Drug Commissioner of the German Federal Government

German Federal Ministry of Health (BMG) • German Medical Association (BÄK) • German Association for Psychiatry, Psychotherapy and Psycho-somatics (DGPPN)

S3 Practice Guideline
Methamphetamine-related Disorders

1st Edition, 2016

Foreword

Why publish an S3 Practice Guideline on "Methamphetamine-related Disorders"?

All appearances might indicate that the increased methamphetamine abuse in Germany is regionally contained. Nonetheless, physicians and staff working in hospitals, private medical practices and addiction treatment centers are confronted with an increasing intensity of this problem. Compared to other stimulants, methamphetamine is a substance with characteristic properties relating to its action, symptoms and potential to create dependence. This is aggravated by the fact that the motives for its use vary greatly across a diverse range of population groups (see Chapter 1 Epidemiology). The special needs of patients with methamphetamine-related disorders pose challenges to conventional addiction services.

The methamphetamine currently manufactured illegally in Germany comes in the form of a potent crystalline drug (street name "crystal meth") and possesses a high concentration of the active substance. This crystalline form is also subsumed under the general term "meth-amphetamine" used in this practice guideline. Crystalline methamphetamine is most typically taken nasally, i.e. "snorted" into the nasal passage. Similarly common routes of administration are smoking and intravenous injection. These forms are particularly problematic given their potential for fast addiction, excessive substance use patterns and risks for users to contract contagious diseases. Frequently, users will additionally take sedative substances, also referred to as functional co-abuse. These particulars already reported overwhelmingly by other countries have also been confirmed for Germany [1].

Unless one is talking about exclusively experimental use, the comprehensively described severe long-term sequelae associated with methamphetamine, even when taken in moderation for non-medical purposes by the typical routes of administration, allow no other overriding conclusion from a therapeutic perspective than that its use is harmful and addictive. There have been certain cases where sporadic oral intake alone might not have a major medical impact [2; 3].

In expert talks between the German Federal Drug Commissioner, addiction prevention and drug policymakers, researchers and stakeholders from practice-based treatment facilities, it became clear that sophisticated evidence-based therapeutic options are needed. This need led the German Federal Ministry of Health (BMG) to initiate a project on the "Development of practice guidelines for the treatment of methamphetamine-dependent individuals". The Agency for Quality in Medicine (AQuMed) was commissioned by the German Medical Association (BÄK) to collaboratively conduct this project with a panel of experts and support them in terms of expertise and methodology. The panel was led by 21 participating experts who included medical practitioners from multiple inpatient and outpatient specialties, psychotherapists, caregivers and social workers.

Editors

The Drug Commissioner of the German Federal Government

www.dogenbeauftragte.de

Die Drogenbeauftragte
der Bundesregierung

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German Association for Psychiatry, Psychotherapy
and Psychosomatics (DGPPN)

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DGPPN
Deutsche Gesellschaft
für Psychiatrie und Psychotherapie,
Psychosomatik und Nervenheilkunde

Authors

Wolf-Dietrich Braunwarth, Michael Christ, Henrike Dirks, Janina Dyba, Roland Härtel-Petri, Timo Harfst, Heribert Fleischmann, Euphrosyne Gouzoulis-Mayfrank, Willem Hamdorf, Ursula Havemann-Reinecke, Peter Jeschke, Marco R. Kesting, Antje Kettner, Michael Klein, Benjamin Löhner, Winfried Looser, Sascha Milin, Josef Mischo, Bernd Mühlbauer, Stephan Mühlig, Jeanine Paulick, Niklas Rommel, Ingo Schäfer, Norbert Scherbaum, Katharina Schoett, Frank Schulte-Derne, Jan-Peter Siedentopf, Frank Vilsmeier, Norbert Wittmann, Norbert Wodarz, Anne Krampe-Scheidler.

Members of the consensus group

Participating experts	Specialty society or organization represented
• Wolf-Dietrich Braunwarth, M.D., Nuremberg Medical Center	Not representing any society or organization
• Roland Härtel-Petri, M.D., Psychotherapeutic Practice Bayreuth	Not representing any society or organization
• Heribert Fleischmann, M.D., Wöllershof District Hospital	German Centre for Addiction Issues (Deutsche Hauptstelle für Suchtfragen e. V., DHS)
• Professor Euphrosyne Gouzoulis-Mayfrank, M.D. Rhineland Regional Council, Clinic Cologne (Landschaftsverband Rheinland, LVR)	German Association for Psychiatry, Psychotherapy and Psychosomatics (Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkund, DGPPN)
• Willem Hamdorf, M.D., Mecklenburg Hospital of the General Hospital Group (Allgemeine Hospitalgesellschaft [AHG] Klinik Mecklenburg)	Professional Association for Addiction (Fachverband Sucht, FVS)
• Professor Ursula Havemann-Reinecke University Medical Center Göttingen (Universitätsklinik Göttingen)	German Society for Addiction Research and Treatment (Deutsche Gesellschaft für Suchtforschung und Suchttherapie e. V., DG Sucht)
• Peter Jeschke, Diplomate in Medicine, Neurological Group Practice, Halle	Not representing any society or organization
• Josef Mischo, M.D., St. Ingbert District Hospital (Kreiskrankenhaus St. Ingbert)	Working Group on Drugs and Addiction of the German Medical Association (Arbeitsgruppe "Sucht und Drogen" der Bundesärztekammer, BÄK)

Participating experts	Specialty society or organization represented
• Professor Bernd Mühlbauer, M.D. Institute for Clinical Pharmacology, Klinikum Bremen Mitte; Bremen Hospital Group	Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft, AkdÄ)
• Professor Stephan Mühlig, Ph.D. University of Technology of Chemnitz (Technische Universität Chemnitz) • Timo Harfst (deputy) German Psychotherapists' Association	German Psychotherapists' Association (Bundespsychotherapeutenkammer, BPtK)
• Ingo Schäfer, M.D., University Lecturer, University Medical Center Hamburg-Eppendorf (UKE)/Centre of Interdisciplinary Addiction Research (ZIS) of the University of Hamburg • Sascha Milin (deputy) Centre of Interdisciplinary Addiction Research (ZIS) of the University of Hamburg	Centre of Interdisciplinary Addiction Research (ZIS) of the University of Hamburg (Zentrum für Interdisziplinäre Suchtforschung der Universität Hamburg, ZIS)
• Professor Norbert Scherbaum, M.D., LVR Hospital Essen	Working Group on Drugs and Addiction of the German Medical Association (Arbeitsgruppe "Sucht und Drogen" der Bundesärztekammer, BÄK)
• Katharina Schoett, M.D., Ecumenical Hospital Hainich	German Society for Addiction Medicine (Deutsche Gesellschaft für Soziale Arbeit in der Suchthilfe, DG SAS)
• Frank Schulte-Derne Regional Council Westfalen-Lippe (LWL)	German Society for Social Work in Addiction Care (Deutsche Gesellschaft für Soziale Arbeit in der Suchthilfe, DG SAS)
• Frank Vilsmeier Rickling Psychiatric Hospital • Winfried Looser (deputy) LVR-Clinic Düren	German Nursing Council (Deutscher Pflegerat)
• Norbert Wittmann, Mudra Drug Counseling Center • Benjamin Löhner (deputy) Mudra Drug Counseling Center	Mudra – Alternative Youth and Drug Aid (Mudra – Alternative Jugend- und Drogenhilfe e. V.)
• Professor Norbert Wodarz, M.D. Department of Psychiatry and Psychotherapy, University Hospital of Regensburg	Bavarian Academy for Questions of Addiction and Health (Bayerische Akademie für Sucht- und Gesundheitsfragen, BAS)

Contributions by external experts to specific chapters of this practice guideline

Moreover, other experts contributed their professional support to the practice guideline group in drawing up certain chapters without being members of the consensus group itself:

Experts	Chapter
• Professor Michael Christ, M.D. Department of Emergency Medicine and Internal Intensive Care Medicine, Nuremberg Medical Center	Acute therapy: Emergency setting
• Niklas Rommel, M.D., D.D.S. • Professor Marco R. Kesting, M.D., D.D.S. Clinic and Polyclinic for Oral-Maxillofacial and Plastic Surgery, Medical Center "Rechts der Isar", Technical University of Munich	Co-occurring disorders: Oral hygiene and dental problems
• Jeanine Paulick Department of Psychology, Chemnitz University of Technology	Pregnant women, young mothers and prenatal harm Psychotherapeutic interventions
• Jan-Peter Siedentopf, M.D., Outpatient Clinic for Addiction and Infections in Pregnancy, Department of Perinatal Medicine - Campus Virchow-Medical Center, University Hospital Charité – Universitätsmedizin Berlin	Pregnant women, young mothers and prenatal harm
• Jürgen Dinger, M.D., University Lecturer, Neonatology and Pediatric Intensive Care Medicine, Clinic and Polyclinic for Pediatrics and Adolescent Medicine, University Hospital Dresden	Pregnant women, young mothers and prenatal harm
• Professor Michael Klein, D.Sc. • Janina Dyba, Psychologist, German Institute on Addiction and Prevention Research, Catholic University of Applied Sciences, Cologne	Methamphetamine abuse in the family context
• Henrike Dirks, D.H.Sc. Department of Addictive Behavior and Addiction Medicine, LVR-Clinic Essen	Methamphetamine abuse among men who have sex with men (MSM)
• Antje Kettner Drug Scouts, Leipzig, Germany	Harm reduction

METHODOLOGICAL ASSISTANCE

Anne Krampe-Scheidler, Corinna Schaefer, Lydia Bothe, M.D. The Agency for Quality in Medicine (AQuMed)

ADDITIONAL DOCUMENTS

Practice Guideline Report, accessible at: www.crystal-meth.aezq.de

COORDINATION

The Agency for Quality in Medicine (a non-profit organization owned by the German Medical Association and National Association of Statutory Health Insurance Physicians)

Commissioned by the Federal Ministry of Health (BMG) and the German Medical Association (BÄK)

EDITORIAL OFFICES

Anne Krampe-Scheidler

CORRESPONDENCE

AQuMed – Editorial Offices
TiergartenTower, Strasse des 17. Juni 106-108, 10623 Berlin, Germany
Phone: +49 (0)30-4005-2504 - Fax: +49 (0)30-4005-2555
Email: mail@azq.de
Internet: www.crystal-meth.aezq.de

– Please submit comments and change proposals to this address only –

VERSIONS OF THIS PRACTICE GUIDELINE

The S3 Practice Guideline "Methamphetamine-related Disorders" is published with the following components:

1. Long version: Graded recommendations and presentation of the evidence basis

2. Summary

3. Practice guideline report

All versions are accessible at www.crystal-meth.aezq.de

Whenever persons and professional designations are referred in this document – even though they are only used in one gender-specific form – it should be understood as referring to both genders equally.

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List of Abbreviations

AAP	Atypical antipsychotic drugs
ACSA	Anamnestic Comparative Self-Assessment
ACT	Acceptance and Commitment Therapy
APGAR	The Apgar score is a numerical expression used for the standardized clinical assessment of a newborn; the sum of points gained by assessing heart rate, respiratory effort, muscle tone, reflex irritability and color.
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
ATS	Amphetamine-type stimulants
AWQ	Amphetamine Withdrawal Questionnaire
BAI	Beck Anxiety Inventory; self-report scale used to measure the severity of anxiety
BDI	Beck Depression Inventory; self-reported rating that measures characteristic attitudes and symptoms of clinical depression
BMG	German Federal Ministry of Health
BTMG	German Narcotics Act
BtMVV	German regulation governing the prescribing of narcotics
BZgA	Federal Center for Health Education
CBT	Cognitive behavioral therapy
CES-D	Center for Epidemiological Studies Depression Scale; used to rate how often symptoms associated with depression were experienced
CIDI	Composite International Diagnostic Interview; used to assess mental disorders
CM	Contingency management
CTG	Cardiotocography; technical method of recording fetal heartbeats
DBT-S	Dialectical behavior therapy for substance use disorders
DDP	Dynamic Deconstructive Psychotherapy
DFST	Dual Focus Schema Therapy
DIP	Diagnostic Interview for Psychosis
DSM IV	Diagnostic and Statistical Manual of Mental Disorders; classification system used in psychiatry, published by the American Psychiatric Association (APA), 4th Edition
ECT	Electroconvulsive therapy
EMDR	Eye Movement Desensitization and Reprocessing
EPMS	Extrapyramidal motor symptoms
ESA	Epidemiological Survey on Substance Abuse
Eu-	European Addiction Severity Index

ropASI	
GC	Gas chromatography
GCTB	Gay-specific cognitive behavioral therapy
GSST	Gay-specific social support therapy,
HAM-D	Hamilton Rating Scale for Depression; clinician-administered test to measure the severity of a depressive disorder
HIV	Human immunodeficiency virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	International Classification of Functioning, Disability and Health
IDCL	International Diagnostic Checklists
KJHG	German Child and Youth Welfare Act
MAP	Methamphetamine-associated psychosis
MBRP	Mindfulness-based relapse prevention
MDA	3,4-methylenedioxyamphetamine; hallucinogenic drug, that belongs chemically and structurally to the group of amphetamines
MDMA	3,4-methylenedioxy-*N*-methylamphetamine; synonym for Ecstasy
MET	Motivational Enhancement Therapy
MI	Motivational Interviewing
MS	Mass spectrometry
MSM	Men who have sex with men
NA	Narcotics Anonymous; self-help group of former drug addicts
NAS	Neonatal abstinence syndrome
NDRI	Noradrenaline and dopamine reuptake inhibitors
NNT	Number needed to treat; number of patients who need to be treated to achieve the desired outcome for one person, such as preventing a disease or death
NPS	New psychoactive substances
PANSS	Positive and Negative Syndrome Scale; used for measuring the severity of symptoms in schizophrenia
PTSD	Post-traumatic stress disorder
QoL	Quality of life
RCT	Randomized controlled trial
RPT	Relapse prevention training
SANS	Scale for the Assessment of Negative Symptoms in Schizophrenia
SAPS	Scale for the Assessment of Positive Symptoms in Schizophrenia
SCID	Structured Clinical Interview for DSM-IV → Axis I Disorders

SSRI	Selective serotonin reuptake inhibitors
STI	Sexually transmitted infections
TCA	Tricyclic antidepressants
THC	Tetrahydrocannabinol; belongs to the class of psychoactive cannabinoids; the principle intoxicant constituent of the hemp plant
VAS	Visual analog scale
YMRS	Young Mania Rating Scale

I Purpose and scope

Issues and objectives

Thus far, there have been no evidence-based medical treatment strategies for patients with methamphetamine-related disorders in Germany. The medical-therapeutic knowledge was mostly limited to empirical reports and isolated case studies. Given these deficiencies, study results and clinical experiences with the therapy of other substance-related disorders were frequently extrapolated to patients with methamphetamine-related disorders. The concept of substance-related disorders was introduced into the vernacular with the DSM-5. Primarily, a methamphetamine-related disorder includes methamphetamine-use disorders (as defined by ICD-10: harmful use, dependence) and, secondarily, the methamphetamine-induced disorders like intoxication, withdrawal or the thereby induced mental disorders (e.g. psychoses) [4].

Against that backdrop, this practice guideline was based on substance-specific studies and designed to enable better care for those affected and give a surer hand to caregivers when taking action in clinical practice. This shall be achieved by

- Making evidence-based statements on the efficacy of pharmacological and psychotherapeutic interventions
- Refraining from ineffective or risk-burdened therapies
- Better networking across the different stakeholders in the medical care of individuals suffering from addictions.

Since the focus was placed on medical-therapeutic interventions, the following key questions were defined as the basis for the systematic literature search:

- What are the merits of psychotherapeutic and psychosocial interventions in the management (weaning) of methamphetamine-dependent individuals?
- What pharmacological therapies have demonstrated efficacy in the management (weaning) of methamphetamine-dependent individuals?
- What therapeutic interventions are effective in the management of co-occurring disorders?

As part of a structured consensus process, the authors similarly addressed the following questions:

- What steps should an appropriate diagnosis comprise and where should it be conducted?
- What special features potentially need to be considered for specific patient groups?
- What harm reduction measures can be helpful?
- What strategic options can be offered that contribute to relapse prevention?
- What warning signs of harmful methamphetamine-use are noticeable in affected individuals who consult a physician or therapist for other reasons?

Given its limited project run time of only one year, this publication makes no claim to completeness.

This practice guideline was written from April 2015 to May 2016.

Methodology

A systematic literature search on therapeutic interventions for methamphetamine-related disorders was performed in the following databases: Cochrane database, Medline via Pub-Med, PSYINDEX via DIMDI, PsycINFO database on the OVID platform, and supplemented by a manual search. Therapeutic studies and systematic reviews on methamphetamine-dependent individuals and users published from the year 2000 and afterwards were included. Additionally, practice guidelines (G-I-N Guideline Library, AWMF database) were systematically searched. The CEBM criteria were used to define the levels of evidence [5]. For rating methodological quality, the German Guideline Assessing Instrument (Deutsches Leitlinien-Bewertungsinstrument, DELBI) was applied to guidelines and the AMSTAR tool to systematic reviews.

Nine out of 265 practice guidelines were deemed relevant. The search for therapeutic studies produced 3,080 hits. After screening title, abstract and full-text, 103 hits were included. Of these, 58 involved pharmacological therapies, 26 psychotherapies, 12 other therapies (e.g. exercise/sports, neurofeedback) and 4 pertained to harm reduction.

The overwhelming majority were RCT conducted in Anglo-Saxon and Asian countries. The RCT on pharmacological therapies, in particular, were replete with methodological deficiencies. Ultimately, the evidence reflected the difficulty inherent to enrolling and then keeping methamphetamine addicts in clinical trials. At several points, the general applicability of studies on psychotherapeutic interventions was put into question. Not all relevant clinical hypotheses could be answered satisfactorily based on the identified evidence. For that reason, the experts oftentimes relied on the growing body of clinical experience for their derivation of recommendations. **All recommended medications are for off-label use** (see Section 4.2.2 Pharmacotherapy, Info Box 2).

The recommendations were adopted using a structured consensus procedure (nominal group technique). Three consensus conferences were held on the following dates: October 29–30, 2015; January 27–28, 2016 and March 11, 2016. A recommendation was approved if the vote resulted in ≥ 75% agreement.

