 2013, 2014; Roncero et al, 2015; Daigre Blanco et al., 2009). This instrument is (for now) only available in English and for a fee, but a Dutch version seems available (van de Glind et al., 2014; Crunelle et al., 2013, 2014).

Diagnostisch Interview voor ADHD bij Volwassenen (DIVA)
J.J.S. Kooij and M.H. Francken (2007) developed an instrument that can be used to assess the current ADHD-symptomatology and to collect anamnestic data. This instrument is based on the DSM-IV criteria. The DIVA can be administered to adults in the presence of partner and relatives to simultaneously collect past history and collateral past history information. The DIVA consists of three parts: the criteria for Attention Deficit (A1), the criteria for Hyperactivity-Impulsivity (A2), and Onset Time of and Dysfunctioning resulting from the symptoms in childhood and adulthood. The DIVA takes about one and one and a half hours to be administered. The instrument has not (yet) been validated in a population of adults with SUD.

Psychiatric Research Interview for Substance and Mental Disorders (PRISM)
PRISM is a semi-structured interview that focuses on comorbid psychiatric diagnosis, i.e., within patients who use and abuse alcohol and other substances. The PRISM is based on the DSM-IV criteria for axis 1 and II disorders, including ADHD. In 80 patients with SUD (40 with and 40 without ADHD), the PRISM had a sensitivity of 80% and a specificity of 87.5% compared to the CAADID (Ramos-Quiroga et al., 2015).

Which specific aspects should be taken into account when ascertaining current ADHD symptomatology and during the anamnestic process in the context of diagnosing ADHD in adults with SUD?

Conclusions:

Level of evidence 2+	The use of questionnaires based on DSM5 criteria for ADHD forms the basis of a good diagnostic procedure. However, a diagnosis solely based on this can lead to false positive or false negative results (Adler & Cohen, 2004). Only three diagnostic scales were evaluated for ADHD in a population of adults with SUD (Cleland et al., 2006; West et al., 2007; Ramos-Quiroga et al., 2015). The CAADID is most often referred to as the golden standard for the diagnosis of ADHD in adults with SUD (van de Glind et al., 2013, 2014; Roncero et al, 2015; Daigre Blanco et al., 2009).
Level of evidence 3	The use of certain drugs can induce symptoms of ADHD without it actually being ADHD (Wilson & Levin, 2001)
Level of evidence 3	Obtaining retrospective data is often a difficult task in a population of adults with SUD. The patient may be reluctant to provide contact information or the family is unwilling to cooperate with the diagnostic procedure (Kalbag & Levin, 2005).
Level of evidence 2	Adults with ADHD are better informants than their parents or partner, but tend to under-report the severity of their symptoms (Kooij et al., 2008). The memory of the parents is not always accurate (Moffit, 2015).
Level of evidence 3	Adults with ADHD often developed compensation strategies, allowing them to limit the impact of the ADHD symptoms (Kalbag & Levin, 2005; Adler & Cohen, 2004).
Level of evidence 3	Substance induced symptoms (including withdrawal symptoms) may sometimes be mistaken for ADHD symptoms (Kalbag & Levin, 2005).
Level of evidence 3	Some patients may exaggerate their symptoms to gain specific advantages of being diagnosed with ADHD (Upadhyaya, 2007).
Level of evidence 4	To date, no history-taking instrument has been tested for its reliability and validity in a population of adults with SUD.

Recommendations:

Level of recommendation C	The use of questionnaires and semi-structured interviews that have been validated in a population of patients with ADHD and SUD is the ideal starting point to proceed to the diagnosis of ADHD. The DIVA and CAADID, both structured interviews, are not yet validated in adults with ADHD and SUD. The diagnostician determines the choice of the appropriate instrument on the basis of his or her clinical experience. The use of such instruments is merely a starting point and should always complement extensive observation, (collateral) history taking and additional investigation.
Level of recommendation D	When the questionnaires are filled out by the patient in the presence of a caregiver, this can be useful as an observation moment.
Level of recommendation C	Comprehensive (collateral) history taking is necessary for a proper diagnosis and can prevent overdiagnosis or underdiagnosis. The memory of the parents may not always be accurate.
Level of recommendation D	Determining a time frame of substance use can help to distinguish symptoms related to drug use from ADHD symptoms. By reporting this back to the patients, the patient could become more aware of their problems.

Level of recommendation C	Involving the patients' parents (or in their absence sibling(s), grandparents, etc.) is essential to gather information from childhood (especially the first twelve years). The partner and/or other relatives can also be interviewed to gain information on the current symptomatology.
Level of recommendation C	Additional information can be gathered from school records with particular attention to the development of school performances, and to comments added by former teachers.
Level of recommendation D	The level of compensation should be taken into account when recording ADHD symptoms.
Level of recommendation D	Be aware of possible profits associated with the disorder that can accompany a diagnosis of ADHD for the patient.
Level of recommendation D	Focus on drug-free and alcohol-free moments in the patient's life during (collateral) history taking.