This guideline was drawn up with substantial consideration given to the concepts of the Guidelines International Network (G-I-N), the Council of Europe's recommendations for drawing up guidelines on best medical practices [6], the guideline assessment criteria of the BÄK and KBV [7], of the "Guideline Manual" of the AWMF and AQuMed [8], of the AWMF Guidance Manual and Rules for Guideline Development [9], the recommendations of the German guidelines clearing procedure [10; 11] and of the German guideline assessment instrument DELBI [12; 13].

A comprehensive presentation of the methodology for developing these practice guidelines can be found in the guideline report at: www.crystal-meth.aezq.de.

Scope and audience

This guideline is intended for:

- Physicians of all healthcare sectors working in addiction services
- Psychotherapists (whether physicians or psychologists)
- All groups of professionals working for outpatient and inpatient addiction services (e.g. psychologists, social workers, nursing staff)

- Caregivers in aftercare and rehabilitation settings
- Self-help organizations

Additional target groups include:

- Cooperation partners to the medical profession (e.g. other occupations involved in healthcare, payer organizations)

Binding nature

As with comparable medical practice guidelines, this guideline is explicitly not to be regarded as a regulation governing acts of commission or omission that a legally legitimated institution agreed to by consensus, set down in writing and published, is binding in the judicial area of this institution and the non-compliance therewith entails defined sanctions being imposed [6; 7]. The decision as to whether recommendations ought to be followed must be made by the physician who gives weight to the individual circumstances specific to the patient and the resources available. Economic aspects have not been accounted for in these recommendations.

II   Levels of evidence and grades of recommendations

The ranking scheme of the Oxford Centre for Evidence-Based Medicine 2011 (CEBM) was used for assessing methodological quality and grading the level of evidence (www.cebm.net) [5]. According to the CEBM hierarchy, a systematic review has a higher level of evidence than a randomized controlled trial (RCT). In turn, an RCT gets a better ranking than an observational study or a case report. In this sense, Level 5 does not refer to a level of evidence, but to an expert consensus (some practice guidelines also refer to this level as "good clinical practice" or call it a "clinical consensus point (CCP)". The present practice guideline relied on the following forms of expert consensus:

- After a systematic search, no studies on the clinical question were identified (=LoE 5).
- An extrapolation from systematically searched studies was used with respect to the clinical question or systematically searched guidelines were used as a reference (= LoE 5, based on [Source]).
- No systematic search was conducted on the clinical question (= LoE not stated).

Table 1 CEBM levels of evidence

Question	Level 1	Level 2	Level 3	Level 4	Level 5
Does this intervention help? (Treatment benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/ follow-up study	Case-series, case-control studies or historically controlled studies	Mechanism-based reasoning

Recommendations were graded according to the basic principles presented in Table 2. To better differentiate between negative and positive recommendations, the "positive" or "negative" arrows are placed in the column to symbolize their respective grades.

Table 2 Ranking of guideline recommendations by Grades of Recommendation [14]

Description	Wording	Symbol
Strong recommenda-	Should/should not	⇑⇑ (⇓⇓)
Recommendation	Ought to/ought not	⇑ (⇓)
Open	may	⇔

When establishing the grades of recommendation, the underlying evidence was considered in addition to aspects, such as ethical obligations, clinical relevance of the studies' effectiveness measures, benefit-harm ratio, applicability of the study results to the patient target group, patient preferences and feasibility in routine medical practice [6].

According to this methodology, the authors of this S3 practice guideline assigned grades of recommendation within a formal consensus process. In light of the aforementioned aspects, the grade of recommendation may be upgraded or downgraded from the evidence level when justified. Frequently, insufficient and/or contradictory evidence mandates that expert opinions be mutually formulated and agreed on in the formal consensus process.

III Formal consensus process

In drawing up these practice recommendations, nominal group techniques [15-17] were conducted in multiple sessions, moderated by the AQuMed. The named experts took part in these processes. The concrete details on the respective formal votes can be found in the guideline report hereto. The minutes of the meeting with the tallied votes can be requested at info@azq.de.

IV Conflict of interest handling

At the outset of the process of drawing up these practice recommendations, all authors disclosed any conflicts of interests in writing (see Guideline Report). Potential conflicts of interests were openly addressed in the guideline group's discussion. No exclusions were deemed necessary.

1 Epidemiology

Sascha Milin, Ingo Schäfer, Stephan Mühlig

1.1   Distribution data

There are no specific or robust epidemiological data on the use of methamphetamine in the total population. The studies that are available have subsumed methamphetamine and amphetamines along with other structurally related substances under indeterminate drug categories like "amphetamines". Based on a representative sample of approx. 9,000 adults aged between 18 and 64 years, the Epidemiological Addiction Survey (ESA) conducted in 2012 on the self-reported use of "uppers/amphetamines" found that the life-time prevalence was 3.1% and the 12-monthly prevalence 0.7%. In the 25- to 29-year-olds, higher prevalence rates (life-time: 6.8%, 12 months: 2.4%, 30 days: 1.5%) were reported for the named drug category. In all age groups under 50 years, men exhibited higher prevalence rates than women, with an approx. 2:1 gender ratio [18].

In Frankfurt am Main, Germany, data specific to "crystal meth" are gathered in a regularly conducted survey on schoolchildren according to which the life-time prevalence among the 15- to 18-year-old adolescents is 1%. Their current use over the past twelve months was stated as being less than 1% [19]. Given the paucity of findings from survey studies specific to methamphetamine (self-reports), there is a suggestion that the prevalence across the total population might hover around 1% nationwide. By contrast, other data sources (e.g. police records) indicate a higher prevalence. Among the illegal drugs confiscated nationwide in 2014, methamphetamine ranked third with 3,905 cases, behind amphetamines (9,853 cases) and cannabis products (36,720 cases) and just ahead of heroin (2,857 cases).

Among first-time offenders of hard drug use, methamphetamine (3,138 cases) took second place after amphetamine (11,356 cases) in the same year [20]. In 2014, the number of first-time methamphetamine offenders increased by around 14% over the previous year [21]. Presumably, data from survey studies underestimates the true prevalence of methamphetamine use in the population. Specific evidence on the proportion of methamphetamine users among the users who turn to addiction aid schemes is similarly heterogeneous and therefore difficult to subject to unequivocal interpretation in light of Germany's general conflation of methamphetamines into superordinate drug categories. In terms of the primary diagnoses rendered at inpatient addiction help centers, stimulants including methamphetamine (18.2%) take third place nationwide among the illegal drugs, behind cannabinoids (27.4%) and opioids (22.1%) [22].

Regional differences

Both quantitative findings and qualitative study results point to major regional differences relating to prevalence and cultural styles of use [1]. At present, several southern and eastern federal states bordering the main country of origin, Czech Republic, are most particularly affected, especially rural regions and medium-sized cities. Take the federal state of Saxony as an example: within a few years, the distribution of methamphetamine use exploded from a phenomenon afflicting medium-sized cities into a widespread blight encompassing rural regions and villages [23]. In several regions, the dramatic rise in first-time methamphetamine offenders seeking help has been striking. Between 2009 and 2014, the number of affected clients visiting addiction counseling centers in Saxony more than tripled from barely 1,500 to

nearly 5,000. In this context, with a proportion of 67% of clients seeking counseling for illegal drug use, methamphetamine represented the prevailing reason [21; 23]. It is assumed that around 21% of addiction counseling in Saxony across all client groups takes place due to a methamphetamine problem [23]. In the period from 2009 to 2014, the number of inpatient admissions due to mental health and behavioral disorders induced by stimulants (primarily methamphetamine) rose from 102 to 832 cases per annum [23]. In Saxony, currently, more than half of all inpatient treatments administered for illegal drugs are attributable to amphet-amines (mainly methamphetamine).

Some of the key factors driving the extremely high prevalence in certain regions include broad availability, easy accessibility among the different age groups and social classes alongside regional traditions of use extending back almost 20 years [1]. In several federal states, it appears to be primarily a phenomenon affecting rural regions and medium-sized cities, whereas its impact on other regions is obviously all-encompassing. The distribution of methamphetamine in large cities is heterogeneous, where special emphasis should be placed on its administration by intravenous injection and on specific groups exhibiting risky sexual behaviors as reported for many cities [24]. In regions where methamphetamine users take particular advantage of addiction aid services, the evidence indicates that there is a substantially high number of unreported cases of abusers and addicts whose medical addic-tion problems remain "under the radar" for years and who are able to hide their methamphet-amine use when visiting their doctors [1] (see also Chapter 3 Awareness and early interven-tion).

1.2   Mortality

Of the 1,032 lethal intoxications registered in Germany in 2014, 238 monovalent-related were attributed to opioids and 28 monovalent-related cases to amphetamine or methamphetamine; whereas methamphetamine was involved in 10 of the polyvalent lethal intoxications [20]. One 9-year prospective study of deaths among methamphetamine users found cardiac complica-tions stemming from overdoses as well as the sequelae of an HIV infection to be the most frequent causes of death [25].

1.3   Intra-user case groups

One qualitative study conducted in Germany demonstrated how particularly heterogeneous the group of methamphetamine users is. Different subtypes were identified across users sur-veyed within and outside of treatment settings (Table 3). Treatment should address each type's particular features [1].

Table 3 Methamphetamine abuser groups [1]

- Recreational users (for partying, reflecting a youthful lifestyle)
- Use in the context of school and education
- Use in professional life
- Users in the context of parenthood
- Users with co-occurring mental disorders/traumatic experiences
- Aberrant subcultures exhibiting risky sexual behaviors
- Users with excessive substance use patterns/indiscriminate mixed use

Recreational gateway settings

The majority of methamphetamine users had their first exposure to the drug through a recreational context. In most cases, they started using it in their youth or in early adulthood with their peers, usually at parties, nightclubs or discotheques. Second to peer pressure, the motives for repeated use were mainly driven by the desire to achieve euphoria and alertness as well as to overcome shyness and social inhibitions. With a similar frequency, methamphetamine is used to keep going despite extreme drunkenness or to overcome alcohol-related fatigue. Even a presumably controlled, but sporadic exclusively recreational use is not without risk over longer periods. Findings from studies suggest that methamphetamine users who take it over longer periods almost always end up using it in other areas of their lives as well [1]. In first-time offenders who are "recreational users", a review of the occasions for them using the drug as well as the frequency of certain patterns of use might expose types of functional use or attempts at self-medication that pose medical risks of addiction (see also Section 2.2 Diagnostics and Chapter 3 Awareness and early intervention).

Use arising from the context of school, education and professional life

Provided that methamphetamine is regionally available and easily accessible to that respective age and social group, its use in the context of school, education or professional life will increasingly play a role. Methamphetamine is taken to be able to "keep going" longer, overcome emergent boredom and thereby subjectively enhance the ability to perform. Psychological anomalies can become manifest within the shortest period of time and cause users to drop-out of school or lose their job. Sometimes, users' irrational expectations of their own ability to perform prevail, while strategies to structure their daily routine and find self-motivation are frequently lacking. Some working users, mostly in construction, the restaurant business, sales or customer service, report having used the drug unnoticed for years before any psychological and social consequences of use were noticed. Some of the impediments to seeking help include the fear of losing anonymity and becoming stigmatized. Additionally, many affected users assume that existing treatment settings will not be compatible with their jobs [1].

Use and parenthood

Parents from regions with high availability will typically have started using methamphetamine in their early youth. The Pediatrics Department of the University Hospital Dresden systematically registered pregnant methamphetamine users [26; 27]. Around one-fifth of these women were under 20 years of age, 28% between 21 and 25, 32% between 26 and 30, and the remaining proportion over 30.

In over two-thirds of the cases, the peripartum urine drug test was positive. In other words, the majority of these pregnant women had continued to use methamphetamine. Beyond this, qualitative findings indicate that there might also be a risk group constituting female users who were able to immediately stop taking the drug once they found out they were pregnant without external help, but only to relapse several months or years after the birth of their child for reasons of subjective or actually over-stressful situations [1] (see also Section 7.1 Pregnant women, young mothers and prenatal harms).

Users with co-occurring mental disorders/traumatic experiences

In addition to the known interrelationships between the use of addictive substances and other psychiatric disorders as well as early experiences with violence, there are characteristic features of methamphetamine use as far as co-occurring disorders are concerned. These have been systematically addressed in a specific chapter (see Chapter 6 Co-occurring organic diseases and mental health disorders). Subjective reports by users indicate that they frequently take the drug to self-medicate symptoms like anxiety and depression or to shield themselves emotionally [28]. Within this group, drug use motives and the achieved effects are described which initially appear pharmacologically unusual. For example, the improvement in sleep reported by women who had experienced abuse might perhaps be attributable to a lessening of the post-traumatic symptoms potentially manifested as nightmares or intrusive memories (intrusions) [1; 28].

Specific groups exhibiting risky sexual behaviors

Study findings on Berlin indicate that a special affinity to methamphetamine exists in certain subcultures of men who have sex with men (MSM). Recent evidence has confirmed these findings for other large cities as well. By contrast, there is no evidence available at present suggesting that methamphetamine is used by MSM beyond the "venues" of large urban cities. The criterion for this risk group is not a homosexual orientation, but can also include bisexual, heterosexual or unspecified sexual preferences. The hallmark characteristic is that the drug is used primarily or exclusively within a sexual context or for sexual motives. Characteristically, the MSM in these subcultures with an elevated risk for methamphetamine use show a strong tendency towards *sexual sensation seeking* and are motivated by risk-taking. Moreover, preferences for public or private sex parties, promiscuous and anonymous sex as well as for aberrant behaviors have been reported, for example, with MSM intentionally refraining from taking protective measures to prevent sexually transmissible diseases *(bare backing)*. Moreover, there are signs that methamphetamine use is widespread among male prostitutes in certain large cities. Some users within addiction aid systems report that, although they were not dependent, without methamphetamines their experience of sexuality was no longer pleasurable and that they suffered from extreme impairments of their mental well-being. One distinguishing feature of the MSM setting is a preference for intravenous use [1] (see also Section 7.3 Methamphetamine abuse among men who have sex with men (MSM)).

Users with excessive substance use patterns/indiscriminate mixed use

In Germany, many of the aforementioned subgroups of users (e.g. intravenous users) exhibit varying degrees of such extremely risky use patterns and types of use. Without exception, nearly all of those users surveyed reported functional co-abuse involving both legal and illegal drugs, mostly those having sedative effects. Furthermore, one analysis of the survey data suggests that a delineable group exists in which regular indiscriminate mixed use and high-risk substance use patterns are particularly pronounced. In this subgroup, their lives revolved around the drug's use and procurement. Users who switched from heroin, users with methamphetamine as their primary substance and users without preference were identified. However, the findings are too equivocal to make a more nuanced and robust differentiation [1] (see Chapter 6 Co-occurring organic diseases and mental health disorders).

Group of users within the criminal justice system

One previously less acknowledged high-risk group constitutes inmates of criminal justice facilities. Among the primary diagnoses relating to illegal drugs (n=1,825) in users utilizing addiction help services within the Saxony federal state criminal justice system, stimulants (67%) played the dominant role, 97% of which pertained to methamphetamine [29]. In other words, out of a total prison population of n=3,300 (including preventive detention, juvenile prisoners, prisoners remanded to custody or kept in detention or in custody for other reasons), approximately one in three prisoners (n=1,186) contacted external addiction counseling services because of a methamphetamine problem. These numbers are based on the prison population statistics issued by the Saxony State Ministry of Justice and for Europe, as per January 1, 2014) [29].

2 Symptoms, diagnostics and treatment planning

Roland Härtel-Petri, Benjamin Löhner, Willem Hamdorf, Timo Harfst, Peter Jeschke, Frank Vilsmeier, Winfried Looser, Stephan Mühlig, Jan-Peter Siedentopf, Norbert Wodarz

2.1 Symptoms

After oral administration of a methamphetamine-based medicine like e.g. Pervitin® (3–5 mg to 30 mg maximum daily dose), the only acute effects to be expected are increased alertness and appetite suppression. The **crystalline** form of methamphetamine hydrochloride ("crystal meth", "C", "crystal speed") currently sold on the street for intranasal use ("snorting") is mostly taken at a dose of as high as between around 80–100 mg, even by first-time users. Dependent users need 0.5–1.5 g daily. Since the high-dose drug is absorbed faster when taken by this means and its metabolism in the liver kicks in with a delay, there is a rapid "flooding" of methamphetamine to the brain where the drug reaches its peak dose quickly. This induces a strong rush. The short time between self-administration and the high gain in pleasure is the reason why users want to keep taking the substance. In addition to intranasal and oral intake, crystalline methamphetamine can also be smoked or injected. Intravenous injection causes an even more rapid effect, while also rapidly leading to the development of a dependence [30; 31].

Frequency of drug use

The frequency of use can be occasional (sporadic), daily or every other day (continuous) or switching between excessive use to the point of exhaustion with longer or shorter drug-free periods (episodic).

In therapeutic studies, slight to moderate use is often defined as less than three days a week or use less than on 18 days in the last month. Drug intake on more than 18 days out of the month is already considered heavy use.

Tolerance development

The physical and pharmacodynamic manifestations of emergent tolerance in the acute (tachyphylaxis) and chronic phases vary individually, with the different effects appearing in variable order. Increasingly greater amounts are required to achieve the desired intensity and duration of the state of intoxication [32-34].

2.1.1 Direct effects

The effects are individually dependent on the dose and the extent of any tolerance. Immediately after taking crystal methamphetamine, users typically feel the rush or "high" of being wired and energetic or "all lit up". Tweaked, spun, twacked, sketched, gacked are other slang terms used to refer to the intoxication experienced on methamphetamine. In a self-confidently elevated mood, the user is frequently more interactive in social situations, less inhibited, shows reduced critical judgment, a reduction in critical thinking coupled with sexual disinhibition. The euphoria can suddenly turn into tension, irritability, aggressiveness, untargeted impulsiveness, but also manifest as diffuse anxiety.

The behavior of users or "tweakers" on a meth high is typified by hyperactivity, fidgeting, "tweaking", verbal diarrhea (babbling on without taking a breath; slang: "motor mouth"), grimaces, odd facial movements and cramps (slang: "meth monkey"), bruxism (grinding and clenching of teeth) and loss of appetite. Objectively boring, abnormally persistent mechanical jobs are rendered fatigue-free—sometimes enthusiastically, sometimes compulsively without pleasure—for hours on end. The slang for this is "tweaking", also referred to as punding; a neuropsychiatric term coined from the Swedish for blockhead. These drug-induced stereotypia can similarly be directed against the user's own body: After hours long of picking at the "meth mites" users feel crawling on their skin (parasitosis or formication), their bodies become covered with visibly open sores and abscesses ("speed bumps") that later turn into permanent scars.

Since their sensation of pain is reduced under methamphetamine, the user's subjective performance ability can be briefly elevated during physically strenuous muscular activity. Their impaired sense of time (like in "time-lapse" photography) and an artificially positive (grandiose) self-estimation lead to performance enhancement. The two factors contribute to the fact that user's ability to react adequately to situations and reach agreements is frequently substantially impaired.

Psychological symptoms

Depending on the tolerance, high doses can lead to signs of heavy intoxication like agitation, mood swings accompanied by aggressive behaviors, extreme psychomotor restlessness and psychotic events with hallucinations and typically paranoid delusions (slang: tweaking, tripping, tripping out). Self-limiting panic attacks may also become manifest.

Physical symptoms

After taking crystal methamphetamine, the most common physical symptoms include racing heartbeat, elevated blood pressure, increased muscle tension, attacks of sweating, hot flashes and shivers. Initially, dilated pupils are also a sign of drug use. Acute complications of an overdose may include blood pressure crises. This increases the risk for stroke, heart attack, cardiac arrhythmia and hyperthermia with multiple organ failure etc. (see Section 4.1 Emergency settings).

2.1.2   Direct effects of drug use

Route of administration-dependent sequelae

Chronic **intranasal** use can lead to inflammation of the paranasal sinuses, mucosal bleeding, anosmia and perforated nasal septum [35]. **Smoking** the drug elevates the risk of pulmonary damage [2; 36]. Potential sequelae of intravenous drug use include infections, endocarditis, abscesses along with track marks or "sooting" tattoos, mostly on the non-dominant forearm. The risk for contracting a hepatitis B/C or HIV infection increases with the duration of **intravenous** injection, needle sharing or mutual use of injection paraphernalia. Sexually transmitted diseases can occur with a clustered frequency given that risky sexual practices are common under the influence of methamphetamine [37-41].

General sequelae

When drug packages swallowed for concealed transport, called "body packing" accidently burst or leak, this can cause a massive **overdose** and damage to the mucosa [42; 43]. Typical **tooth damage** accompanied by gingival disease, caries and thrush ("meth mouth") arises from reduced saliva secretion and the grinding and clenching of teeth that occur during intoxication [44; 45]. **Weight loss** tends to be more of a transient problem.

Neurocognitive impairment is prevalent among methamphetamine users during withdrawal and for several months into the abstinence phase [46]. On the management of these and other typical sequelae like stroke, cardiac complications, psychoses, dental problems etc., see Chapters 4 Acute therapy and 6 Co-occurring organic diseases and mental health disorders [47-50].

One prospective longitudinal study found that the **violence** observed under methamphetamine was dose-dependent (on this subject, see Section 7.2 Methamphetamine abuse in the family context) [51].

2.1.3   Withdrawal symptoms

A list of annotated ICD-10 diagnostic criteria can be found in Appendix 1.

The **post-use syndrome** (slang: coming down, sketching, crash) after the occasional methamphetamine high takes an opposite run to the drug's original effects. Extreme exhaustion with long, deep sleep followed by depressive mood accompanied by total loss of feeling normal pleasure (anhedonia), fatigue, lack of motivation, general weakness and irritability. In general, these symptoms normalize within 2–3 days. This syndrome has not been entered into the ICD-10 or DSM 5 diagnostic classification systems.

Chronic users commonly develop a **withdrawal syndrome** lasting weeks to months. Frequently, depressive symptoms with anhedonia and suicidal tendencies are reported. This impaired drive is experienced as anergia (lethargy, lack of energy). The fact that those undergoing withdrawal are often irritable and concurrently emotionally unstable has a negative impact on their social contacts. They have waves of intense craving for the drug; bradycardia and weight gain are the somatic symptoms observed. After a crash phase, the need for sleep is great. However, this sleep is usually subjectively not restful, but typically disturbed by drug dreams. At the beginning of withdrawal, there is a subjectively marked reduction in cognitive capabilities [52]. The symptoms usually last for four days to three weeks, in isolated cases for several months. Chronic methamphetamine users frequently develop conditioned reaction patterns to substance-related stimuli (e.g. crystalline substances).

Polyvalent use

Many of those affected try to alleviate the adverse effects or withdrawal symptoms with other (illegal) drugs. As a consequence, polyvalent use patterns can develop. The resulting dependence on sedative substances or their withdrawal symptoms are frequently the motivating factor that treatment is sought in addiction-specific settings. Then, the general basic principles of treatment apply to the substance that has now become the principle substance (see Section 6.2 Co-occurring addictive disorders).

2.2   Diagnostics

The recommendations in the sections "Diagnostics" and "Treatment planning" are based on the conventional classification systems (ICD-10, DSM 5), expert opinions and clinical experience. An extensive list of annotated ICD-10 diagnostic criteria can be found in Appendix 1.

Recommendations	Grade of recommendations
<u>2-1</u> When patients/clients report on stimulant use in any medical-therapeutic setting, information necessary for a risk assessment should be collected that allows a decision to be made about further measures. Expert consensus Vote: 85%	⇑⇑⇑

2.2.1   Initial contact in diagnostic settings

Initial contacts with methamphetamine users can take place in settings staffed with a variety of different types of personnel:

- Addiction-specific settings with professionals trained in addiction therapy

- Contacts in general medical settings (visits to the dentist due to dental problems, to the general practitioner, e.g. because of pimples, visits to emergency rooms for heart complaints etc.)

- Contacts in general help and counseling settings

- Contacts with public agencies and authorities, e.g. in talks for discussing the barriers in job placement, youth services, routine police contacts

It is desirable to obtain as much information, commensurate with the possibilities, training status and responsibilities of each of the facilities (see also Appendix 2). The acute risks posed by intoxication, an impending withdrawal syndrome as well as an acute threat to oneself and others due to a methamphetamine-associated psychosis should be ascertained in order to initiate the necessary measures (see also Chapter 3 Awareness and early intervention).

2.2.2   Diagnosis

The diagnosis of a methamphetamine-/amphetamine-related disorder is rendered according to ICD-10 Code F15.X. A diagnostic aid with *annotated* and *supplemented* ICD-10 diagnostic criteria can be found in Appendix 1 [53].

Recommendations	Grade of recommendation
2-2 If there is a suspicion of co-occurring mental disorders, medical discipline-specific diagnostics (differential diagnosis) should be performed or referrals made. Expert consensus Vote: 100%	⇑⇑⇑

2.2.3   Medical history

In order to be able to identify the psychotropic substances responsible for the presenting symptoms, it is best to draw upon as many sources of information as possible. This includes information reported by the patients themselves, their behavior, characteristic physical or psychological symptoms, clinical hallmarks and other clues like the substances in the patient's possession, reports and medical histories from other doctors. Analyses of blood samples or other bodily fluids may also provide helpful evidence.

Structured clinical interview manuals like SCID, DIPS and CIDI are available to guide clinically less experienced examining personnel. International diagnosis checklists like the IDCL for ICD-10 can be helpful [54-56]. The freely accessible multidimensional European Addiction Severity Index (EuropASI) is designed for global assessment of addiction problems [57] and can be downloaded from the following link: www.emcdda.europa.eu/html.cfm /index3647EN.html.

A collection of non-standardized critical objective items can be found in Appendix 2 of this publication, listing the information to be ideally gathered for practical application. There are no German translations available on stimulant withdrawal instruments like the Amphetamine Withdrawal Questionnaire (AWQ) or Anamnestic Comparative Self-Assessment (ACSA).

Recommendations	Grade of recommendation
2-3 If it is not possible to confirm the diagnosis during the initial contact, an attempt should be made to elicit a willingness in the patient to present themselves in more suitable, e.g. addiction-specific settings. Expert consensus Vote: 100%	⇑⇑⇑

More comprehensive diagnostics for co-occurring disorders should be aimed at – as in all diseases of addiction.

An initial educational briefing of the patient about the particular harms associated with the substance can take place during the consultation and be supported by informational brochures. It has proven useful to hand out to users the addresses of local addiction counseling centers and point out helpful websites (see Appendix 4).

2.2.4   Diagnostic content

A substantive and comprehensive **addictive substance history taking** typically asks the following questions:

- Current use of which substances

- Last time and amount used

- Routes of administration (oral, intranasal [snorting], inhaled [smoking], intravenous, rectal etc.)

- Usual dose, with/without tolerance development, i.e. elevation in the amount taken

- Occurrence and severity of withdrawal symptoms

- Co-abuse (e.g. concomitant medication, THC, alcohol) to "come down from a high", other/currently preferred substance

- Time of first use, frequency, transition from occasional use to daily use

- Order of use and amount of concurrently used substances with/without dependence

- If possible, document the initial and later motives for use, e.g. having fun at parties, to experience sexuality, primary performance enhancement on the job, weight control, endurance when playing computer games, other functionalities like self-medication for depressive disorders, including the typical places of use (parties, clubs, events, gambling halls, home, alone)

- If possible, determine any negative consequences of use like excoriations (skin picking), tooth damage and decay, phases of cachexia during use and uncontrollable increases in appetite with undesirable weight gain during withdrawal above the patient's "ideal weight", persecutory delusions (paranoia), hallucinations, states of anxiety

- Touching on the following topics may provide encouragement to change: "Use-related accidents" (overdoses), judicial or other social repercussions (loss of job, forfeiture of driver's license etc.), irritability accompanied by emotional instability leading to problems in social interactions during withdrawal (violence against family members or uninvolved individuals).

- Relevant to further treatment recommendations: duration and reasons for abstinent phases, reasons for ending such abstinent phases, pre-treatments, current abstinence motivation. The expectations of the user themselves and other stakeholders (partner, family, judiciary, guardians etc.) should be asked about.

- **Special attention** should be focused on paranoid, psychotic symptoms that could endanger the patient themselves or their environment.

- **Questions about depressive symptoms** during withdrawal and the extent of suicidality should always be posed; they count as the most serious complication of methamphetamine withdrawal. The endangerment of dependents (under-aged children) must be weighed against the current symptoms that gave rise to the contact taking place.

The patient's **social medical history** provides clues as to the resources and social barriers impacting the user's decision to change their use behavior or their desire to abstain. Helpful and social impact factors should be assessed in order to incorporate them into the treatment strategy. The **social medical history** comprises family circumstances, schooling or educational and professional situation, financial situation, living situation as well as potential legal problems.

In **medical** settings, the symptom-guided general **somatoneurological examination** should particularly focus on the typical sequelae of stimulant use so that the appropriate treatments can be initiated:

- Excoriations

- Ground-down posterior teeth, spaces, carious dentition

- Signs of cachexia

- Anosmia and nasal damage

- Physical signs of trauma (status post fall, genital injuries)

- Puncture sites with/without recent/older abscesses

- Heart murmur, cardiac arrhythmias, hypertension

- Signs of infection

- Evidence of liver disease

- Nasal damage

Depending on the symptoms, the relevant medical discipline-specific, instrument- or laboratory-based tests should be initiated. The list in Table 4 summarizes the recommendations for clinical examinations, concomitant therapies and screening tests to be administered to outpatient methamphetamine users in basic medical care settings (e.g. general physician's practices, emergency rooms etc.).

Table 4 Examinations, tests and follow-ups in methamphetamine users

Parameter	First exam	Repeat follow-ups			
		1 week	4 weeks	3 months	6 months
Blood pressure/pulse	xxx	xxx			
Weight	xxx	x	xx		
Whole-body ultrasound	xxx			xxx	
UK/SpT	xxx	xxx			
AAT/EtG (Alc)	xxx	xx			
ECG	xxx			xx	x
Blood count/liver function tests	xxx			xxx	

| | | Repeat follow-ups | | | |
Parameter	First exam	1 week	4 weeks	3 months	6 months
Hep ABC/HIV	xxx				xxx
TSH	xxx			xx	x
HCG	xxx		xxx		
Referral for chest x-ray	xxx				
Referral to dentist	xxx				
Referral to gynecologist	xxx				
Vaccinations?	xx				
xxx – Highly important		xx –Important		x – Recommended	
Tests printed in blue appear to be urgently advised (risks!)					

The guidelines issued by the respective medical societies concerning whichever symptoms occasioned treatment recommend that consideration be given to the interactions between the planned medication and the acute effects caused by the psychostimulants and/or how continued use impacts medication compliance and therapy adherence in users not capable of abstinence. Harm-mitigating measures like hepatitis B vaccination should also be weighed in the balance.

Beware the danger of misdiagnoses:

Not rarely, both users and their family members will describe symptoms that are typical symptoms of intoxication or withdrawal (ICD-10/DSM-5), but see them as separate and independent diseases:

- Hyperkinetic withdrawal syndrome ➔ self-diagnosed attention deficit hyperactivity disorder (ADHD) with the desire for treatment with methylphenidate, particularly when this was experimented with "in the scene" and led to a positive outcome

- Withdrawal-related anhedonia, depressiveness ➔ Repeatedly diagnosed depression

- Emotional instability and dissocial, less empathic behavior in the first year of abstinence after chronic use ➔ Personality disorders like borderline personality disorder, narcissist personality disorder and dissocial personality disorder

- Methamphetamine-induced anxiety disorder versus anxiety disorders

- Methamphetamine-induced sleep disorders versus e.g. narcolepsy

- Methamphetamine-induced maniform syndrome versus bipolar disorder

- In methamphetamine-associated psychoses (MAP, ICD-10: F15.5, F15.7), avoid labeling the patient *too* early as "schizophrenic", since this can have serious implications for the prognosis relating to the surroundings and the affected individual (long-term medication with the negative consequences of side effects, intrinsic hopelessness, exclusion of rehabilitation by hospitals and payers).

- Many of those affected take several substance classes (polydrug use) for self-medication to treat the adverse reactions or withdrawal symptoms. At present, benzodiazepines, synthetic opioids, opiates and pregabalin are used for this. Another psychoactive substance dependence (ICD-10 F19.2) is only coded if its use takes a chaotic and indiscriminate course or if components of various substances are inseparably mixed.

2.2.5   Drug screening

2.2.5.1   Methods

Between 30–50% of the racemic form (d- and l-)methamphetamine of the crystal meth currently obtainable in drug circles is renally eliminated unchanged and is therefore directly detectable in the urine. The same applies to several of the active metabolites of methamphetamine, e.g. amphetamine. Special methamphetamine tests, but also conventional amphetamine assays can frequently detect abuse for up to 1–3 days and for up to 7 days when high daily doses are taken (> 500 mg/day) [58; 59].

Recommendations	Grade of recommendation
2-4 Suitable drug screening tests ought to be performed and available in medical-therapeutic settings where basic and primary care is administered. Expert consensus Vote: 100%	⇑
2-5 If the rapid test is positive and the implications are relevant (drop-out of therapy etc.), an appropriate confirmatory test should be performed, at best on the same sample. Expert consensus Vote: 92%	⇑⇑⇑

Under questionable circumstances, specialized laboratories can be relied on to determine whether the metabolites involved are amphetamine derivatives from medicines or degradation products from "prodrugs" by determining chirality (l or d enantiomer) [60; 61].

Potential manipulation of the results (dilution, adulteration with vitamin C or zinc) should be addressed when issues like traffic and other legal violations are involved [61].

Rapid drug tests

Preliminary remarks: Reimbursement for the provision of rapid drug tests is not currently guaranteed in all treatment settings. By intentionally choosing the wording "drug screening tests [...] that should be able to be carried out and be available," the authors are purposely recommending the rapid drug testing system, with the intention of raising awareness of the need to secure appropriate funding. The authors are aware that individual stakeholders can only deploy rapid drug tests in diverse treatment settings as permitted by the respectively existing structural requirements.

Rapid drug tests (immunological urine dip tests or saliva tests) are cost-effective pre-screens for general orientation (in medical practices, hospitals, obstetric departments, addiction advice centers, outpatient and inpatient rehabilitation centers). Results are immediately available, for example, from a urine sample, obtained under observation. Manufacturer-related false positive results on certain medications are possible due to immunological cross-reactions.

Occasional drug use cannot be excluded by standard urine tests. The current detection of methamphetamine during a routine check is not in itself evidence of drug dependence.

As is common with alcohol detection, it is important to treat these results confidentially so as not to jeopardize trust, e.g. of women in labor [62]. Although not funded to date, the provision of pregnancy tests would be a simple way to support female users in their wish to remain abstinent (often expressed once pregnancy is confirmed) (see also Chapter 3 Awareness and early intervention and Section 7.1 Pregnant women, young mothers and prenatal harm).

The most important aspects of the available options and fundamental principles to be observed are summarized in the box below.

- No specific patient preparation is required as urine can be collected at any time. Remember that first morning urine is more concentrated and will contain higher drug concentrations.

- In abstinence-oriented settings, urine collection is carried out under supervision or monitoring to prevent tampering.

- The following should be considered when collecting urine in abstinence-oriented settings:

  o Urine samples can, for example, be diluted with tea, water or apple juice.

  o Urine from another person can be provided (e.g. hidden in latex gloves/condoms etc.).

  o Urine can be adulterated by excipients that produce false-negative results (depending on the testing method used, e.g. liquid sweetener, vitamin C, zinc).

- Tampering can be identified, for example, by checking creatinine and/or by testing in specialized laboratories.

- In order to exclude the dilution of urine, urine creatinine strips can be used. This immediately ensures that creatinine is in the expected range and allows a second urine sample to be requested within a specific time window.

- The urine temperature should be measured if the urine sample is suspected to be from another person.

  o The urine temperature must be between 32–36.5 °C immediately after the sample is provided.

  o Fast cooling can produce values of about 31 °C within a short time. Therefore, it is important to measure the temperature immediately after the urine sample is provided.

  o Do not accept urine samples < 30 °C and check body temperature when > 37.0 °C.

- The urine sample should be stored in a refrigerator at approx. 4 °C until the final result is available. Depending on the reason for the test, take and/or store several test tubes (second sample) to allow re-testing from the whole sample.

- Be aware of the laboratory specific pre-analytical transport chain.

- Pay attention to hygiene; wear gloves when receiving and processing urine samples.

Evaluation

Consider possible fluctuations, e.g. due to:

- The patient's individual metabolism and degradation of the substance

- Fluctuations in the sample urine concentration: the higher the concentration, the higher the measurement.

- pH

- Concomitant medications (enzyme induction, e.g. with antibiotics or anticonvulsants)

- Possible (intentional/unintentional) adulterations caused by the co-administration of certain medications

Both false-positive and false-negative results are possible. In the case of uncertainty:

- Consult back with the laboratory: which analysis method (GC, HPLC, immunoassay etc.) was used for which (legal) issue? What preliminary (quantitative and qualitative) results are available? Are other factors (substances/concomitant medications) relevant?