5.6.3. Focusing on specific groups within the ADHD population and diagnostics

Although there is strong evidence for the role of biological processes responsible for the symptoms associated with ADHD, another key player includes the environment in which the individual functions. This environment determines, among other factors, the degree of structure, which would influence the development and appearance of ADHD symptoms. Although research into the impact of these environmental influences on individuals with ADHD is rather scarce, it is still important for the detection and diagnosis of ADHD to pay sufficient attention to any specific influences of the patient's gender, cultural background or socioeconomic status (SES). To make a proper diagnosis, understanding the effects that these variables may have on behaviour is a must for the diagnostician. These elements can be very important when looking at how ADHD symptoms manifest within an individual (Gingerich et al., 1998).

5.6.3.1. Gender-specific characteristics

The literature on gender-specific characteristics in ADHD mainly focuses on children. Traditionally, three aspects of ADHD have been described that indicating a significant influence of gender. First, differences in the pattern of ADHD symptoms between boys and girls have been observed. Girls with ADHD are generally less impulsive, while boys display more problems with discipline and externalizing behaviour. Another difference between boys and girls concerns the ADHD subtypes. Several studies (Biederman et al., 2002; Weiss et al., 2003) show that girls are more often diagnosed as inattentive compared to boys.

Research on similar characteristics in adult populations with ADHD is considerably more scarse. One of the first major investigations on this theme was research by Biederman et al. (1994) in which showed that men with ADHD more frequently had behavioural problems and take more time to complete their studies than women with ADHD. Other studies show that psychiatric and cognitive impairments occur in both sexes (Biederman et al., 2004), but that women with ADHD exhibit more problems such as depression, mood and anxiety disorders and low self-esteem compared to men with ADHD (Katz et al.., 1998; Arcia & Conners, 1998; Biederman et al., 2006). This may be related to the fact that women are often diagnosed with ADHD later in life than men, and that they developed better coping strategies. This may result in embarrassment and low self-esteem, but also a form of learned helplessness. As a result, it is possible that these women experience more important social isolation, misinterpreting their symptoms and thereby obscuring the underlying ADHD (Waite, 2007).

More recent research by Robison and colleagues (2008) found gender differences in various domains. In contrast to the findings from studies in children, women are diagnosed more often as combined presentations than men and less frequently as inattentive presentations. Women also consistently suffer more from the condition than men, especially with regard to emotional instability. The complexity of the emotional symptoms characteristic of ADHD in many women, expressing it in different domains of psychosocial functioning, is an important factor in the diagnostic process. The presence of these symptoms makes it difficult for the clinician to establish an accurate diagnosis and can lead to underdiagnosis. This has to do with the fact that women generally exhibit fewer symptoms of hyperactivity but rather less typical symptoms such as forgetfulness, disorganization, restlessness and low self esteem (Waite, 2007; Quinn, 2008). The higher prevalence of emotional symptoms and their more complex expression may hamper the diagnosis of ADHD in women. Therefore, it is recommended to carry out an in-depth analysis of these emotional dimensions in the diagnostic process (Robison et al., 2008).

A naturalistic study following 208 young individuals with ADHD (183 boys, 25 girls) up to their 31ste year, provides evidence that girls with ADHD have a higher risk of developing ADHD later in life, especially when conduct disorder is present, and when pharmacotherapy has been initiated at a later age (Dalsgaard et al., 2014).

5.6.3.2. Culture-specific characteristics

Although the diagnosis of ADHD is recognized in different countries and cultures (Faraone et al., 2003), there is evidence for the presence of culture-specific differences in temperament. This has implications for the assessment of ADHD within a culture. What in considered normal within one culture can be described as problematic in a different culture. The restrictions imposed by the disorder assume significance only in the context of the characteristics of the (sub) culture in which a person functions and thus bears a certain degree of subjectivity. Cultural differences in terms of expectations (at home, at work, in the community, etc.), attitudes towards illness, access to care, confidence in the medical world, religious beliefs and tolerance towards certain behaviours all have an impact on whether or not one is receptive for treatment. This means that cultural differences may affect both the diagnostic process (bias formation) and the treatment of ADHD (Rohde et al., 2005; Adler & Cohen, 2004).

Because ethnic minorities often live in stressful circumstances, it is important for the clinician to take into account the patient's social environment in the diagnostic process. Symptoms such as concentration problems, impulsivity, distractibility and overreacting can also be the result of living in a chronically stressful and unpredictable environment. Furthermore, the interaction between the ethnicity of the patients and the ADHD symptoms exhibited should be meticulously investigated (Gingerich, 1998).

5.6.3.3. Socioeconomic status (SES)

It is important for the diagnostician to be aware of the fact that people from lower social classes have increased vulnerability to ADHD (Gingerich 1998). Monuteaux et al. (2007) found that within a population of young adults with ADHD the association between socioeconomic class and addiction problems is U-shaped, with an increased risk in both the higher and lower social classes. One explanation for this lies in the fact that young adults with ADHD are extremely sensitive to the pathogenetic mechanisms that are associated with certain socioeconomic environments, causing them to consistently develop more drug-related problems.
These findings indicate that asking about the SES can be helpful in the diagnostic process.

To what extent do personal characteristics of the patient play a role in the course of the diagnostic process and how this can be anticipated for during the diagnostic process?