Depending on the reason for the test and in coordination with the laboratory, request that the simultaneously collected second sample be analyzed using more sensitive testing!

Laboratory immunoassays

As immunoassays conducted in the laboratory (saliva or urine tests) provide semi-qualitative results, they are mainly deployed during the drug withdrawal and rehabilitation phases **in known users** to monitor their clinical course. Results are available within a few hours to several days.

Like strip tests, they can deliver false-positive and false-negative results (e.g. bupropion can lead to false-positive results). If the clinical picture is unclear, further tests are often required to clarity legal aspects [63; 64].

Gas chromatographic/mass spectrometric (GC/MS) analyses

GC/MS analyses of urine, saliva, blood or hair are confirmatory for verifying the immunological pre-test results. To answer forensic questions as in long-term drug monitoring, detection is possible during the period of hair growth (usually for up to approx. 90 days). Processing times of days to weeks should be allowed for [65-67].

2.2.5.2   Potential discrepancies

When the client consents during a verified abstinent state, a clinical estimation as to whether abstinence has been interrupted is facilitated by colleagues sharing information within experienced teams. The frequency of use tends to be statistically underestimated when judging both the clinical picture and rapid screening tests [68; 69].

It is important to consider that many new psychoactive substances (NPS), e.g. most of the newer amphetamine-type stimulants (ATS) or cathinones, sold as research chemicals or legal highs, will produce false-negative results in routine screening tests for amphetamines. This, in fact, limits detection to (meth-) amphetamine. Increasingly, toxicology laboratories are becoming better able at detecting these substances (but at high cost) [70].

2.3   Treatment planning

The authors of these guidelines are not aware of any scientifically proven evidence regarding which treatment is most effective for which methamphetamine users with what substance use pattern/frequency. The recommendations below are based on clinical experience.

Recommendations	Grade of recommendation
2-6 Any user actively seeking help who recognizes their own harmful drug use should be supported at all primary contact settings and referred to the addiction help services. Expert consensus Vote: 100%	⇑⇑
2-7 Any user actively seeking help from the addiction help services for the first time ought to be given an appointment for counseling within 24 hours. Expert consensus Vote: 100%	⇑
2-8 All users who attend counseling and treatment centers should be educated about the particular dangers of methamphetamine and be particularly made aware of the hazards associated with its crystalline form and other high-risk routes of administration and patterns of use. Expert consensus Vote: 91%	⇑⇑
2-9 In addition, all users should be made aware of the local self-help groups or other self-help options. Expert consensus Vote: 100%	⇑⇑
2-10 The therapeutic goals of the user should also be taken into account when planning treatment. Expert consensus Vote: 100%	⇑⇑

2.3.1 Selecting the suitable treatment setting

According to the general recommendations of the S3 clinical practice guideline "Psychosocial treatment of severe mental disorders", treatment "*should always align itself along the individual needs of the sufferers and the intensity of required interventions at each point in time throughout the treatment process.* Applying the motto of promoting outpatient treatment over hospitalization, inpatient treatment should be avoided whenever possible*.*" [71]

The choice of treatment setting depends on:

- The clinical severity and nature of substance-related disorder (amount of drug used)
- Route of administration
- The extent of additional (addictive) drug use
- Physical sequelae requiring treatment
- Co-occurring mental disorders
- Treatment options available locally
- Patient's motivation for a particular intervention
- Patient's dependence and treatment history

A user actively seeking help is a sign that the time is right for intervention [72]. Ideally, an offer of help should be made to a user who shows a willingness to change before they start using again. Where resources are limited, an appointment should be made within 24 hours to establish a positive relationship, particularly for clients seeking help from the addiction help services for the first time. Follow-up interventions such as reminder text messages on the same day as the appointment can help improve attendance rates. Sufferers tend to accept offers of immediate treatment.

Users should be educated about the current scientific evidence. An essential component of the consultation is to explain to users the particular dangers of crystal meth (see also Chapter 9 Harm reduction):

- Severe overdose from high-purity crystal meth, particularly when taken by nasal, intravenous or inhaled routes.
- Leads to quicker dependence than cocaine
- Quicker development of mental disorders than in cocaine users
- Lethargy, depression and suicidal thoughts during withdrawal
- Higher risk of aggressive behavior when intoxicated
- Higher risk for triggering psychosis
- Higher risk of permanent damage such as memory loss and Parkinson's disease
- Higher likelihood to engage in high-risk sexual behavior associated with the potential for unwanted pregnancies, experiencing mistreatment and infection with hepatitis B, C and HIV.

Users should make a decision about the choice of an appropriate treatment setting once they are in a cognizant state. The address of the nearest addiction counseling center, the URLs of specific Internet sites as well as contacts for local self-help groups should be provided in all service settings regularly visited by addictive substance abusers (e.g. by means of posters/flyers laid out in emergency rooms, safer use information material etc. at parties, addic-

tion support folders and self-help flyers in medical practices etc.; see Appendix 4).

An individual suffering from a substance use disorder will seldom walk a straight path to abstinence. Therefore, it is important to check whether the support and treatment modalities offered are appropriate and meet the personalized needs effectively. The treatment chosen by users usually pivots on their desire for self-monitoring and freedom of choice within the treatment setting. To identify local treatment needs, stepped intervention targets have been developed based on the central WHO strategies designed to help heroin users (harm reduction and risk reduction) [73-75]. These protocols can also be considered when planning strategies to treat crystal meth users:

Table 5 Interventional goals within the stepped care approach; adapted from [76]

Goals	Measures
Ensuring survival	Crisis intervention; emergency measures; first aid; stabilization of vital signs
Health promotion	Education interventions; referral to (self-)help services; facilitating adherence; encouraging willingness for therapy
Social outreach	Measures for structuring the day; promotion of everyday and social competency; securing living accommodations, securing income
Stabilization of abstinent phases	Change or adaptation of stimulus reaction patterns to the addictive substance; promoting the ability to compensate for cravings; referral to low-threshold help services; brief therapeutic services; reduction of ambivalence conflicts
Acceptance of the dependence	Facilitate acknowledgement of the chronic vulnerability to substance-related dependence; foster knowledge about the existing and impending health consequences
Acceptance of the need for therapy	Motivational encouragement; appreciation of disorder-specific therapies; encouraging self-help strategies and assumption of personal responsibility
Abstinence	Acceptance of the abstinence goal; goal-focused, self-effective and socially competent reaction to use triggers; systematic modification of lifestyle
Constructive coping with relapses	Referral to coping strategy services
Occupational and social integration	Social (re-)integration (living space, job, financial situation)

2.3.2 Supportive and therapeutic services

A variety of supportive and therapeutic services come into question, depending on the users' desires and goals in terms of abstinence, controlled use and the psychosocial possibilities. The options available from the addiction help services are presented in the following table (see also Chapter 8 Relapse prevention).

Table 6 Treatment services offered for methamphetamine-related disorders

Type of service	Task, goal, objective (non-exclusive lists)	Average treatment duration	Payer
Self-help	*Self-organized networks of individuals with addiction problems – with or without professional supervision* Goals: To promote a sense of community and sharing, encourage change motivation, mutual support in changing use patterns, self-efficacy reinforcement, stabilize successful therapeutic outcomes in everyday life, relapse prevention. Available services: Group sessions, online self-help	Patient-dependent – potentially life-long	Free-of-charge
Low-threshold & outreach services	*Near-scene and acceptance-oriented services available to drug users* Goals: To ensure survival, health-related, social, economic and legal harm reduction, psychosocial stabilization, education about drug-specific topics, referral to more comprehensive help services. Services offered: Needle and syringe programs, safer use / safer sex counseling, street social work, contact centers, drug use room, emergency sleeping facilities, outreach services in party settings	Patient-dependent	Usually free-of-charge
Outpatient addiction counseling	*Professional counseling on drugs and drug abuse as well as any necessary referral to more comprehensive help services* Goals: Client contact, information and psychological education, clearing, referral to more	Patient-dependent	Free-of-charge through counseling centers funded by community payers or non-governmental

Type of service	Task, goal, objective (non-exclusive lists)	Average treatment duration	Payer
	comprehensive help services, motivational interviewing and promotion of change motivation, supporting abstinence or change in use patterns, relapse prevention. Services offered: Counseling in individual settings for drug abusers, acute assistance/crisis intervention, group session options (e.g. relapse prevention groups), family member counseling, possibly including outpatient rehabilitation and aftercare services secondary to inpatient treatments.		welfare agencies
Outpatient medical rehabilitation	*Therapeutic services offered to individuals who want to remain and deal with their addiction problem in their own surroundings (work, family etc.).* Goals: Achieving and stabilizing abstinence, eliminating physical and mental disorders, participation in the workforce, professional life and society. Services offered: Individual and group therapy, family and couples sessions.	Up to 18 months	Pension scheme, German statutory health insurance, responsible social welfare authorities in the case of welfare dependents pursuant to Book XII of the German Social Code (SGB XII) (integration aid)
Outpatient (guideline-driven) psycho-therapy	*Therapeutic services offered to individuals who want to remain in their own surroundings (work, family etc.) and at the same time deal with their addiction problem there* Goals: Reinforcing and maintaining abstinence, relapse prophylaxis, management of co-occurring disorders, participa-	Patient-dependent: initially up to 5 probationary sessions (subsidized under some German statutory health insurance policies).	German statutory health insurance, responsible social welfare authorities in the case of welfare dependents in accordance

Type of service	Task, goal, objective (non-exclusive lists)	Average treatment duration	Payer
	tion in the workforce, professional life and society. Services offered: Individual and group therapy, family and couples sessions, also with physician-supervised co-treatment.	Brief treatment 25 h, an extension can be applied for. Since 2011, also possible before abstinence is achieved if suitable steps initiated (e.g. self-help group, addiction counseling) and abstinence appears achievable over the course of 10 hours; proof of abstinence can be produced over clinical course (verified by external physician) and in the event of relapse during "Guideline-driven psychotherapy'" abstinence is reinstated by suitable interventions	with Section 40 SGB XII (integration aid) under a private health insurance, depending on the policy
Inpatient detox	*Acute medical services for detoxification of addictive substances* Goal: To manage states of intoxication and/or withdrawal symptoms. Services offered: medical care, psychiatric assistance	Limited to the duration of the intoxication or withdrawal symptoms, 7–14 days	Statutory health insurance, private health insurance, responsible social welfare authorities in the case of welfare dependents in accordance with Section 37 SGB XII (legal entitlement to help during

Type of service	Task, goal, objective (non-exclusive lists)	Average treatment duration	Payer
			illness under German law)
Qualified withdrawal treatment	*Acute treatment by an addiction psychiatrist or doctor extending beyond the physical detoxification and integrating treatment elements with respect to the underlying disease "Dependence"* Goals: To manage intoxication and withdrawal symptoms, diagnosis and management of mental and somatic sequelae and concomitant diseases, ensuring seamless transition to any withdrawal treatment or suitably client-personalized specific treatment modalities. Services: Multidisciplinary psycho- and sociotherapeutic interventions to promote the change readiness (motivational interviewing), change competency and facilitate abstinence stabilization. Enhance the motivation to utilize more comprehensive help services	At least 21 days	Statutory health insurance, private health insurance, responsible social welfare authorities in the case of welfare dependents in accordance with Section 37 SGB XII (legal entitlement to help during illness under German law)
Inpatient medical rehabilitation	*Inpatient modalities for managing addictive substance dependence comprising both medical and therapeutic elements* Goals: To achieve and stabilize abstinence, eliminate physical and mental disorders, participate in the workforce, professional life and society. Services: Provision of medical care, individual and group therapy, adjuvant therapeutic	Usually, 12–26 weeks, lengths of treatment vary according to the individual conditions (short- and medium-term treatment, longterm management)	Pension scheme, German statutory health insurance, responsible social welfare authorities in the case of welfare dependents pursuant to SGB XII (integration aid)

Type of service	Task, goal, objective (non-exclusive lists)	Average treatment duration	Payer
	modalities (e.g. sport and exercise therapy, occupational therapy, relaxation and music therapy, social therapy, work-related interventions).		
Inpatient social therapies	*Inpatient modalities for managing addicts with severe physical or mental sequelae* Goals: To establish and stabilize abstinence, prevent further severe sequelae and alleviate symptoms, foster social integration, learn to organize and structure a daily routine. Services: Provision of medical care, psychiatric assistance, individual and group therapy, adjuvant therapeutic modalities (e.g. sport and exercise therapy, occupational therapy, relaxation and music therapy, social therapy, work-related benefits)	About 12-24 months	Social welfare authorities pursuant to SGB XII (integration aid)
	In justified isolated cases (order for involuntary commitment), treatment can be carried out in a protective department.		
24-hour outpatient rehabilitation (formerly semi-inpatient)	*Therapeutic services offered to individuals who want to remain in their own surroundings (home, family etc.) and at the same time deal intensively with their addiction problem there* Goals: To achieve and stabilize abstinence, eliminate physical and mental disorders, participate in the workforce, professional life and society.	Up to 18 months	Pension scheme, German statutory health insurance, responsible social welfare authorities in the case of welfare dependents pursuant to SGB XII (integration

Type of service	Task, goal, objective (non-exclusive lists)	Average treatment duration	Payer
	Services offered: Medical care, individual and group therapy, sport and exercise therapy, occupational therapy		aid)
Outpatient aftercare, post-inpatient treatment	*After-care services after discharge from a completed inpatient treatment* Goals: To stabilize abstinence, relapse prevention, professional re-integration, daily structure implementation. Services: See outpatient psychotherapy, assisted single living, supervised apartment sharing	Patient-dependent	Pension scheme, German statutory health insurance, responsible social welfare authorities in the case of welfare dependents pursuant to SGB XII (integration aid)
Assisted single living	*Intensive counseling and assistance in their own home environment* Goals: To cope with the impacts and effects of addiction, making and shaping social relationships, job-related integration, structure a daily routine, live independently, achieve effective organization of leisure time, participate in a social life	Patient-dependent	Social welfare authorities pursuant to SGB XII (integration aid) or juvenile authorities
	Services offered: Individual sessions, group interventions, everyday assistance, support in dealing with authorities, debt settlement, recreational services		
Supervised accommodation-sharing	*Usually involving aftercare services secondary to completed inpatient therapy* Goals: To stabilize abstinence, making and shaping social relationships, job-related integration, structure a daily routine,	Patient-dependent	Social welfare authorities pursuant to SGB XII (integration aid) or juvenile authorities

Type of service	Task, goal, objective (non-exclusive lists)	Average treat- ment duration	Payer
	self-care and living, effective organization of leisure time, participation in a social life. Services: Opportunity for com- munity life and living, daily rou- tine counseling, support in dealing with the authorities and the bureaucracy, individual and groups sessions, relapse pre- vention, interventions for daily routine structuring, leisure-time activities.		

3   Awareness and early intervention

Roland Härtel-Petri, Frank Schulte-Derne, Jan-Peter Siedentopf

This guideline also provides information for non-dependent users who may not yet have developed a need for therapy themselves. It makes sense to also offer these individuals supportive services early to prevent them from developing dependence. This is also a way to help prevent users from self-medicating their withdrawal symptoms or the side effects of their methamphetamine use with other illicit drugs or addictive pharmaceuticals (see Chapter 6 Co-occurring organic diseases and mental health disorders). Based on expert opinions and clinical experience, suggestions are given as to which settings, symptoms and behaviors are suggestive of methamphetamine use.

Frequently, addictive substance use is not reported voluntarily during contacts with physicians even though occasioned by physical symptoms (for a detailed description, see Section 2.1 Symptoms). Stimulant users frequently do not attribute the cause of their tachycardia or even anxieties to this or they intentionally refuse to report it.

Because of their lack of knowledge or understanding about the stepped care and guided help options offered by youth services, women who are pregnant or in labor may hold back from reporting their illegal use for fear that they will immediately lose custody of the child. As with most addictions, the user must primarily be asked directly about or tested for it (see Sections 2.2 Diagnostics and 7.1 Pregnant women, young mothers and prenatal harm).

Recommendations	Grade of recommendation
3-1 Methamphetamine-using women should regularly be offered pregnancy tests, also in addiction counseling settings. Expert consensus Vote: 100%	⇑⇑⇑

Methamphetamine use can lead to risky sexual behavior [77; 78]. In this context, the higher incidence of sexually transmitted diseases is also accompanied by unwanted pregnancies. By offering to conduct pregnancy tests at addiction counseling centers and on other occasions featuring low-threshold contact opportunities ("party projects" at raves or techno parties etc.), the problem is not only addressed, but can also lead to an early diagnosis of pregnancy. This, in turn, mandates early risk education about methamphetamine use in pregnancy as well as counseling whenever a pregnancy conflict arises (see Section 7.1 Pregnant women, young mothers and prenatal harm). At present, these costs are not yet covered (cf. Comments on Recommendation 2-5, Rapid drug tests).

Examples of contacts where the methamphetamine problem is not explicitly reported or non-dependent users become conspicuous:

- At the offices of general practitioners, specialists (e.g. dermatologists, cardiologists, psychiatrists, dentists, gynecologists etc.), based on clinical findings and somatic particulars

Methamphetamine intoxication or withdrawal symptoms complicate somatic treatments or are the causal, albeit not the stated reasons for the user seeking medical help (cardiac symptoms, skin excoriations, cachexia, sexually transmitted diseases, anxiety, lack of drive). The question as to whether addictive substances are being used is part of every medical history taking. The treatment team should be aware of the typical signs of methamphetamine abuse (as with alcohol). Hectic behavior as well as obvious signs like dilated pupils, tooth damage and decay, excoriations, cachexia combined with (unreliable) "typical" scene-related attributes like e.g. wearing sunglasses in weak lighting and unkempt clothing can provide initial clues to methamphetamine abuse (see Section 2.1 Symptoms). When noticing signs of abuse, physicians should ask the person about it. Educational and informational materials and other addresses from public institutions should be made available (see Appendix 4).

Screening tests, for example, like the interviewer-administered ASSIST can be given by medical professionals if they suspect abuse in a patient. The test can be downloaded from the following website: www.who.int/substance_abuse/activities/assist_3.1_german.pdf

The ASSIST manual includes interventions and is generally also used to identify persons with drug dependence [79; 80]. Rapid urine dipstick tests can confirm the suspicion (see Section 2.2 Diagnostics).

- In the dentist's practice

  Visits to the dentist by younger persons presenting with tooth damage and decay that is otherwise atypical for their age are ideal occasions to introduce early interventions. The treatment team should be aware of the typical signs of methamphetamine abuse. When signs of abuse are noted, it is recommended to take the most detailed medical history possible about the abuse and any co-use of other addictive substances (see Section 2.2 Diagnostics). Informational brochures on "meth mouth" (in preparation) and contact data on addiction help services should be made available (see Appendix 4). A critical appraisal of the infection status (HIV, hepatitis) is advised (further instructions are provided in Chapter 6 Co-occurring organic diseases and mental health disorders.

- Preclinical and clinical emergency situations

  Besides stabilizing the vital functions, particular attention should be paid to paranoid, psychotic symptoms that can lead to an endangerment of the environment (helpers) or to self-endangerment (see Section 4.1 Emergency settings)

- Contact in specific use-related settings through peers, educators, correctional officers etc.

  As with other substances, the attending team should be aware of the typical signs of methamphetamine abuse (typical behaviors, hallmark symptoms; see Section 2.1 Symptoms). Where indications of abuse are noted, it is recommended to ask the affected individual about them. Informational materials and other addresses from public institutions should be made available.

- Liaisons in formal youth service settings, authorities, government agencies or the likes

  As with other addictive substances, the team should be aware of the typical signs of methamphetamine abuse (typical behaviors, dilated pupils). Particular focus should be directed at the paranoid, psychotic symptoms that can endanger anyone or anything in the user's vicinity. Especially during the withdrawal phase, the client will be in an irritated mood, institutions and government agencies are perceived as "bullying and anti-

hedonistic". De-escalating interview techniques are recommended during situations characterized by intoxication and withdrawal or if a psychotic experience is suspected. On de-escalating strategies, see Chapter 4 Acute therapy or e.g. (in German):

- o Institute for Psychology & Threat Management

  www.i-p-bm.com/images/stories/pdf/Deeskalation_Seminarkatalog.pdf

- o Institute for Professional De-escalation Management

  www.prodema-online.de/professionelles-deeskalationsmanagement/unsere-fachbereiche

- Educational institutions

  Addictive substance-using parents who no longer sufficiently comply with their parenting responsibilities require help. As with other addictive substances, the team should be aware of the typical signs of methamphetamine abuse (characteristic behaviors, mydriasis [dilated pupils]) and be able to provide information about the local help services available (see Section 7.2 Methamphetamine abuse in the family context).

- Teachers of all school branches

  Due to the current reporting on some of the apparently positive effects of crystal methamphetamine on its ability to enhance performance, an increase in experimental use by schoolchildren and trainees can be anticipated. The issues and problems associated with this "brain doping" renaissance can be addressed in an interdisciplinary manner through the provision of suitable teaching materials. As with other addictive substances, the staff should be aware of the typical signs of abuse (characteristic behavior of the intoxicated state, irrepressible need for sleep during the acute post-use/withdrawal phase, dilated pupils). The facial excoriations of acne noticeable during puberty do not constitute evidence of abuse, while emotional instability and irritability can also be typical of pubertal behavior.

  Further reading for teachers:

  Crystal Meth. Materials for addiction prevention in grades 8-12 (BZgA 2015)
  www.bzga.de/infomaterialien/unterrichtsmaterialien/?idx=2619&sub=1

  Arzneimittel. Sachinformationen zum Thema Arzneimittel und Bausteine für die Suchtprävention [Pharmaceuticals. Factual materials on the topic of pharmaceuticals and building blocks for addiction prevention in grades 5 to 10 issued by the German Clearing House for Health Education.]
  www.bzga.de/infomaterialien/unterrichtsmaterialien/?idx=1087&bestell_bestellnummer=20430000

- Company doctors

  An increase in experimental use by workers, employees and trainees can also be anticipated given the current publicity on some of the subjectively positively perceived effects of methamphetamine relating to its ability to enhance performance. Cooperation with vocational schools is recommended. The issues and problems associated with this disinformation can be addressed with suitable teaching materials.

  Not only company doctors, but also the superiors should be able to identify the typical signs of abuse and be in a position to counsel endangered staff members during precari-

ous situations in their lives. As in dealing with the dangers of alcohol addiction development, addiction helpers at companies should be as equally aware of the "seductive allure" posed by the presumable performance enhancement attainable with psychostimulants like methamphetamine.

- Early intervention in first-time drug offenders (FreD)

FreD targets juveniles and adolescents who have become first-time narcotic drug offenders. The aim of FreD is to motivate young people to reflect on their drug abuse and prevent them from developing dependence. This selective addiction prevention program has been implemented at more than 140 locations and is being extended by the "FreD-Crystal/ATS" program for stimulant users. After their first offense, users should be referred to the regionally competent FreD provider. This referral can be made by the police, courts, juvenile authorities, school and company or even the youth welfare services (www.lwl.org/FreD).

4   Acute therapy

Euphrosyne Gouzoulis-Mayfrank, Norbert Wodarz, Michael Christ, Heribert Fleischmann, Winfried Looser, Katharina Schoett, Frank Vilsmeier

Acute therapy consists of emergency interventions for intoxication syndromes, alleviation of withdrawal symptoms, qualified withdrawal treatment with motivational and psychoeducational elements along with the treatment of psychiatric complications such as substance-induced psychosis. Designed for an interdisciplinary community, the recommendations in this chapter are directed at all professional groups involved in care and management.

4.1   Emergency settings

4.1.1   General principles

It is the emergency physicians and/or emergency room staff who always come into contact with individuals suffering from acute drug intoxication whenever intoxication or an acute high has led to complications in the users themselves or in their interactions with their surroundings. Fundamentally, the hallmarks of methamphetamine intoxication can include: somatic medical complaints (uncontrolled blood pressure, cardiac arrhythmias, cardiovascular problems, seizures, respiratory depression, chest pain, stroke, cerebral hemorrhage, impairment of consciousness) or psychological symptoms (expansive-aggressive states, agitated states with [difficult-to-control] outbreaks of aggression, stereotypia, anxiety-agitated, delirious or psychotic pictures involving hallucinations and delusions of grandeur) with psychosocial complications (violence against oneself or others, road traffic offenses, crimes). The manifestations depend on the individual's circumstances as well as on the dosage and duration of their methamphetamine intake. The symptoms can last several hours (cf. Section 2.1 Symptoms). There is a particularly high risk for aggressive outbreaks as part of a psychotic clinical picture and/or whenever there is concurrent alcohol abuse [51].

During the acute situation, it is usually difficult to take a medical history from those affected, thus making external medical history and other information from their personal environment pivotal for the diagnosis. Usually, amount and type of substance used or a mixed use are initially unclear so that it is difficult to predict clinical courses. Accordingly, a syndrome-oriented approach, including monitoring of the physical-vegetative and clinical-psychopathological findings, is decisive until the symptoms have resolved. Signs of the sympathomimetic toxidrome manifesting as symptoms like hypertensive blood pressure levels, tachycardia, hyperthermia, diaphoresis, mydriasis and agitation suggest the differential diagnosis of intoxication with methamphetamine. The extent of tachycardia or hypertension is a good indicator for the extent of the methamphetamine intoxication. A positive result from a qualitative urine test ("tox screening") increases the probability that the patient is suffering from methamphetamine intoxication, although this test does not permit a reliable diagnosis due to its diagnostic inaccuracy. A negative test never rules out life-threatening methamphetamine intoxication (cf. Section 2.2 Diagnostics).

Recommendations	Grade of recommendation
<u>4-1</u> A person suffering from methamphetamine intoxication ought to be treated in an environment that is as quiet as possible and shielded from outside stimuli; the person ought not to be left alone at any time. Expert consensus (LoE 5), based on [81] Vote: 82%	⇑

Whenever a patient presents with diaphoresis and hypertension, tachycardia, severe agitation or psychosis, the attending physicians should consider intoxication with methamphetamine. The primary objective focuses on verbal de-escalation and deescalating communication strategies, on safeguarding against and preventing sequelae due to states of panic or irrational, impulsive and aggressive behaviors as appropriate. The aforementioned goes hand in hand with a reinforcement of the user's treatment readiness, e.g. in the case of injuries. Clinical experience has shown that merely creating quiet, shielded surroundings and comforting words can produce a marked improvement, i.e. merely by "talking them down". As far as possible, the consistently same reference person should remain in contact with the patient. It may also be helpful to seek the involvement of any acquaintances present who have a comforting influence on the patient. The attending professional caregivers (physicians, nursing staff, paramedics etc.) should listen to the sufferer, try to explain the situation and how they will proceed, and do so at best in simple short sentences. The basic attitude should convey empathy and acceptance (avoiding recriminations or confrontations). Potentially irritating and misinterpretable behaviors like abrupt movements or rapidly approaching the acute sufferer should also be avoided. Clinical experience indicates that sedative medication can be refrained from when these basics are observed. The same principles have also been described in the Australian guidelines on the emergency management of patients with psychostimulant toxicity, as recommendations by a panel of experts [81].

When faced with aggressive patients in emergency department settings, the safety and health of oneself and of the helpers are paramount. For example, an escape route should be kept open and safety in numbers ensured by having at least a second individual present who could intervene or get help. Established de-escalation management protocols, some of which have been evaluated, are available to assist healthcare staff and social workers.

Depending on the severity of any physical complications, hospitalization involving intensive care may be indicated beyond the care given by the emergency clinicians and/or in emergency departments. In Germany, the emergency physician must establish the indication for this on a case-by-case basis by applying AEP criteria (www.medizinische-abkuerzungen.de/files/media/PDFDateien-Sonderteil/G-AEP-Kriterien.pdf, see also Appendix 3).

Recommendations	Grade of recommendation
4-2 Any individual intoxicated with methamphetamine exhibiting severe psychopathologic symptoms and behaving in a manner that presents a concrete risk of harm to themselves or to others ought to be admitted to a psychiatric ward, if necessary, against their will, given that no somatic symptoms mandating acute treatment are prominent. Expert consensus (LoE 5), based on [82] Vote: 100%	⇑

When psychiatric symptoms manifesting as irrational, impulsive, aggressive, agitated, delirious or psychotic behaviors are prominent and accompanied by hallucinations and delusions and/or the risk of harm to oneself or others, or if the symptoms are so severe that the behavior is difficult to predict and the risk of harm to oneself or others is presumed to be imminent (ICD-10 Codes F15.0x), the patient must be admitted to a psychiatric ward for treatment or to intensive care, if necessary, against their will. This constitutes an absolute indication for hospitalization according to the criteria developed by an expert panel within the framework of a consensus process [82].

As far as possible, physical restraint should be refrained from, seeing that it generally leads to further escalation and has additionally been suggested to worsen the endangerment of the restrainee's life (e.g. rhabdomyolysis, hyperthermia etc.). In exceptional situations, e.g. aggressive outbursts by the patient, it may nevertheless be necessary to use temporary physical restraint. For this purpose, a standardized protocol providing for an appropriately staffed team (mostly five individuals) and personal safeguards should be in place. Because the patient is at jeopardy, the presence of a qualified nursing specialist is recommended (1:1 attendance).

> **Info Box 1: General principles concerning involuntary commitment and coercive measures**
>
> The legal prerequisites and regulations governing involuntary commitment and coercive measures are laid down in commitment laws or in the laws on aids and protective measures in cases of mental illness, i.e. the German Mental Health Act (Psych-KG). These laws have mutual commonality across the German Federal States. Pursuant to the Mental Health Act, measures under an involuntary commitment law are fundamentally allowed to be implemented if a mental disorder, a psychological impairment or an addiction is associated with any risk that the individual will cause substantial harm to themselves or to others and there are no other effective ways of averting such danger. As part of the involuntary commitment procedure, a physician must file a short petition in writing justifying the necessity to treat the patient in question against their will. The patient in question will then be brought involuntarily by the police or fire department to a psychiatric facility, and committed temporarily *ex officio* until a judge makes a final decision after a personal hearing of the patient. The deadline for the court hearing varies from 24 to 72 hours, depending on the federal state. When coercive measures like physical restraint and/or coercive medication are unavoidable in an emergency, they are undertaken pursuant to Section 34 of the German Criminal Code (StGB) (justifiable state of emergency).

Recommendations	Grade of recommendation
<u>4-3</u> After an episode of methamphetamine intoxication, patients should be recommended to undergo more detailed psychiatric/addiction-specific medical diagnosis and treatment as appropriate. Expert consensus Vote: 100%	⇑⇑⇑

Clinical experience has shown that once the intoxication has resolved, those affected are frequently still so impressively impacted by their experience that they tend to be most receptive to any counseling services offered. These measures include more comprehensive medical and psychiatric addiction diagnostics and differential diagnoses of co-occurring disorders coupled with psychoeducative measures and, as appropriate, liaising the patient with professional addiction help services for further therapeutic interventions (e.g. psychiatrists, outpatient clinics specialized in addiction, counseling centers (cf. Section 2.3 Treatment planning).

4.1.2 Pharmacological interventions in emergency settings

A systematic search identified no study results on pharmacological interventions with methamphetamine users in the emergency setting. The following recommendations are hence based on expert opinions or on clinical experience. The systematic search for guidelines produced a consensus-based guideline of moderate methodological quality relating to the emergency management of intoxication with psychostimulants [81]. Overall, this correspondingly reflects a weak level of evidence [83; 84].

4.1.2.1 Sedative and antipsychotic medication

Recommendations	Grade of recommendation
<u>4-4</u> Absent sufficient monitoring options or exact knowledge of poly intoxication, the administration of medication ought to be refrained from. If medication appears necessary, the two recommendations mentioned below apply. Expert consensus (LoE 5) Vote: 100%	⇑
<u>4-5</u> In patients with methamphetamine intoxication characterized by extreme agitation, aggression or psychotic symptoms and need for pharmacological treatment, benzodiazepines should be used as medication of first choice. Expert consensus (LoE 5), based on [81] Vote: 100%	⇑⇑

Recommendations	Grade of recommendation
<u>4-6</u> When the administration of benzodiazepines is not sufficient to treat the methamphetamine intoxication, an antipsychotic may be given additionally. Expert consensus (LoE 5) Vote: 100%	⇔

Since it is frequently unclear in acute situations which substance or substance combination is involved, caution is advised before administering any medications if and as long as no adequate monitoring is possible. The reason for this is the potential for interactions that can potentiate consciousness-altering and respiratory depressant effects, for example with benzodiazepines mixed with intoxication by alcohol, liquid ecstasy or certain natural hallucinogens like psychedelic mushrooms, angel's trumpets among others. Patient monitoring equipment must be available and it must be ensured that treated patients are monitored for the duration of action corresponding to the medication administered.

According to expert opinion, fast-acting **benzodiazepines** that have a sedative, shielding and anti-anxiety effect are the medication of choice for patients with severe agitation, exhibiting imminent or manifest aggressive behaviors indicative of harm to oneself or others or exhibiting psychotic symptoms. Among other benzodiazepines, these include **diazepam, lorazepam or midazolam**, administered by the oral or i.v. route. An Australian guideline from 2006 on the emergency management of intoxication with stimulants makes the same expert recommendation [81]. Conventional doses and dosing intervals are presented in Table 7. The patient should not be sedated to unconsciousness. Clinical experience has shown that medication with benzodiazepines is sufficient in most cases given that the highly acute intoxication symptoms usually only last a few hours.

This protocol also applies if any suicidal ideations are present. For managing patients at risk of suicide and when inpatient therapy is indicated, reference is made to the pertinent Chapter (3.11) of the S3 Guideline/National Disease Management Guideline "Unipolar Depression" [85].

If sedation with the benzodiazepine proves ineffective and psychotic pictures involving hallucinations and delusions of grandeur in particular are present, it may be reasonable to administer an **antipsychotic** in addition to the benzodiazepine. In the first line, clinical experience has shown atypical antipsychotic drugs like oral olanzapine can be used. According to expert opinion, butyrophenones, like haloperidol given orally or parenterally, are only second-line medicines, namely, only to be administered if oral medication is not possible or if the patient responds insufficiently to the atypical antipsychotic. The reason for the cautious recommendation of butyrophenones lies in their potential acute side effects (early dyskinesia, above all) which can frequently affect adherence to further treatment. Moreover, clinical experience has shown that butyrophenones can exacerbate states of dysphoria and anxiety [86; 87]. Conventional doses and dosing intervals are similarly presented in Table 7.

Table 7 Sedatives in patients with methamphetamine intoxication

First-line: Benzodiazepines	
Substance	**Conventional doses and dosing intervals**
Diazepam	10 mg oral, repeat if needed after 30 min; alternatively: 2.5–5 mg i.v. bolus, repeat if needed after 5–10 min
Midazolam	5–10 mg oral (tablets or drops), repeat if needed after 30 min; alternatively: 2–2.5 mg i.v. bolus or i.m., repeat if needed after 5–10 min
Lorazepam	1–2.5 mg oral, repeat if needed after 60 min; alternatively: 2–4 mg i.v. bolus, repeat after 5–10 min
Add-ons: Antipsychotics	
Substance	**Conventional doses and dosing intervals**
Olanzapine	10 mg oral (orodispersible pills), repeat if needed after 60 min; alternatively: 5–10 mg i.m., repeat if needed after 120 min
Risperidone	2 mg oral (orodispersible pills), repeat if needed after 60 min
Second-line: Haloperidol	5 mg oral (tablets or drops), repeat if needed after 60 min; alternatively: 5–10 mg i.m., repeat if needed after 5–10 min
Mostly, high cumulative doses are to be expected.	
ECG monitoring required, cumulative doses after weighing efficacy against safety.	

Cerebral seizures are a frequent complication encountered in methamphetamine intoxication. According to expert opinion, benzodiazepines are the medication of choice. By contrast, antipsychotics can generally lower the seizure threshold; another reason why their use should be handled restrictively in methamphetamine-intoxicated persons.

Frequently, methamphetamine-induced psychosis resolves within days: if no other methamphetamine is taken, the body excretes the remaining amphetamine and the ability to sleep sets in again. For this reason and due to the potential side effects, the administration of any antipsychotic medication should be reappraised after three days at the latest and the necessity for it monitored continuously over the further clinical course [81; 86].

4.1.2.2 General/emergency medication

Airway management: In exceptional situations, it may be necessary to intubate severely intoxicated and/or hyperthermic patients and place them under general anesthesia. In such cases, anesthesia induction and maintenance with **propofol or barbiturates** have proven their merits. Due to the risk of rhabdomyolysis, muscle relaxation with a depolarizing muscle relaxant like succinylcholine is contraindicated. Non-depolarizing agents like **rocuronium or vecuronium** are recommended. The administration of bicarbonate to treat lactic acidosis is controversial and not recommended as a routine measure.