Conclusions:

Level of evidence 3	The environment in which the individual functions is important in the diagnostic process. This environment provides the structure that impacts the development and appearance of ADHD symptoms (Gingerich et al., 1998).
Level of evidence 2	Women with ADHD exhibit more psychological disorders - such as depression, mood and anxiety disorders and low self-esteem (Katz et al., 1998; Arcia & Conners., 1998; Biederman et al., 2006).
Level of evidence 2++	Cultural differences may affect the detection of ADHD and whether or not one is receptive to treatment (Rohde et al., 2005).
Level of evidence 3	Symptoms such as concentration problems, impulsivity, distractibility and overreacting may also be the result of living in a chronically stressful and unpredictable environment (Gingerich, 1998).
Level of evidence 2+	Within a population of adults with ADHD, the association between socioeconomic class and SUD is U-shaped, with an increased risk in both the upper and lower social classes (Monuteaux et al., 2007).

Recommendation

Level of recommendation C	Gender-specific aspects, cultural background and socioeconomic status (SES) of the patient should be taken into account.

5.6.4. Additional diagnoses (differential diagnosis)

Comorbidity is an important issue in the diagnosis of ADHD: many symptoms of ADHD overlap with other disorders (being easily distracted, intense motor activity, impulsivity, irritability, attention problems, etc.), but there is also overlap in diagnostic criteria between related disorders (Kim et al., 2002). This is e.g., the case for comorbidity of ADHD and mania. It is difficult to diagnose (hypo) mania if there is a history of ADHD. In other words, different comorbid disorders may influence the symptoms associated with ADHD. Moreover, ADHD often occurs at a much younger age. Therefore, it is always important to collect retrospective data, to assess psychiatric comorbidity extensively and to involve the family of the patient in the diagnostic process (by assessing family history) (Wilson & Levin, 2001; Wilens et al., 2005).

Research by Wilens and colleagues (2005) shows that the combination of ADHD and SUD entails a much greater risk of depression and anxiety disorders. It is therefore recommended to screen for mood and anxiety disorders in adults with SUD.

Current substance use
As mentioned earlier, given the complexity of diagnosing ADHD in adults with SUD, one cannot rely merely on a diagnostic scale. Specific attention should also be paid to the effects (intoxication and withdrawal) of the substances used by the patient. These effects (restlessness, irritability, difficulty in concentrating, excitability, etc.) often camouflage the typical symptoms of ADHD. This makes it imperative for the clinician to include a comprehensive assessment of the current substance use in the diagnostic process (Faraone et al., 2007).

The best way to establish a history of the substance abuse is by personal interview. This interview should be strictly confidential and carried out with an empathetic, non-judgmental attitude. In the course of this interview the current drug use (frequency of use, social context of use, etc.) including alcohol and tobacco, should be assessed. The extent of the disruption in different life domains (social, schooling, work) as a result of the drug use should also be assessed. Because substance use problems are often associated with other risky behaviour, an inquiry into such behaviours (e.g., reckless driving) can be a useful addition to the diagnostic process (Bukstein, 2008). The personal interview may be supplemented by a toxicological confirmation (Upadhyaya, 2007).

It is important to look at the relation between ADHD symptoms and current drug use, detoxification or withdrawal symptoms. For example, cocaine-dependent patients may display symptoms of ADHD after a period of regular use, but they do not recollect having had these during childhood. It is appropriate to establish a timetable of use (Wilson & Levin, 2001). The expert group indicates that such a timetable may also increase the motivation of the patient to proceed in the diagnostic process.

Two generally accepted screening instruments for drugs and alcohol can be used: the **DAST** (Drug Abuse Screening Test) and **AUDIT** (Alcohol Use Disorders Identification Test). Both were investigated for their construct validity and reliability in a population of adults with ADHD symptoms (n = 139), and results indicate that both the DAST and the AUDIT are acceptable screening instruments, respectively, for drug and alcohol abuse in adults with ADHD (McCann et al., 2000).

(Neuro) psychological research
In adults with ADHD many dysfunctions are linked to the frontal subcortical circuit: inhibition of behaviour, auditory verbal learning, planning and organizing, controlling movement, verbal fluency, information processing, etc. (Kooij, 2002). Although these dysfunctions are present in all areas of functioning, a meta-analysis has shown that no single specific neuropsychological deficit can be demonstrated in ADHD (Hervey, Epstein & Curry, 2004). Nevertheless, neuropsychological testing can be used for the more in-depth ADHD diagnosis and to obtain a better perception of the

patient's functioning in terms of attention, memory, flexibility of thinking, planning and organizing, etc. In addition, it makes it possible to investigate secondary aspects of ADHD, such as motivation and social and emotional functioning. The cognitive functioning of the client can be assessed and behavioural observation can be carried out in situations requiring lengthy concentration. In this way, information can be collected about the size of the effects of the disorder and the extent to which they may affect functioning. This provides an indication of other possible problems and provides a basis for personalized therapy with regard to cognitive functioning (Van de Glind et al., 2004). Summarized, (neuro)psychological research is important for a multidisciplinary approach to assess the presence of ADHD, to assess whether comorbid problems are present and to address cognitive problems. In the context of this guideline, we did not include instruments here. The use of such instruments is based on assessment according to the clinical experience of the diagnostician.

In a direct comparison of several neuropsychological functions including flexibility, time reproduction, and working memory, patients with ADHD and SUD do not perform worse than patients with ADHD but without SUD (Crunelle et al., 2013). Another study in cocaine-dependent patients indicates that having ADHD negatively influences neurocognitive functioning, including sustained memory, working memory, declarative memory and executive functions (Vonmoos et al., 2013). Regarding impulsivity (both motor and cognitive impulsivity), patients with ADHD and SUD are a more impulsive population than ADHD patients without SUD (Crunelle et al., 2013). Based on impulsivity measures, patients exhibit a different response to stimulant medication: a small study in 24 adults with ADHD showed that methylphenidate's occupancy to the brain dopaminergic receptors is related to a decrease in cognitive impulsivity measures, but not with an improvement of motor impulsivity (Crunelle et al., 2014).

In a comparative study in SUD patients (N=120), ADHD patients (N=107) and patients with both ADHD and SUD (N=60), lower intellectual capacities and reduced scores on executive functioning tests have been described in patients with ADHD and SUD, which can complicate treatment (Bihlar Muld et al., 2013).

Until now, no neurocognitive test is sensitive and specific enough to be used as a standard diagnostic tool. Substantial heterogeneity is present in neuropsychological research in ADHD (Sonuga-Barke et al., 2010), and deficits in cognitive control, timing and reward sensitivity have been described. In 80% of patients, these deficits are present in only one of these three functions (Zeeuws et al., 2012).

Which specific aspects should be taken into account when performing additional research regarding the diagnosis of ADHD in adults with SUD?

Conclusions

Level of evidence 3	Comorbidity is a challenge in the diagnosis of ADHD: a large number of ADHD symptoms are present in other disorders, but there is also an overlap in the diagnostic criteria for related disorders. Symptoms of comorbid disorders are often wrongly attributed to ADHD (Kim et al., 2002; Kalbag & Levin, 2005).
Level of evidence 3	Various comorbid disorders can influence symptoms associated with ADHD (Wilson & Levin, 2001; Matthys et al., 2013).
Level of evidence 2+	The combination of ADHD and SUD entails an increased risk of depression and anxiety disorders (Wilens et al., 2005).
Level of evidence 2+	The effects of (or withdrawal from) certain substances may camouflage ADHD symptoms (Faraone et al., 2007).

Recommendations:

Level of recommendation C	The diagnostic process should include a comprehensive assessment of the current and past substance use (frequency of use, social context, etc.).
Level of recommendation D	Assess any psychiatric comorbidity extensively and formulate both an individual and a family history.
Level of recommendation C	Mood and anxiety disorders often co-occur with both ADHD and with SUD. As a result, screening for mood and anxiety disorders is important for a proper diagnosis.
Level of recommendation D	(Neuro) psychological tests can be useful for the determination of individual deficits, and are a good supplement to the actual diagnostic process.

6. Treatment of ADHD in adults with SUD

There is a general consensus that proper treatment of ADHD in people with substance use disorder (SUD) comprises several components. In addition to psycho-education and medication, individual and/or group therapy as well as peer support should be offered (Goossensen 2006).

In children with ADHD and conduct disorder who are at risk of developing SUD later in life, combined therapy (medication and intensive behavioural therapy) had a better effect than pharmacotherapy alone (Jensen, 2001). Also in adults with ADHD and SUD, research indicates the use of combined pharmaco- and psychotherapy (Wilens, 2004; Aviram et al., 2011; Schubiner 2005; Zulauf et al., 2014).

The treatment of ADHD should be integrated into the treatment of SUD. This is important because the ADHD symptoms (such as impulsivity and impaired planning and organization) can interfere with the SUD treatment and/or the SUD can complicate the treatment of ADHD (Mariani, 2007). It is advisable to start SUD treatment immediately, followed by ADHD treatment shortly after (Wilens & Morrison 2011). When the SUD is too severe, residential treatment may be appropriate (Wilens, 2004).

Adults with ADHD usually have two desires in addition to the wish to reduce their ADHD symptoms: they want to develop coping mechanisms to deal with their symptoms and they wish to handle the persistent emotional and functional problems associated with ADHD (Ramsay, 2005). If there is also a SUD, there are two additional goals: keeping the patients in treatment and a change for the better in the substance abuse (Wilens, 2004).

Most adults with ADHD have a negative self-image and low self-esteem. Providing perspective and a long-term vision are essential bases for treatment. If the diagnosis of ADHD is made during adulthood, an emotional adjustment phase often occurs, in which relief and recognition are followed by anger and sorrow at how different life could have turned out if the diagnosis had been made earlier (Murphy, 2005). This adjustment and any secondary psychiatric problems should also be involved in the treatment (Murphy, 2005).

It is recommended to involve the family in treatment: when they are well informed, they can deal more effectively with the patient and, where appropriate, monitor the use of medication to prevent abuse (Wilens, 2004).

De combination of ADHD pharmacotherapy with other pharmacotherapy (e.g., for the treatment of SUD) is not a problem.

What includes proper treatment of ADHD in adults with SUD?

Conclusions

Level of evidence 3	The treatment of patients with ADHD and SUD is possible when substance use is stabilized (Expert opinion).
Level of evidence 2	Combined pharmaco- and psychosocial therapy is more effective than pharmacotherapy alone (Wilens, 1999; Safren, 2005; Rostain & Ramsay, 2006).
Level of evidence 3	If the ADHD remains untreated, it may hamper with the treatment of SUD (Mariani, 2007).
Level of evidence 3	Accepting the diagnosis is an essential part of treatment in ADHD patients with SUD (Murphy 2005).
Level of evidence 3	Treatment affectivity will be increased if the family is involved in the treatment (Wilens 2004).