Management of hypertension: There are exceptional situations where refractory hypertension can be present despite sufficient medical sedation. This usually mandates treatment with vasodilating, peripherally acting antihypertensive medicines **(urapidil, prazosin, glyceryl trinitrate or sodium nitroprusside, phentolamine)**.

Management of dysrhythmias: Isolated tachycardia rarely requires pharmacological therapy. Adequate sedation and correction of abnormal electrolytes, dehydration, metabolic disorders etc. reduce the risk of life-threatening arrhythmias. According to current resuscitation guidelines, supraventricular tachycardia is treated with **adenosine bolus injections or calcium antagonists**. The administration of beta-blockers is a relative contraindication. In the event that beta-blockers are required, the ultra-short-acting beta-blocker **esmolol** should be used under appropriate cardiovascular monitoring.

Management of hyperthermia: Hyperthermia can usually be controlled by **external cooling measures** (cooling blankets, ice packs etc.). A body temperature of > 41 °C requires active intervention that aims to control increased muscle activity. Here, non-depolarizing neuromuscular blockers **(rocuronium, vecuronium)** are recommended; while aggressive sedation and adequate volume replacement are additionally important. Antipyretics are not relevant for managing methamphetamine-induced hyperthermia.

Management of electrolyte and fluid balance: As indirect data on fluid management are lacking (tachycardia and blood pressure are unreliable indicators), aggressive volume replacement should not be undertaken. Volume replacement should be administered with caution, conventionally using balanced electrolyte solutions. Hyponatremia can be avoided by not administering hypotonic solutions. In non-dehydrated patients, hyponatremia can be resolved with fluid restriction [88].

Management of rhabdomyolysis: Rhabdomyolysis should be treated with adequate volume replacement to ensure a urine output of > 2 mL/kg/h. Because it inhibits amphetamine elimination, urinary alkalinization should be avoided.

Other measures: Activated charcoal for methamphetamine intoxication is only useful in exceptional cases, as the drug has usually already been absorbed. Exceptions apply to body packers and stuffers. The standard dose is 1 g activated charcoal per 1 kg body weight, given together with a laxative (e.g. sorbitol). In exceptional situations, gastrointestinal decontamination (e.g. polyethylene glycol) may be helpful to treat body packers [89]. If large amounts of methamphetamine are found in the gastrointestinal tract and acute abdominal pain is present, immediate laparotomy may be indicated in exceptional cases.

Urinary acidification is not recommended because it may potentially worsen any acidosis.

The management of (suspected) acute methamphetamine intoxication is summarized in Table 8 (adapted from [86]).

Table 8 Management of suspected acute methamphetamine intoxication

- Watch out for clinical signs of acute toxicity
  - Chest pain
  - Rapid rise in body temperature
  - Seizures
  - Blood pressure rise / crisis

- Vital signs monitoring: Pulse, blood pressure, temperature, respiration rate, core body temperature, oxygen saturation

- Verbal de-escalation
  - Speak quietly and calmly
  - Low-stimulus environment (without objects that could be used as a weapon)
  - If possible, avoid physical fixation as it often causes further escalation

- Sedation, if necessary

- Hydration and regular monitoring

4.2 Qualified withdrawal treatment

4.2.1 General principles

4.2.1.1 Objectives, settings and elements

In withdrawal management, a distinction is made between "body detoxification" and "qualified withdrawal treatment" (cf. S3 Clinical practice guideline "Screening, diagnosis and treatment of alcohol-related disorders" [90]). The primary objectives of body detoxification are to alleviate withdrawal symptoms, prevent complications and long-term sequelae. The broader objective of qualified withdrawal treatment, as practiced in Germany and, for example, recommended by Australian guidelines, is to educate users about the effects of drug use (psychoeducation) and to reinforce their motivation to remain abstinent and/or to encourage them to undergo further treatment aimed at overcoming dependence and discovering and achieving other lifestyles ("recovery") [86]. Withdrawal management also incorporates diagnostics, counseling and, if necessary, initiation of treatment for physical and psychiatric sequelae and comorbidities, coupled with social counseling and the introduction of initial steps towards social rehabilitation. The key aspects of qualified withdrawal treatment are therefore the integration of somatic, acute psychiatric, psychotherapeutic and social work elements. Given the multidisciplinary nature of the treatments rendered, qualified withdrawal treatment takes longer than body detoxification, also because it allows time for ensuring adequate differential diagnosis, management of psychiatric and somatic sequelae and co-occurring diseases (see Section 2.3 Treatment planning).

Recommendations	Grade of recommendation
<u>4-7</u> Qualified inpatient withdrawal treatment should be offered to patients with methamphetamine dependence. Expert consensus Vote: 82%	⇈⇑

Recommendations	Grade of recommendation
4-8 Inpatient qualified withdrawal treatment should last at least 3 weeks, depending on individual needs. Expert consensus Vote: 100%	⇑⇑
4-9 The involvement of needs-specific self-help groups and family support should be an integral part of qualified withdrawal treatment. Expert consensus Vote: 100%	⇑⇑
4-10 Following the withdrawal phase, post-acute interventions should be offered seamlessly to patients in the form of ongoing treatment. Expert consensus Vote: 100%	⇑⇑

Clinical experience has shown that individuals with methamphetamine dependence have comparable treatment needs to heroin or cocaine addicts. During withdrawal, symptoms such as fatigue, poor concentration, sleep problems, irritability, restlessness and anxious-depressive mood swings extending to suicidality can become manifest in addition to cravings. Severe withdrawal symptoms can be expected to persist for at least a week and continue in a milder form for up to another two weeks at least [91]. Cravings persist for much longer and are indicative of a high risk of relapse, especially during outpatient treatment [92-94] (cf. Section 2.1 Symptoms).

Due to the very high relapse risk, the duration of qualified withdrawal treatment should be aligned along individual needs and continue beyond the resolution of acute withdrawal symptoms, aimed at achieving sufficient psychiatric, somatic and social stabilization for further treatment. According to clinical experience, treatment for at least three weeks is advisable and necessary, particularly in patients with high and regular substance use [91; 95]. In addition, persistent cravings observed are associated with a high relapse risk, particularly during outpatient treatment [92-94].

Besides the aforementioned elements, any qualified multimodal withdrawal treatment should include education about and referral to a self-help organization and encouragement to utilize the existing regional addiction help services (cf. Section 2.3 Treatment planning and 5.1 Care delivery structures in post-acute management). This includes family member education and counseling as well as other elements like topic-centered individual and group therapy, occupational therapy, physiotherapy, exercise therapy, relaxation methods and acupuncture. As a fundamental rule, the therapeutic attitude should be hallmarked by friendliness, calm, appreciation and respect towards the patient; it should be supportive and comforting, not confrontational or moralizing, while conveying reassurance and competence [95; 96].

4.2.1.2 Monitoring

Recommendations	Grade of recommendation
4-11 To verify that the treatment setting is drug-free, repeated drug tests ought to be performed. Expert consensus Vote: 100%	⇑

According to expert opinion, toxicological urine screening tests should be performed as part of qualified inpatient withdrawal treatment to ensure a drug-free treatment setting [95]. Checks (also of bags, clothing, body) primarily serve to protect other vulnerable patients from drug availability during inpatient withdrawal. As part of the basic therapeutic approach, they can also be used for monitoring and/or verification of outcomes. Since amphetamines are only detectable in urine tests for approximately three days, negative results at the end of inpatient treatment serve as proof of abstinence. For methodological aspects and basic principles to be observed when screening urine for drugs, please refer to Section 2.2 Diagnostics.

4.2.2 Pharmacotherapy

A systematic meta-analysis of pharmacological treatment options was undertaken when drawing up these practice recommendations. In total, 58 relevant publications were identified. However, only a few studies had looked at pharmacological approaches in the context of qualified withdrawal treatment for methamphetamine-dependent patients. Moreover, these studies showed significant methodological limitations (small patient numbers, high drop-out rates). There are significantly more studies on the treatment of cocaine or stimulant dependence in general. Furthermore, only a few studies focused on the phase of acute and/or withdrawal treatment. Hence, this chapter is limited in that there are only a few verified study results on methamphetamine withdrawal; a large number of the recommendations are based on expert opinion and extrapolations from studies on cocaine and stimulant-dependent patients. In other words, their transferability is unverified.

Info Box 2: Off-label use of medications

When making decisions about treatment, it is important to also be aware that none of the medications are approved for the treatment of methamphetamine dependence in Germany. Therefore, their use is deemed off-label. Requirements for the off-label use of medications are:

- Proven efficacy
- Favorable benefit-risk profile
- Lack of alternative drugs

A reasonable prospect for a positive treatment outcome must be founded in current scientific knowledge. Furthermore, there is a particular obligation to obtain informed consent. All patients need to be informed of the reasons why they are receiving an off-label drug and the potential liability consequences arising therefrom. Shared decision-making is required.

4.2.2.1   Antidepressants

Recommendations	Grade of recommendation
<u>**4-12**</u> If symptoms of anxiety, depression, fatigue and/or hypersomnia predominate during methamphetamine withdrawal, bupropion or a tricyclic antidepressant with stimulant properties, such as desipramine, may be used. Expert consensus (LoE 5) Vote: 93%	⇔
<u>**4-13**</u> An antidepressant with sedative properties may be used when sleep problems and/or restlessness predominate during methamphetamine withdrawal. Expert consensus (LoE 5) Vote: 93%	⇔

Evidence

There are only two small randomized, controlled trials on the use of antidepressants for withdrawal treatment in methamphetamine addicts. One trial involving 20 participants showed that **bupropion** was associated with a reduction in subjective methamphetamine-induced effects ("highs") and cue-induced craving, but had no effect on depression and anxiety [97]. Another study (n=31) showed that **mirtazapine** was not effective with regard to retention rates and accompanying symptoms, such as sleep problems, anxiety and depression [98-100].

The efficacy of **serotonin reuptake inhibitors** (SSRI) to alleviate methamphetamine withdrawal symptoms is unproven. Furthermore, there is a risk of serotonin syndrome, recognizable by a markedly increased rate of the side effects frequently described for SSRIs [101].

Likewise, there are no studies on **tricyclic antidepressants** (TCAs) for the acute treatment of persons suffering from methamphetamine dependence [102]. In persons with cocaine dependence, TCAs with stimulating properties such as **desipramine** are effective in treating withdrawal symptoms [103]. Since both the pharmacology and the acute and withdrawal symptoms of methamphetamine are similar to that of cocaine, expert opinion suggests that TCAs with stimulant properties might also be helpful for methamphetamine withdrawal.

Overall, data is limited, inconsistent and presumed to be very highly dependent on the samples examined (including duration and pattern of use) and the treatment setting [100; 104]. Hence, no clear recommendations can be given at present about a particular class of antidepressants as a whole or for one particular substance. If symptoms of anxiety, depression, fatigue or hypersomnia predominate during methamphetamine withdrawal, **bupropion** could be considered or TCAs with stimulating properties such as **desipramine**. The experts believe that an antidepressant with sedative properties can be tried whenever sleep problems and/or restlessness are the predominant symptoms. These recommendations refer to symptoms that occur during acute withdrawal. For the treatment of depressive symptoms in the context of co-occurring diseases, please refer to Section 6.4 Depression.

4.2.2.2 Antipsychotics

Recommendations	Grade of recommendation
4-14 High-potency antipsychotics ought not to be used for the acute treatment of methamphetamine-dependent patients to alleviate withdrawal symptoms. LoE 2 [98; 105-107] Vote: 86%	⇓
4-15 In methamphetamine-induced psychosis, an antipsychotic ought to be given as the drug of choice; the indication should be reviewed after six months at the latest. Expert consensus (LoE 5), based on [87] Vote: 100%	⇑
4-16 In methamphetamine-induced psychosis, an atypical antipsychotic ought to be preferred due to its more favorable side effect profile. LoE 2 [98; 105-107] Vote: 100%	⇑
4-17 Treatment of methamphetamine-induced psychoses with neuroleptics should be reviewed after six months and an attempt made to taper them off. Expert consensus vote: 100%	⇑⇑⇑

Evidence

There is no rationale for the use of high-potency typical antipsychotics to help alleviate withdrawal symptoms. Among the atypical antipsychotics (see Info Box 3), **aripiprazole** has shown no or only marginal benefit versus placebo in clinical trials [98; 105-107]. One study reported a worsening of methamphetamine craving on aripiprazole [106]. There are no studies on the treatment of withdrawal symptoms with sedative low-potency or atypical antipsychotics. Nevertheless, expert opinion suggests that medicines like **olanzapine** and **quetiapine** can confer benefit in the management of restlessness, tension or sleep problems during methamphetamine withdrawal.

> **Info Box 3: Definition of "atypical antipsychotics"**
>
> In this context, a differentiation is made between the older conventional or typical neuro-leptics (prototypically haloperidol) and the usually more novel agents which manufactur-ers attribute with a different mechanism of action than conventional neuroleptics (e.g. clozapine, olanzapine, quetiapine, aripiprazole). Atypical neuroleptics have a lower inci-dence of extrapyramidal side effects than typical neuroleptics. However, other side ef-fects like metabolic syndrome can predominate, particularly during long-term use. For simplicity and because the term has become accepted in the vernacular, drugs of this novel class—more heterogeneous in both their efficacy and side effect profile—will be referred to as "atypical neuroleptics" in this guideline.

Antipsychotics are specifically indicated when methamphetamine or amphetamine use leads to a **psychosis** that persists beyond the pharmacological effect of the drug. According to ICD-10 (F 15.5x) criteria, (meth)amphetamine-induced psychosis occurs immediately or with-in a few days after the most recent drug use and lasts for a few days to several weeks, where mild (residual) symptoms may persist for up to six months [53]. This cluster of psy-chotic phenomena can present in a similar way to those occurring as complications during the "high" phase, particularly involving psychoses with hallucinations and paranoia. Accord-ing to clinical experience and expert opinion, antipsychotics are the treatment of choice for methamphetamine-induced psychosis. Typical as well as atypical antipsychotics can be ad-ministered, with preference always given to the latter owing to their more favorable side ef-fect profile.

In one randomized controlled trial (RCT) on 58 patients with amphetamine psychosis, **olanzapine** and **haloperidol** showed similarly good efficacy. Whereas haloperidol caused significantly more acute extrapyramidal side effects and therefore had a higher drop-out rate, while olanzapine was associated with more frequent weight gain [108]. Another RCT on 80 patients with methamphetamine-induced psychosis showed that quetiapine and haloperidol at respectively lower doses showed comparably good efficacy and tolerability [109]. In an-other RCT, **risperidone** was superior to aripiprazole in reducing positive psychotic symptoms [110]. Finally, another randomized trial on 42 patients with methamphetamine psychosis showed comparable efficacy between **risperidone** and **aripiprazole**, although risperidone was better tolerated and, consequently, aripiprazole had a correspondingly higher drop-out rate [111].

Overall, the limited body of evidence permits no clear recommendations on the use of a par-ticular atypical antipsychotic at the current time. For the practical aspects of antipsychotic administration and the necessary follow-ups, including drug monitoring, please refer to the S3 Guideline "Schizophrenia" from 2006 [112]. Do note that the guideline's validity has ex-pired, with a revised version announced for 2016 or 2017.

There are no scientific studies on the optimal duration of treatment with antipsychotics for methamphetamine-induced psychosis. According to expert opinion, if the patient responds positively, antipsychotic medication should be reviewed after six months at the latest and, at best, the medication tapered off. If further treatment is still required, the diagnosis of meth-amphetamine-induced psychosis should be reviewed (the differential diagnosis can consider psychosis from the group of schizophrenia and schizophrenic disorders); see Chapter 6 Co-occurring organic diseases and mental health disorders.

4.2.2.3   Benzodiazepines

Recommendations	Grade of recommendation
<u>4-18</u> Benzodiazepines may be administered for qualified inpatient methamphetamine withdrawal treatment to de-actualize self-harm or harm to others or to treat severe anxiety symptoms. Expert consensus (LoE 5) Vote: 93%	⇔
<u>4-19</u> In methamphetamine-induced psychosis, benzodiazepines may be administered temporarily as add-on to an antipsychotic. Expert consensus (LoE 5) Vote: 100%	⇔
<u>4-20</u> Benzodiazepine treatment of methamphetamine-dependent patients should be time-limited and given at the lowest possible dose, considering the potential for benzodiazepine addiction. Expert consensus Vote: 100%	⇑⇑⇑

Evidence

There are no scientific studies on benzodiazepines for withdrawal management of methamphetamine addiction or the treatment of methamphetamine-induced psychosis. Nevertheless, expert opinion states that benzodiazepines may also become necessary during withdrawal treatment after cessation of intoxication-related agitation, e.g. if psychotic symptoms persist and antipsychotic medication is still not effective or for de-actualization of self-harm or harm to others, e.g. in severe depressive mood swings or in acute anxiety. Benzodiazepines can also lead to dependence. Therefore, the dose should be as low as possible and treatment duration limited. The general use of benzodiazepines for uncomplicated methamphetamine withdrawal does *not* seem sensible.

4.2.2.4 Stimulants

Recommendations	Grade of recommendation
4-21 Sustained-release dexamphetamine may be used for the inpatient treatment of methamphetamine-dependent users to alleviate withdrawal symptoms in justified isolated cases once other withdrawal treatment options have failed. LoE 2 [98; 102; 113] Vote: 80%	⇔
4-22 If dexamphetamine is used to alleviate withdrawal symptoms during inpatient withdrawal treatment, the dose should be titrated individually and then gradually tapered off so that the drug is discontinued by the time of discharge. Expert consensus (LoE 5), based on [98; 102; 113] Vote: 93%	⇑⇑
4-23 Dexamphetamine should not be given in outpatient settings. Expert consensus Vote: 93%	⇓⇓

Evidence

A small RCT on 49 methamphetamine-dependent persons receiving sustained-release **dexamphetamine** versus placebo investigated the reduction in use after three months. The average dose at the end of the "stabilization phase" (withdrawal phase) was 80 mg/day. Although the primary endpoint did not differ significantly versus placebo, the secondary endpoint showed a reduction in withdrawal symptoms during the "stabilization phase". The study had some limitations (secondary endpoint, small case number, high drop-out rate of 53%) [98; 102; 113].