Recommendations

Level of recommendation D	The treatment of ADHD can be initiated when the SUD is stabilized.
Level of recommendation D	Pharmacotherapy should be combined with psychotherapy.
Level of recommendation C	It is advisable to integrate the SUD and other psychiatric comorbidity treatment within ADHD treatment.
Level of recommendation D	Organize peer support.
Level of recommendation D	Involve the family in the treatment

6.1. The effect of medication on ADHD symptoms

Several studies provide evidence for a minor to moderate effect of medication on reducing ADHD symptoms in patients with both ADHD and SUD (Cunill et al., 2015; Pérez de los Cobos et al., 2014; Wilens & Morrison 2012). While these studies are usually performed over a limited time and with small sample sizes, several double blind and placebo-controlled trials are available:

- Schubiner (2002): a placebo-controlled trial with short-acting methylphenidate. Significant effect on ADHD symptoms. No effect on cocaine use.
- Riggs et al. (2004): placebo-controlled trial with Pemoline in adolescents (12 - 19 years old). Significant effect on ADHD symptoms (not on drug use).
- Carpentier (2005): placebo-controlled trial with low dose (up to 45 mg/day) short-acting methylphenidate in adults with ADHD en SUD (mainly alcohol and cocaine). No significant difference with the placebo group that also showed good outcomes. Carpentier mentions an important placebo effect. Methylphenidate doses were low.
- Collins (2006): placebo-controlled but unblinded study using long-acting methylphenidate in cocaine users. At high doses, there is evidence that the reinforcing effects of cocaine decrease.
- Levin (2006): placebo-controlled trial using long-acting methylphenidate and long-acting bupropion in adults with ADHD in methadone substitution treatment. Significant reduction in ADHD symptomatology in all groups. However, no significant differences between groups.
- Levin (2007): placebo-controlled trial using long-acting methylphenidate in adults with ADHD and cocaine dependence. No significant difference with placebo. However, reduction in cocaine use in the subjects in the methylphenidate group who have a good response to the medication.
- Szobot (2008): placebo-controlled trial of long-acting methylphenidate in adolescents with ADHD and SUD (cannabis and partly cocaine). Significant reduction in ADHD symptoms, but not in drug use.
- Wilens (2005): meta-analysis showing little effect of pharmacotherapy on ADHD symptoms in patients with SUD.
- Wilens (2008): placebo-controlled trial of atomoxetine in adults with ADHD and alcohol dependence. Significant effect on ADHD symptoms, inconsistent effect on drinking.
- Konstenius (2010): placebo-controlled trial of long-acting methylphenidate (72 mg) in 24 adults with ADHD and SUD. No significant differences in ADHD or SUD symptoms.
- Thurstone (2010): placebo-controlled trial using atomoxetine in 70 adults with ADHD and SUD during 12 weeks. No significant differences in ADHD or SUD symptoms.
- Winhusen (2010): placebo-controlled trial using long-acting methylphenidate (72 mg) in 255 nicotine-dependent ADHD patients. Improvement of ADHD symptoms, no effect on smoking cessation.
- Riggs (2011): placebo-controlled trial using long-acting methylphenidate for 16 weeks in 303 adults with ADHD and SUD. No effect on ADHD symptoms, no effect on SUD symptoms.

- Konstenius (2014): placebo-controlled trial using long-acting methylphenidate (72 mg for 24 weeks) in 54 adults with ADHD and amphetamine dependence. Reduction in ADHD symptoms, more drug-negative urines, and a better retention in treatment.

While not placebo controlled, an open trial in 19 ADHD patients with SUD provides evidence for the effectiveness of bupropion to reduce ADHD symptoms (but not for SUD symptoms) (Wilens et al., 2010). In several studies, ADHD symptoms improved in all groups, indicating an important placebo effect. Other psychopharmaca such as antidepressiva pharmacotherapies also have a more important placebo effect in adults compared to children (Michelson, 2003).

Research that investigates the underlying working mechanism of ADHD and SUD, questions the use of higher doses of methylphenidate in adults with ADHD and SUD, and whether to use other pharmacotherapies not primarily acting on the dopaminergic system, such as atomoxetine (Crunelle et al., 2013). A study using much higher doses of methylphenidate (up to 180 mg/day) in adults with ADHD and SUD however indicate an improvement in ADHD symptoms and a lower risk of relapse (Konstenius et al., 2014).

6.2. The effect of medication on the use of alcohol and other drug

Because ADHD is considered a complicating factor in the treatment of SUD, the reduction of ADHD symptoms could make the SUD more manageable.

Research on the effects of ADHD pharmacotherapy in patients with SUD, however, show that pharmacotherapy has only limited effect on reducing the drug- and alcohol use of the patient (Cunill et al., 2015; Pérez de los Cobos et al., 2014), with the exception of smoking cessation (Schoenfelder et al., 2014). A placebo-controlled trial in smokers with ADHD thereby mentions a different response to methylphenidate dependent on the clinical ADHD presentation (inattentive versus combined presentation) of the patient and the severity of the nicotine dependence (Covey et al., 2011). The first studies (Levin, 1997; 2002; 2003), often open label studies in small sample sizes without a control group, were enthusiast regarding the relation between the treatment of ADHD and the improvement in SUD. Unfortunately, this enthusiasm was reduced with later studies (Shubiner, 2002; Levin, 2006 & 2007; Wilens, 2008; Szobot, 2008). A few recent studies, however, present hopeful results:

- Wilens (2011): A post-hoc analysis of a placebo-controlled trial with atomoxetine in adults with ADHD and SUD (N=147) indicates that a reduction in ADHD symptoms is associated with a decrease in alcohol craving.
- Tamm (2013): A placebo-controlled trial in 299 adolescents with ADHD and SUD evidences that long-acting methylphenidate is associated with an improvement in SUD outcome in adolescents with comorbid behavioural disorders.
- Konstenius (2014): More drug-negative urine screens were measured in 54 adults with ADHD and amphetamine dependence after being treated with long-acting methylphenidate (72 mg for 24 weeks) compared to placebo.
- Bihlar Muld (2015): ADHD patients with SUD who were treated with pharmacotherapy (N=30) showed fewer relapses after 18 months, had more housing, and had a higher employment rate than ADHD patients with SUD who did not receive pharmacotherapy (N=30).

Other studies indicate, as mentioned earlier, rather negative findings (i.e., no effect on SUD) (Riggs et al., 2011; Thurstone et al., 2010; Wilens et al., 2010; Winhusen et al., 2010).

Several studies have shown that he administration of stimulants for the treatment of ADHD does not increase the risk for the development of SUD later in life (Faraone, 2003; Kollins, 2003; Wilson 2007). Children with ADHD are more likely to develop a SUD. Treating them for ADHD with stimulants thereby reduce the chances of developing SUD later in life by half (Wilens, 2003). A

prospective study that followed children with ADHD for up to ten years specified that treatment of ADHD with stimulants in adulthood does not increase or decrease the risk of SUD (Biederman et al., 2008). A recent meta-analysis on the subject states that the treatment of ADHD does not influence the later development of SUD, but it is neither a protective factor for the later development of SUD (Humphreys et al, 2013; Molina et al 2013; Zulauf et al, 2014).

6.3. Discussion of the different pharmacotherapeutical agents

Methylphenidate (Rilatine ®): up to 1.3 mg/kg/day. Only the studies using relatively high doses (up to 180 mg/day) show effectivity (Konstenius et al., 2014). It works fast, but has a high abuse potential and can cause side effects: mild dysphoria, nervousness, headache, hypertension, irritability, tremor and, exceptionally, loss of appetite. A rebound effect may also occur in the form of lethargy and irritability when it is suddenly stopped (Dodson, 2005). In the focus groups for physicians, caregivers and other professionals as well as patients, it was mentioned that patients (and their families) sometimes additionally experience some form of numbing and reduced emotional expression.

Dextro-amphetamine (up to 0,5 mg/kg/day). Has the same effectiveness as methylphenidate and may be an alternative. Research in 82 patients with cocaine dependence mentions that long-acting methamphetamine (compared to placebo) increases the amount of negative drug urine screens and reduces cocaine craving (Grabowski, 2004; Mooney, 2009).

Long-acting methylphenidate (Rilatine MR ® and Concerta ®): these agents release methylphenidate over a sustained period in time (8 to 12 h). They begin to work as quickly as the short-acting form and can cause the same side effects. They have a lower abuse potential because the molecule is released slowly (Bright, 2008). Ritalin MR ® can be pulverized and injected unlike Concerta ®. Both products have sale potential. RIZIV, the Belgian National Health and Disability Institute, does not intervene for the reimbursement of either Rilatine MR ® nor Concerta ®.

Atomoxetine (Strattera ®) is a noradrenaline uptake inhibitor. Has a proven effect in children and adults. Has no stimulant effects and no abuse potential. Side effects include: dry mouth, sleeping problems, hypertension, nausea, reduced appetite, reduced libido, erectile dysfunction and dizziness. There is no reimbursement by RIZIV.

Bupropion (Wellbutrin ® and Zyban ®) are antidepressants. Wellbutrin ® is patented as antidepressant, while Zyban ® is indicated for reducing withdrawal symptoms in smoking cessation. Bupropion is proven effective to reduce symptoms of ADHD. Side effects include headache, dry mouth, sleeping problems, nausea, chest pain, dizziness and irritability. Seizures are possible, especially in situations where the seizure threshold is lowered, e.g., during alcohol and benzodiazepine withdrawal (BCFI, 2010). No abuse potential is known.

Tricyclic antidepressants such as imipramine (Tofranil ®): (100 - 200 mg/day). Reduces ADHD symptoms in adults, but has not been investigated in patients with SUD. Side effects include sleeping problems, orthostatic hypotension, constipation, urine retention, cardiac arrhythmia and toxicity at overdoses (Dodson, 2005).

Modafinil (Provigil ®): a central stimulant used to treat narcolepsy. Research is available on the effect of modafinil in cocaine dependence (Anderson, 2009; Mann, 2009). Side effects include headache and nausea. Modafinil has an abuse potential due to its stimulant effect (Turner, 2004).

The available pharmacotherapeutical agents are listed below, and graded as positive or negative depending on several criteria that impact patients with SUD. The degree of evidence of the impact should be balanced against the risk of abuse. On the other hand, treatment retention in these patients is important, given the chronicity of their dual problems and the long duration of their

treatment. Finally, individuals with SUD often have important financial problems, which should also be taken into account.