Another small RCT on 60 subjects with methamphetamine dependence showed that sustained-release dexamphetamine at a dose of 60 mg/day was just as well tolerated as placebo (primary outcome measure: safety) [114]. No difference in use was found in the secondary outcome measures, although there was a significant reduction in withdrawal symptoms (as per Amphetamine Withdrawal Questionnaire, AWQ) alongside a significant reduction in cravings (measured on a visual analogue scale). The clinical relevance of the effects observed seems limited, e.g. a significant difference in the severity of withdrawal by approx. 3 points (score of 15 versus 12) occurred only at 2 of 8 assessment time points. Also, significant craving reduction was documented at 2 of 8 assessment time points only. This study has comparable limitations (secondary outcome measures, small case numbers), but the same low drop-out rate in both groups (each 13%).

Due to the limited evidence, no general recommendations can be made at present. Because of the high drop-out rate in individuals with methamphetamine dependence during withdrawal, it would seem justified to attempt treatment with off-label dexamphetamine in qualified inpatient withdrawal treatment settings, e.g. if the individual has already dropped out of withdrawal treatments. In such cases, sustained-release dexamphetamine should be individually titrated and tapered off again after three weeks at the latest. It is important to note that dexamphetamine is a federally controlled narcotic (under the German Narcotics Act (BtMG) and also has its own potential for abuse. Therefore, it should not be prescribed at discharge from inpatient treatment or provided for outpatient use. Studies on long-term treatment with dexamphetamine have consistently shown that it has no superiority over placebo (see Chapter 5.3 Pharmacological post-acute therapy).

General instructions for off-label use are given in Info Box 2.

> **Info Box 4**
>
> Sustained-release dexamphetamine is a federally controlled narcotic (BtMG). In Germany, it is approved for the treatment of children and adolescents with ADHD not sufficiently controlled by other medicines. The treatment of methamphetamine-dependent patients with sustained-release dexamphetamine constitutes off-label use. Regarding the requirements for off-label drug treatment see, Info Box 2.

Concerning other stimulants, there are either no studies available on the acute treatment of methamphetamine-dependent patients (methylphenidate), or the studies available have either shown no or only marginal advantages over placebo. A number of small RCTs with modafinil showed no effect or clinically doubtful improvements in some cognitive functions [115-119].

4.2.2.5 Other pharmacological agents

Recommendations	Grade of recommendation
4-24 Acetylcysteine may be considered if severe craving is a predominant symptom during methamphetamine withdrawal. LoE 2 [120] Vote: 92%	⟺

Evidence

A small (n=32), but otherwise methodologically well-designed crossover, randomized, placebo-controlled trial showed a positive effect of **N-acetylcysteine** on craving suppression during the acute treatment phase with good safety. The dose was 600 mg in week 1 and 1200 mg in week 2 to 4, followed by a three-day washout period [120].

In another very small randomized, placebo-controlled trial on 18 participants, suppression of some subjectively positive methamphetamine-induced effects (attention, concentration, psychomotor performance) was shown with the calcium channel antagonist **israpidine**, which, however, was poorly tolerated during methamphetamine withdrawal [121]. Another small randomized, placebo-controlled study (n=30) showed blunted cue-induced cravings and some attenuated hedonic subjective effects of methamphetamine with **naltrexone**. This trial not only had a small sample size, but also other methodological flaws [122]. Further RCTs with **topiramate**, **ondansetron** and a combination drug (**flumazenil and gabapentin** or **N-acetylcysteine and naltrexone**) showed no advantages over placebo [123-126].

One very small placebo-controlled RCT (n=26) showed a positive effect of **varenicline** on the reaction time of patients who demonstrated significant slowness during the withdrawal phase as well as an attenuation of subjectively positive methamphetamine-induced effects. Otherwise, no effects on other cognitive impairments or on craving were found [127; 128]. The power of this study is very limited due to its significant methodological flaws (small sample size, single-blind design, conflicts of interest). Two additional small placebo-controlled RCTs showed no improvement in cognitive function with **rivastigmine**, although both study populations showed no cognitive deficits at baseline [129; 130].

Based on these trials, only a "can recommendation" can be given currently for N-acetylcysteine, which is well tolerated for severe craving during withdrawal treatment. There is preliminary evidence that N-acetylcysteine may have a beneficial effect on craving and the risk of relapse [131-134]. The exact action mechanism is unclear although it is thought to be linked to a modulation of glutamatergic transmission [135]. Continuation of the medication in the post-acute phase as a therapeutic trial seems possible due to its very good tolerability.

4.2.2.6 Synopsis: Symptom-oriented approach

The recommendations for pharmacological management during acute therapy of methamphetamine dependence are summarized according to target symptoms in Table 9 "Symptom-oriented approach" below.

Table 9 Symptom-oriented pharmacological treatment

Symptom	Therapeutic options	Recommendations
Methamphetamine intoxication with acute agitation or markedly **fluctuating state with unpredictable responses**	Once psychotherapeutic de-escalating measures have been exhausted, **benzodiazepines** are the treatment of choice, as soon as adequate provisions for intervention and monitoring are in place	4-5 ⇑⇑
Depressive-anxious symptoms with exhaustion and/or hypersomnia during methamphetamine withdrawal	Bupropion or a drive-increasing TCA, such as desipramine	4-12 ⇔
Sleep disturbances and/or agitation during methamphetamine withdrawal	As the drugs of choice, experts recommend **sedating antidepressants or low-potency sedating antipsychotics** Avoid hypnotics!	Antidepressants: 4-13 ⇔ Low-potency sedating antipsychotics: see Section 4.2.2.2
Methamphetamine-induced **psychotic symptoms**	**Atypical antipsychotics** Benzodiazepines, added as needed, but for a short time only Reappraise the indication and discontinue within 6 months if possible	4-16 ⇑ 4-19 ⇔
Acute depressive and/or anxious state with endangerment to self or others during methamphetamine withdrawal	**Benzodiazepines** as needed, for a short time only	4-18 ⇔
In case of multiple unsuccessful prior withdrawal attempts	**Dexamphetamine** only in individual cases & in an inpatient setting Taper to off within 2 weeks	4-21 ⇔ 4-22 ⇔
Marked **craving** during methamphetamine withdrawal	**Acetylcysteine** as needed, 600–1200 mg/day	4-24 4-24⇔

4.2.3   Psychotherapeutic interventions

4.2.3.1   Qualified withdrawal treatment

Recommendations	Grade of recommendation
<u>4-25</u> A patient with a methamphetamine-related disorder should be offered psychotherapeutic interventions such as psychoeducation and motivational interviewing in an inpatient setting as part of qualified multimodal withdrawal treatment. Expert consensus (LoE 5) Vote: 100%	⇑⇑⇑
<u>4-26</u> In the early stages of acute treatment of methamphetamine dependence, other psychotherapeutic techniques may be offered as part of qualified withdrawal management with coordinated interventions. Expert consensus (LoE 5) Vote: 100%	⇔

Evidence

Against the backdrop of a biopsychosocial understanding of the disease, psychotherapeutic intervention techniques are indispensable to the treatment of methamphetamine-related disorders. This applies not only to the post-acute management, but also to the acute phase and in the early stages of qualified withdrawal treatment. The objective is not only to encourage users by means of psychotherapeutic elements to initially deal with their addiction problem, but above all to motivate them to take advantage of addiction help services over the longer term in order to achieve abstinence at best or at least turn to less risk-burdened types and patterns of use. The possibilities and limitations of psychotherapeutic methods are explained in greater detail in Chapter 5 Post-acute management. When viewed longitudinally, it is the complex, tightly coordinated packages of multiple interventions that are more promising than the sum of distinct interventions [86]. Thus, acute and long-term measures should be combined in order to successively build up brief interventions and long-term psychotherapeutic measures during psychotherapeutically supported withdrawal ("qualified withdrawal treatment"). The choice of a specific psychotherapeutic method itself is less decisive than ensuring that suitable therapeutic elements are introduced early in the phase of acute treatment at all.

To date, no validated findings are available from studies on the individual psychotherapeutic methods and techniques administered as part of the acute treatment of methamphetamine-dependent persons. Hence, these recommendations are based on expert consensus and extrapolations from studies on post-acute management; i.e. they are not guaranteed to be generally transferable. Psychotherapeutic methods like psychoeducation and motivational interviewing can be pivotal to inpatient qualified multimodal withdrawal management:

- *Psychoeducation*: The provision of interdisciplinary information, education and training sessions in groups or individually on the symptoms and management of the disease aimed at improving an understanding for the disease, identifying early warning signs, training the user's ability to implement symptom-oriented coping strategies, reinforce adherence and foster health competency. Psychoeducation is designed to lower the risk of relapse and relies on disorder-specific manuals [136].

- *Motivational treatment:* The measures for reinforcing abstinence motivation are based on the experiences gathered from users of other illegal drugs and founded on the principles of motivational interviewing [137].

Further details on these and other methods – including the current evidence – are summarized in Chapter 5 Post-acute management.

Elements of other psychotherapeutic methods can be deployed early in qualified withdrawal treatment. (Cognitive) behavioral therapy, contingency management, methods for increasing self-efficacy expectations and systemic therapeutic approaches deserve particular mention.

Irrespective of the method selected, the following principles apply to the psychotherapeutic management of withdrawal:

- Contact at close intervals;

- Building a therapeutic relationship aimed at maintaining relationship constancy

- Measures for defusing anxiety, particularly in the presence of psychotic symptoms (low-stimulus environment, non-confrontational techniques, helping the user gain or stay in touch with reality).

The focus of the psychotherapeutic interventions varies as a function of the phase of the qualified withdrawal treatment. For example, the (first) interview after the intoxication or withdrawal syndrome has resolved should specifically revolve around establishing the goals of therapy with regard to use and psychosocial exigencies. Over time, the focus should be on topics like harm mitigation measures and relapse prevention (see Chapter 9 Harm reduction). Finally, critical emphasis should be placed on motivational work to encourage the user to take longer-term advantage of help and support services, thereby smoothing the transition into the appropriate post-acute management.

5   Post-acute management

Wolf-Dietrich Braunwarth, Roland Härtel-Petri, Willem Hamdorf, Timo Harfst, Heribert Fleischmann, Peter Jeschke, Stephan Mühlig, Jeanine Paulick

Post-acute management is distinct from the narrowly time-limited treatment of intoxication and withdrawal symptoms. It applies both to individuals who are currently abstinent and current users. Given that cerebral functions take a long time to recover in chronic users, the boundaries between the phases of post-acute management and longer-term relapse prevention are less sharply delineated.

5.1   Care delivery structures in post-acute management

Recommendations	Grade of recommendation
5-1 Indications for the different settings of post-acute management (including weaning) ought to be made individually for each patient. Expert consensus vote: 100%	⇑
5-2 Patients with methamphetamine-related disorder ought to be advised to set methamphetamine abstinence as the primary goal of their therapy. Expert consensus vote: 100%	⇑
5-3 In patients who are currently unemployed, it is preferable to offer settings that foster re-integration back into the workforce. Expert consensus vote: 100%	⇑
5-4 Soon after post-acute treatment (including weaning), coordinated addiction-related care ought to be delivered for at least a year to achieve sustainable abstinence stabilization and prevent relapse. Expert consensus vote: 100%	⇑

Recommendations	Grade of recommendation
5-5 The involvement of needs-specific self-help groups and family support should be an integral part of all services offered. Expert consensus vote: 100%	⇑⇑⇑
5-6 Participation-oriented support and assistance services like outpatient supervision, accommodation services and outpatient sociotherapy ought to be considered whenever patients are observed to have problems with structure and daily routine and appear incapable of solving these problems on their own. Expert consensus Vote: 91%	⇑
5-7 Social work-related support and supervision should always be considered when other individuals in need of protection (i.e. children, relatives, partners) could be affected by a potential relapse (see also Section 7.2 Methamphetamine abuse in the family context). Expert consensus Vote: 100%	⇑⇑⇑

5.1.1   Possible settings for post-acute management

After detoxification or qualified withdrawal, immediate post-acute management should be offered in order to prevent any relapse events and drive the convalescence process. Many post-acute management settings orient themselves on achieving abstinence. Patients with methamphetamine-related disorder should be advised to set methamphetamine abstinence as the primary goal of their therapy.

Post-acute management can be delivered either as outpatient, all-day outpatient or semi-inpatient or inpatient withdrawal treatment; it can also consist of adaptation therapy (second phase of medical rehabilitation) or of other forms. These include but are not limited to care by a physician under the statutory health insurance scheme or outpatient guideline-driven psychotherapy and psychiatric follow-up treatment on an inpatient or outpatient basis. Other post-acute interventions comprise services offered by sociotherapeutic centers for suffers of severe addiction-related disorders, integration aid programs, low-threshold aid services, counseling services alongside interventions for work promotion and occupational rehabilitation (see also 2.3 Treatment planning).

Since the peculiarities of the German healthcare system are hardly depicted in the international literature if at all, particularly with regard to the complex setting of post-acute treatment modalities, the German S3 Practice Guideline on "Alcohol-related disorders" is referenced for

an appraisal of post-acute treatment forms [90]. The experts believe that the care structures described therein are fundamentally transferrable to methamphetamine users.

5.1.2 Stakeholders and liaison management

Under German social law, affected persons have defined entitlements to many treatment-relevant help resources, enabling them to avail themselves of an array of counselling and support options offered, for example, by social services or (often jointly run) service and counselling centers of the payer organizations. These basic entitlements under social law are set forth in the German Social Code books (SGB I–XII) and other social legislation. Care delivery processes are always bound to certain structures (institutions) and settings (outpatient, semi-inpatient, inpatient) and delivered by different professional groups (physicians, psychotherapists, psychologists, social education specialists etc.). After a delineated medical addiction intervention (e.g. withdrawal treatment, weaning treatment, psychotherapy), funding of a sustainable treatment outcome is often necessary, in some cases extending over many years. This care can be delivered by general practitioners, specialists and outpatient addiction counseling and addiction treatment centers, working in close and mutual collaboration and, if possible, getting the affected users involved in a self-help group. Sustainable care is flanked by the active supervision of those affected in their home environment, e.g. through regular contacts, risk prophylaxis and promotion of a healthy lifestyle, as well as fast help and referrals in the case of relapses (see also Chapter 8 Relapse prevention).

The care delivered to individuals with methamphetamine-related disorder (and usually co-occurring problems) is based on a complex system of varying structures and processes. Thus, liaison management, i.e. control and coordination of the delivery of care services on both the institutional and individual levels is pivotally important for ensuring a continuity of care. As part of care organization, liaison management may be regarded as the targeted communication and governance needed to ensure the continuity of care. It aims to connect, interlink and coordinate the many different interventions in the most sustainable manner.

5.1.3 Caring for users with co-occurring mental disorders

A multidisciplinary S3 Guideline "Psychosocial therapies in severe mental illness" was developed by the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). It targets individuals suffering from severe mental disorders who are impacted by the sequelae of a serious and protracted mental illness. The recommendations therein should also be applied to the care of individuals with methamphetamine-related disorders (see also Chapter 6 Co-occurring organic diseases and mental health disorders) [71].

5.1.4 Forms of post-acute management

5.1.4.1 Weaning (medical rehabilitation)

Recommendations	Grade of recommendation
5-8 Patients with methamphetamine-related disorder should be educated about the options for vocational and medical rehabilitation and receive the appropriate referrals. Expert consensus (LoE 5) Vote: 100%	⇑⇑⇑

5.1.4.1.1 Goals and elements

The post-acute management of methamphetamine-dependent persons mostly involves medical rehabilitation to wean them off illicit drugs. Besides preserving, improving or reinstating the functional and performance capability of addiction sufferers, another objective is to promote their participation in the workforce and society. Medical rehabilitation interventions rendered on drug-dependent persons are overwhelmingly carried out under the auspices of the German statutory pension insurance. The principles of rehabilitation are anchored in the German Social Code books (mainly SGB IX [Rehabilitation and participation of persons with disabilities] and SGB VI [Statutory pension insurance] as well as SGB V [Statutory health insurance, mainly for young patients who do not meet the conditions for SGB VI under the insurance laws]).

Weaning takes place as a multimodal form of treatment. It encompasses interventions by physicians, psychotherapists, sport and exercise therapists, social workers and occupational therapists as well as health training elements [138]. In addition to the abstinence-oriented management of the addiction itself, special emphasis is placed on the treatment of the co-occurring physical, mental and social illnesses and on re-integration into the workplace. Great importance is also placed on relapse prevention. In Germany, most weaning interventions take place on an inpatient basis. Special treatment needs and co-occurring disorders are described in Chapter 6 Co-occurring organic diseases and mental health disorders and 7 Special situations.

5.1.4.1.2 Settings

Basically, withdrawal treatment can be administered on an outpatient, all-day outpatient or semi-inpatient or inpatient basis. It may also consist of adaptation therapy (second phase of medical rehabilitation). Inpatient withdrawal treatments for drug-related disorders last up to 26 weeks and brief treatments last between 12 and 16 weeks. In patients with drug-related disorders all-day outpatient rehabilitation usually takes 16 weeks. Outpatient addiction rehabilitation interventions are administered over a longer duration of up to 18 months [138; 139]. The aim of combination treatment (with inpatient and outpatient elements) is to optimally utilize the advantages of the individual types of services, personalized to the patient's needs within a rehabilitation process [140]. In drug-dependent persons, inpatient rehabilitation takes up the major proportion of benefits provided. Within the system of psychosocial help services,

the aim is to refer patients with a methamphetamine-related disorder to withdrawal treatment conducted by:

- Addiction counseling centers;
- Withdrawal treatment;
- Specialist outpatient clinics;
- Medical and psychological psychotherapists;
- Company-based social services;
- Private-practice physicians.

5.1.4.1.3   npatient or outpatient? Decision-making criteria

The decision as to whether an inpatient or outpatient rehabilitation is more suitable for achieving the rehabilitation objective in the individual case is predicated on sufficient knowledge being available about the insured party, their motivation, their social situation, their previous clinical course and their current physical and mental condition. Thus far, these facts have usually emanated from the differential diagnosis report drawn up by a counselling center/specialist outpatient clinic (e.g. statutory "social report") and the medical records. In many instances, a seamless transition from withdrawal treatment is necessary, e.g. by referral directly from withdrawal to weaning treatment. The preeminent criteria to be weighed into the differential decision about outpatient or inpatient treatment are [140]:

- Severity of the bio-psycho-social disorders;
- Nature of the addict's social environment in terms of its exerting a supportive function;
- Occupational integration of the addict;
- Existence of stable living circumstances;
- Capability of the rehabilitation candidate to participate regularly, proactively and adhere to the therapy regimen;
- Capability to achieve and maintain abstinence;
- Duration and intensity of the drug dependence;
- Estimation of the rehabilitation candidate and of the supervising addiction counseling center/specialist outpatient clinic.