	Proven effectivity in ADHD and SUD	Effect on SUD	Retention	Risk for abuse	Price
Short-acting methylphenidate	++	+/-	++	--	+
Long-acting methylphenidate	++	+/-	++	-	-
Atomoxetine	++	?	+	+	-
Bupropion	+	?	?	+	+
Modafinil	+	?	?	-	-
Imipramine	?	?	?	+	+

Which medication is effective in the treatment of ADHD in adults with SUD and what is the effect of this medication on the use of alcohol and other drugs?

Conclusions

Level of evidence 3	Long-acting methylphenidate seems effective for the treatment of ADHD in adults with SUD (Collins, 2006; Levin, 2006 & 2007; Szobot, 2008).
Level of evidence 3	Long-acting bupropion seems effective for the treatment of ADHD in adults with SUD (Levin, 2006).
Level of evidence 3	There are indications that short-acting methylphenidate has an effect on ADHD in adults with SUD (Schubiner, 2002).
Level of evidence 2	There are indications that atomoxetine has an effect on ADHD in adults with SUD (Wilens, 2008).
Level of evidence 1	The effect of all the products is smaller in adults than in children (Faraone, 2003; Mészàros, 2009).
Level of evidence 1	There is a strong placebo effect (Michelson, 2003).
Level of evidence 1	Treatment of ADHD with stimulants does not increase the risk of developing SUD (Faraone, 2003; Kollins, 2003; Wilson, 2007).
Level of evidence 2	There are indications that the treatment of ADHD does not reduce the risk of SUD (Biederman, 2008).
Level of evidence 2	There are indications that stimulants in the dosages needed to treat ADHD do not decrease the substance abuse (Schubiner, 2002; Carpentier, 2005; Levin, 2006; Szobot, 2008).

Recommendations

Level of recommendation C	Atomoxetine is preferred due to its low abuse potential.
Level of recommendation C	Long-acting methylphenidate may also be used, provided that it is dose delivered and/or under adequate supervision.
Level of recommendation C	Bupropion or imipramine are possible choices for the treatment of ADHD.
Level of recommendation C	Because of its abuse potential short-acting methylphenidate can only have a place in the start-up phase in a residential treatment setting in order to assess its effectiveness.

6.4. Treatment retention

It is not clear whether individuals with ADHD and SUD perform less well in treatment programs. While results are inconclusive, the severity of the SUD seems to be a key factor (Levin, 2006). In cocaine users with ADHD it appears that the cocaine dependence and not the presence of ADHD is a predictive factor for drop-out (Levin, 2008).

In a study of cocaine users with ADHD, the group who also used cannabis moderately remained stay in addiction treatment longer than those who did not use cannabis or those who used a large amount of it (Aharonovich, 2006). A recent meta-analysis provides evidence that ADHD pharmacotherapy in adults with SUD has no effect on treatment retention (Cunill et al., 2015), but that adult ADHD patients with SUD who were treated with methylphenidate had better retention in treatment than ADHD patients who did not receive methylphenidate treatment (i.e., who received a placebo) (Konstenius et al., 2014).

From the focus groups for physicians, other professionals and patients, it appeared that patients often regard treating ADHD as a sign of recognition of their problems. This can increase treatment retention. However, medication that takes effect only after a few weeks is often a reason for substance using and impatient patients to drop out.

How can we improve retention in adults with ADHD and SUD?

Conclusions

Level of evidence 3	Not the presence of ADHD but the severity of the SUD is a predictive factor for retention in SUD treatment (Levin, 2006; Levin, 2008).
Level of evidence 3	It seems that moderate cannabis use increases treatment retention in cocaine users with ADHD (Aharonovich, 2006)

Recommendations

Level of recommendation D	Recognizing and treating ADHD strengthens the therapeutic relationship (Expert opinion) and can reduce drop out.

6.5. The risks of ADHD medication in individuals with SUD

Especially with SUD, there has been much concern regarding prescribing stimulant pharmacotherapy to patients with SUD. Although methylphenidate - because of its pharmacological properties (slower absorption) and in therapeutic doses - would have less potential for abuse then cocaine (Kollins, 2003; Volkow, 2003) it remains a product that in higher doses has a stimulating effect and for that reason can be used by the patients themselves or people close to them. There is no effect of methylphenidate (60 mg) on the reinforcing effects of cocaine, and the treatment is considered safe in active cocaine users (Winhusen et al., 2006).

Hoarding medication to get high using higher doses and selling or giving away the medication to friends or relatives is fairly common. In studies, 16.5% give a positive answer to the question whether they share medication with others (Bright, 2008). Fast-acting agents are more risky than long-acting stimulants. Modafinil also demonstrates an abuse potential (Turner, 2004). Atomoxetine has no abuse potential (Wilens, 2008; Jasinski, 2008).

A case-report describes a psychosis in a patient with cocaine-induced psychosis following methylphenidate treatment (Delavenne et al., 2013). This seems to be a single observation, as other studies and literature overviews unanimously mention no additional risk with prescribing pharmacotherapeutic agents in this patient population (Pérez de los Cobos et al., 2014; Wilens & Morrison 2012). Also abuse and sharing of pharmacological agents is contradicted, even with more severe SUDs (Wilens & Morrison 2012; Winhusen et al., 2011). Summarized, pharmacotherapy should not be avoided in patients with ADHD and SUD, with a preference for long-acting agents (Schubiner 2005), and treatment of ADHD is useful to reduce ADHD symptoms without worsening the SUD (Klassen et al., 2012).

6.6. Non-pharmacological interventions for the treatment of ADHD in adults with SUD

Given the risks of medication and because both SUD and ADHD are chronic conditions, it is appropriate to examine which treatment, counselling, education, information and psychotherapy are (or can be) effective in this group. Research is not easy for several reasons:

- Blinded studies are not possible (Wampold, 2005);
- Therapy consists of many different elements, which cannot be kept constant: so we do not know what exact effect is being measured (Luborsky, 1975);
- The personality of the therapist often appears to be more important than the methodology and experience does not appear to be the decisive factor (Leysen, 2006).

Several non-pharmacological interventions have been investigated for their effects on ADHD in adults. These treatment methods are usually well accepted and have been studied in addiction care (Rigter, 2004, 2006; APA Guidelines, 2006).

Psycho-education is not considered curative, but an aid to cope with the symptoms and to deal with the problems that arise from ADHD in the course of life. It may also be appropriate to provide information and psycho-education to parents and/or partner (Murphy, 2005). An important first step for the patient and his/her family is the acceptance of the ADHD diagnosis.
Psycho-education also plays an important role in the treatment of SUD.

Cognitive behavioural therapy: There is preliminary evidence that cognitive behavioural therapy (CBT) is effective in adults with ADHD for both reducing the core symptoms as well as the associated problems (Virta, 2008). A first randomized controlled trial is available describing an integrated CBT for both SUD and ADHD. The two first case-reports show promising results (van Emmerik-van Oortmerssen K et al., 2015).
CBT is effective in both SUD as in ADHD *treatment.*

Structured skills training: There are indications that intensive training of the attention function is effective, but there is no difference between those with and those without ADHD (White & Shah, 2006). There is preliminary evidence that targeted training in time management, organization and planning has a positive effect on these skills (Solanto, 2008; Stevenson, 2002 & 2003).
This method is also applied in the context of relapse prevention in SUD treatment.

Dialectical behaviour therapy: Group dialectical behaviour therapy improves depression scales as well as ADHD symptomatology. However, these results come from a small study, where the control group consisted of people on the waiting list. In the control group, four of seven participants were lost to follow up; in the treatment group no one was lost to follow up (Hesslinger, 2002).
In a larger trial including 72 patients, a wide range of interventions was integrated (psycho-education, information, mindfulness, organizational training, behaviour analysis, emotional skills training, impulse control, stress management, respect/self-respect, dealing with drugs), and the effects were measures as self-report (Philipsen, 2007).
This method is also applied for SUD treatment.

Mindfulness: Mindfulness group training reduces attention deficits and impulsivity (Zylowska, 2008).
This method is also applied in SUD treatment.

Individual coaching with short-term objectives seems to have a positive effect on ADHD symptoms. The contact can also be carried out by phone or email, ranging from once a week for one hour, to ten minutes daily (Murphy, 2005). The combination of cognitive remediation and individual coaching may increase effectiveness (Stevenson, 2002, 2003). In a qualitative study, patients with ADHD and SUD also mention their wish for a coaching attitude (Kronenberg et al., 2015).

Neurofeedback in children with ADHD is effective on reduction of the core symptoms of ADHD (Gevensleben, 2009). However, no controlled trials are available in adults, and no trials are available whatsoever in adults with ADHD and SUD.

Peer support: Group therapy with peers is often illuminating and stimulating. The group should not be too large, and should be well guided in a semi-structured way (Murphy, 2005).

Which non-pharmaceutical interventions are effective for the treatment of ADHD in adults with SUD?

Conclusions:

There is little evidence for the effectiveness of a psychotherapeutical approach in the treatment of ADHD in adults. There are indications, in the literature as well as by experts, that adapted psychological interventions can play an important role in their treatment. No evidence exists on the effect of all these interventions in patients with SUD and ADHD. Expert opinions on the matter are available (Goossensen, 2006; Knouse, 2008).

Because of the chronicity of the disorder and the repercussion on all life domains of ADHD and SUD, treatment should employ as many instruments as feasible, and this should be adapted to the individual situation and problems of the patient.

According to the experts from the focus groups, many therapeutic interventions are appropriate for both SUD and ADHD. These include providing structure, time management and organisation skills, learning to cope with impulsivity and mood swings. In a residential setting, there is sufficient time and human resources available to offer such a program. In an outpatient setting, time is often too limited and contacts are too fragmented. Yet, also in an outpatient setting it would be beneficial to use a combination of individual therapy (from coaching to training to CBT) with group training and peer support.

Recommendations:

Level of recommendation D	Given the disorder's complexity, a multimodal approach should be preferred.
Level of recommendation D	A first phase includes psycho-education. Providing information regarding the disorder, its causes, possible treatment options and prognosis is an important first step to increase the motivation and cooperation of the patient.
Level of recommendation D	In a second phase, individual coaching and peer support should be offered along with pharmacotherapy.
Level of recommendation B	In a third phase, CBT and skill training (individuals or in group) is advised.
Level of recommendation D	Mindfulness and dialectic behaviour therapy should be offered.
Level of recommendation D	System therapeutic interventions should be considered.
Level of recommendation D	Comorbid disorders necessitate treatment.

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