In practice, the complex interwovenness of the aforementioned criteria frequently makes it difficult to establish an unequivocal differential diagnosis. Therefore, the special aspects of each individual case must always be considered. Pursuant to Section 35 of the German Narcotics Act (BtMG), drug-dependent insured parties who are mandated to undergo therapy will receive rehabilitative treatment (usually on an inpatient basis) at an approved facility. Notes on indication criteria and assignment to treatment forms can be found in Section 4.3 of the S3 guideline "Psychosocial therapies in severe mental disorders" which, itself, is transferrable to persons affected by methamphetamine-related disorders [71].

5.1.4.1.4   re-integration

In Germany, a follow-up on patients from the inpatient drug weaning treatments exemplified the particular difficulties inherent to re-integrating patients with methamphetamine-related disorder back to gainful employment. One year after completing withdrawal treatment, there continued to be a high proportion of persons receiving unemployment benefits (in German: ALG-II). In the year after completing withdrawal treatment, many rehabilitation candidates who were abstinent from their addictive substance were still receiving unemployment benefits or were "without gainful employment" [141]. This contrasts with the currently good chances for placement in a traineeship or job. As part of giving stronger weighting to gainful employment in medical rehabilitation, more emphasis should be placed on improving job re-integration. The German program titled "Vocational orientation in the rehabilitation of persons with substance dependence" (BORA) has already established itself as an integral component in withdrawal therapy at several specialized clinics [142]. Among other features, the focus here is on the close cooperation between employers, the state-run employment agencies and job centers.

5.1.4.1.5   Withdrawal in patients with methamphetamine-related disorder

A survey of specialized clinics across a variety of federal states showed that the number of patients with methamphetamine-related disorder undergoing inpatient drug rehabilitation has grown in the past 10 years. Particular aspects like younger age, higher female proportion and cognitive deficits in methamphetamine-dependent patients were highlighted [143]. The great importance of co-occurring mental disorders and their connection to the management of addictions is discussed in Chapter 6 Co-occurring organic diseases and mental health disorders.

The efficacy of inpatient abstinence-oriented drug withdrawal treatment has been proven in several cross-institutional follow-up surveys [144]. An analysis of discharge letters on a total of 1,761 patients from different drug withdrawal clinics showed that patients with stimulant-related disorder (ICD-10 Code F15) as primary diagnosis fully completed inpatient withdrawal treatments with a greater frequency than a comparator group of patients using other drugs [145].

A one-year standardized follow-up survey collected data on the addictive substance abstinence and employment status of former methamphetamine-dependent patients one year after completion of the inpatient withdrawal treatment; the data were classified according to main addictive substance [141]. The clinical courses in methamphetamine-dependent patients was compared those of persons dependent on other drugs. Methamphetamine-dependent patients who participated in the follow-up survey scored at least exactly as high as the group of the other drug-dependent patients in the hospital follow-up survey [141] (analysis adapted from: German Society for Addiction Research and Treatment (Deutsche Gesellschaft für Suchtforschung und Suchttherapie e. V. 1992, DGSS 3 [146]; abstinent a year after discharge: Methamphetamine 39.3%, other drugs 27.2%). Specifically, methamphetamine-dependent patients completed withdrawal treatments with a greater frequency, which can be considered a positive predictive factor for persistent abstinence [141]. In the hospital follow-up survey (n=1.275) conducted by "Sucht e. V.", a professional addiction association in Germany, similar abstinence rates were collected on drug-dependent patients one year after discharge as in the aforementioned study [144].

International data confirm the efficacy of inpatient treatment. In a study from Thailand, the efficacy of an intensive inpatient therapy was compared to an outpatient model. Six months after discharge, the relapse rates were 18.6% and 21%, respectively [147]; to read more, see also Section 5.2.2 Post-acute psychotherapy of methamphetamine-related disorder.

One analysis of natural history interviews of 350 randomly selected subjects with methamphetamine-related disorder in the United States and response rates of over 75% found a relapse rate of 61% in the first year after discharge from treatment. Another 14% relapsed in subsequent years. Significant relapse protective factors proved to be longer treatment duration and participation in self-help and additional substance-use disorder treatment during the abstinence period [148]. These data underscore the need for intensive follow-up measures, given the relapse risk being highest within the first weeks after completing withdrawal treatment [144]. Furthermore, the great importance of self-help became clear. However, the widespread use of methamphetamine – across rural regions among other places [149] – makes referrals to individualized follow-up rehabilitation treatments particularly difficult due to the care provision structure. It is necessary to improve networking of the existing and build up newer follow-up care options.

5.1.4.2 Other forms of post-acute management

A number of sophisticated systems for addiction help services and care provision in Germany have been developed over the past decades. The objective has been to deliver the different counselling, treatment and intervention options with high quality and in an indication-related, needs-appropriate and patient-oriented way. More detailed explanations of this can also be found in Chapter 8 Relapse prevention.

There are multiple post-acute management options alongside the acute treatment of individuals with methamphetamine-related disorder in psychiatric and general hospitals. When covered by the statutory health insurers, post-acute management takes place

- Under the care of statutory health insurance physicians and psychotherapists as well as
- At psychiatric hospitals and the outpatient departments of psychiatric institutions.

To date, there has been a paucity of evidence-based scientific literature on other post-acute intervention models. That said, it is exactly those services codified in social legislation that reflect the real care given to individuals with methamphetamine-related disorders in Germany:

- The various counselling services offered as other forms of post-acute management subsidized by the municipalities and federal states should also be mentioned: Addiction counseling centers, psychosocial counselling centers, counselling at schools and parenting counselling centers as well as counseling by youth services agencies and the judicial authorities.
- Low-threshold facilities offer survival help services, including medical care funded by the communal and federal governments.
- Social rehabilitation within the occupational integration services comprises social therapy, assisted living, educational opportunities to obtain school-leaving certificates along with occupational, qualificational, educational, employment and self-help services. These are funded by the supra-regional payers of the social welfare system and the German Federal Employment Office.

- Transitional institutions (sociotherapeutic centers) with therapeutic elements as funding agencies of the supra-regional payers of the social welfare (integration aid) are particularly indicated for treating chronic multiply-damaged addicts, polyvalent addicts or patients with serious co-occurring mental disorders.

- Another key segment of care provision is the funding of participation in the workforce for unemployed drug-dependent persons, etc. as provided by subsistence provision centers, job centers and the Federal Employment Office. If applied for properly, occupational reha-bilitation measures are also possible.

5.2 Psychotherapeutic interventions

5.2.1 Introduction

Psychotherapeutic interventions play a pivotal role in both outpatient and inpatient withdrawal management of substance-use disorders and are accordingly emphasized in virtually all pertinent guidelines and treatment recommendations on addiction therapy [71; 90; 150]. The clinical practice in Germany, outpatient and inpatient addiction help is chiefly provided by addiction therapists and counselors with specialization and qualifications in social pedagogy or sociotherapy [140; 143-145]. This contrasts with the rather subordinate role currently played by the treatment of substance-use disorders given by psychologists or psychotherapists administering guideline-driven outpatient psychotherapy. That said, there is a discrepancy here between the evidence primarily relating to psychotherapeutic methods and the reality of care as provided by addiction help services that is oriented along sociotherapeutic or social counselling. Nevertheless, addiction therapists not licensed as psychologists or psychotherapists will apply the pertinent psychotherapeutic methods and intervention techniques that are the subject of this chapter.

The term "psychotherapeutic interventions" subsumes a number of psychotherapeutic measures, methods and treatment techniques designed to achieve sustained abstinence from substance abuse or to markedly reduce use to a controlled level (< 50%). This includes techniques that are integrated components of comprehensive therapy services offered along with independently interventions administered. These do not necessarily involve psychotherapeutic interventional methods in the sense of guideline-driven psychotherapy. Such interventions are administered both alone as well as combined with pharmacotherapy.

Despite the high prevalence rates and the meanwhile 20 years of therapeutic practice in the USA, the body of international evidence on the efficacy of psychotherapeutic interventions during withdrawal and withdrawal treatment for methamphetamine-related disorders (dependence or abuse) is comparatively limited.

A systematic search of the evidence in the pertinent databases produced a total of 26 relevant RCTs on psychotherapeutic methods and three studies on combined treatment methods relating to methamphetamine withdrawal/weaning therapy (see the chapter on Methodology as well as the guideline report at www.crystal-meth.aezq.de). To date, no systematic reviews by the Cochrane Collaboration or any other systematic meta-analyses have become available on the efficacy of psychotherapeutic interventions in the management of methamphetamine-related disorders. All identified studies selected a reduction in methamphetamine use as the main goal of therapy and primary endpoint.

None of the studies explicitly pursued abstinence-oriented treatment goals, but only reported (temporary) abstinence as a side effect of therapy or as a secondary endpoint.

To enumerate, clinical efficacy studies were identified on the following interventional methods for the psychotherapeutic post-acute management of methamphetamine dependence:

- Psychoeducation;

- Motivational interviewing (MI);

- Motivational enhancement therapy (MET);

- Contingency management (CM);

- Cognitive behavioral therapy (CBT);

- Acceptance and commitment therapy (ACT);

- MATRIX and FAST;

- Stepped-care approaches;

- Community-based approaches.

Several papers pay specific attention to the family and family functions as resources for psychotherapeutic management [151-156].

5.2.2   Post-acute psychotherapy for methamphetamine-related disorder

Recommendations	Grade of recommendation
5-9 Regardless of whether they are diagnosed with dependence or not, every methamphetamine user should be offered needs- or motivation-centered psychotherapeutic counseling and treatment services. Expert consensus (LoE 5) Vote: 100%	⇑⇑⇑
5-10 According to the stepped-care approach, this ought to range from low-threshold education, psychoeducation and (motivational) counseling services extending through behavioral therapeutic treatments (e.g. contingency management) up to multimodal use reduction and withdrawal treatment programs in an outpatient or inpatient setting. LoE 3 [157] Vote: 75%	⇑
5-11 If willing, methamphetamine users meeting the diagnostic criteria for a substance-related disorder ought to be offered and referred to psychotherapeutic services. LoE 2 [147; 158; 159] Vote: 91%	⇑

Recommendations	Grade of recommendation
5-12 Depending on their willingness to undergo such treatment and its availability, methamphetamine users meeting the diagnostic criteria for a substance-related disorder ought to be offered behavioral therapy or multimodal methamphetamine-specific regimens aimed at use reduction or weaning. LoE 2 [147; 158; 159] Vote: 100%	⇑

5.2.2.1 Psychoeducation

Method

Psychoeducation comprises systematic, didactic-psychotherapeutic measures that are suitable to educate patients and their family members about the drug (pharmacological mechanisms of action, dependence potential, harm risks etc.), the resulting substance-use disorder and its management, to promote an understanding for the disease and a personally responsible handling of the disorder and to support them in dealing with the illness. Psychoeducational methodology is essentially based on psychological learning theories and behavioral therapy. Within the realm of psychotherapy, psychoeducation refers to the treatment component that focuses on the active transfer of information, the exchange of information among those affected and their interaction with the general aspects of the disease [160].

Psychoeducational measures can be administered in the individual or group setting and comprise different methodological-didactic tools (lectures, group discussions, dialogues, demonstrations, behavioral exercises and role-playing). Primarily, verbal forms of communication are used as the medium, although written material are possible like those used in bibliotherapy (e.g. self-help manuals, further reading materials, brochures etc.), videos and other visual aids (e.g. graphical displays of the vulnerability stress model of schizophrenia, anatomic models for illustration pulmonary function in asthma) or the Internet. In most treatment approaches, psychoeducational elements are used as effective adjuvants in later treatment phases as well.

The decisive factor critical to a positive treatment outcome is that the competencies discussed or practiced in the therapeutic setting are incorporated into the patient's daily routine, aimed at ensuring transferal, independent implementation and generalization effects. What is important is "helping achieve self-help" in general, while preventing relapses and making it easier for sufferers to deal with future setbacks in particular.

Self-documentation (e.g. keeping a diary) has frequently been employed successfully for this purpose. For years, psychoeducational interventions and patient training sessions have been internationally recognized in the respective treatment guidelines and broadly established in practice as an integral part of treating chronic organic diseases [161].

Evidence

One randomized, controlled trial (RCT) from Iran is available on the efficacy of psychoeducation in methamphetamine-dependent patients (n=190) and family members during withdrawal treatment [152; 162]. The subjects were randomized to three study arms (educational intervention for methamphetamine users, for their family members and one control group): The study group participants received a family-centered educational intervention over nine sessions. The clinical endpoints were a) health-promoting lifestyle and b) health-related quality of life (QoL). The retention rate was 92%. Overall, the before-and-after comparison showed a significant improvement in lifestyle and QoL across all subscales in both users and family members. Moreover, a significant improvement in social support and QoL over the course therapy was observed in the intervention groups, but not in the control group. The authors additionally found a positive relation between social support and QoL.

The validity of the results is lessened by gaps in the information reported on sample, conduct of the intervention and limitations.

5.2.2.2   Therapy motivation and preparation

Method

The method of *motivational interviewing (MI)* was developed by Miller and Rollnick for addiction counseling and therapy [137]. It is based on empirical tests over the specific factors affecting therapeutic change processes and the systematic analysis of clinical experiences in true-life therapeutic practice. MI is a client-centered approach with directive elements aimed at resolving the fundamental ambivalent stance towards change residing within addicted or substance-dependent patients. The approach thus primarily targets individuals with low or ambivalent motivation to quit and is accordingly mostly applied at the beginning of addiction treatment. Meanwhile, MI is now being deployed successfully across a broad spectrum of mental disorders and in different stages of psychotherapy.

In patients who lack sufficient (intrinsic) willingness to change, phase 1 initially constitutes the use of different intervention techniques to facilitate a willingness to change. To this end, the use behavior of the patient is analyzed in a non-judgmental way without confrontational or argumentative attempts to convince the patient. Next, the patients' state the way they see the pros and cons themselves and the ambivalence of their use behavior elicited (discrepancies with conflicting life goals). This helps the patient in building up or strengthening an intrinsic motivation to quit ("change talk") and make a clear decision to change ("commitment"). In the second phase of MI, specific goals and ways to achieve them are identified. *Motivational enhancement therapy (MET)* is a variation of MI. In MET, the principles and interventions of MI are offered in a highly standardized and compressed form over four sessions.

Evidence

A total of four relevant clinical studies on the efficacy of MI were identified: three on MI and one on MET. An additional trial on MET with a cohort design was conducted on 30 patients without a control group and is therefore not discussed at this juncture [163].

A trial conducted by Polcin et al. (2014) in the United States compared a single 90-minute session of standard MI plus eight nutrition education sessions with an Intensive MI session (9 hours) administered to a total of 217 methamphetamine-dependent persons [164]. Over nine weeks, all study participants received one session weekly as well as a group intervention of cognitive behavioral therapy three times a week over twelve weeks. The primary endpoints

were a) self-reported reduction in methamphetamine use, b) reduction in methamphetamine use (urine test), c) Addiction Severity Index (ASI) status and d) psychiatric symptoms. Secondary endpoints investigated were a) anxiety status and b) and depression. In the two groups, the retention rates were > 90% after six months. Both groups showed an improvement in self-reported methamphetamine use and addiction severity. Methamphetamine use was reduced most significantly between baseline and 2-month follow-up; there were hardly any further changes observed after 4 and 6 months. Over the course of the trial, a reduction in psychiatric symptoms occurred in the Intensive MI group, but not in the Standard MI group. Over the course of the trial, no significant differences were found in anxiety, neither between nor within the two treatment groups. A significant reduction in depression was observed in the Intensive MI, but not in the Standard MI group (see also Chapter 6 Co-occurring organic diseases and mental health disorders).

In one RCT, Srisurapanont et al. (2007) compared a brief MI intervention without cognitive-behavioral interventions) with a psychoeducation (PE) session in 48 adolescent methamphetamine-dependent persons in Thailand [165]. The participants received either a 20-minute brief MI intervention or a 15-minute psychoeducation session twice weekly for 8 weeks. The primary endpoints were a) reduction in methamphetamine use (days per week, urine test) and b) the reduction in daily methamphetamine tablets. Secondary endpoints were a) the numbers of participants with positive urine tests, b) relapse and c) days of abstinence. Endpoints outcomes were assessed at week 0 (baseline), 4 and 8. The drop-out rate at week 8 was 12% in the MI brief intervention versus 7% in the PE group. At the 8-week follow-up, a significant reduction in methamphetamine use as well as a significant reduction in the number of used methamphetamine tablets was found in each of the two groups. The MI brief intervention group showed a significantly greater reduction in the days of methamphetamine use and a trend towards a decrease in the number of tablets taken. There were no differences between the groups with regard to abstinence and freedom from relapse.

Farabee et al. (2013) conducted a five-arm RCT in the USA comparing the efficacy of four MI variants: unstructured/non-directive, structured/non-directive, unstructured/directive, structured/directive or standard referral to aftercare without telephone call (control) [166]. The participants in the four MI groups received a total of 7 telephone calls from trained research staff. The sample consisted of 302 stimulant users (primarily methamphetamine and/or cocaine) who had almost (or had) completed a structured stimulant abuse treatment. Data were collected at baseline and 3- and 12-months' follow-up. The primary endpoint was the efficacy in reducing methamphetamine use in aftercare a) compared to the four MI forms and b) compared to MI versus control and c) measured by ASI drug problem score or urine test. There were no differences found between the individual MI forms at 3- and 12-months' follow-up. However, the aggregated analysis of all four call-based MI groups versus control (no-calls) in the intervention aggregate of all four variants at the 3-month follow-up showed a significant reduction in ASI drug use composite scores, which even increased in the control group by comparison.

In the two-arm RCT conducted by Huang et al. (2011), the efficacy of standard motivational enhancement therapy (MET) versus control (education; ED) was investigated in 94 Taiwanese juveniles with methamphetamine or methylenedioxymethamphetamine (MDMA) use [167]. The participants were recruited from a one- to two-month inpatient detoxification program and received three weekly sessions lasting 45–60 minutes each for a period of three weeks. The contents were: 1) Building a relationship, gathering information, motivation to change; 2) Readiness to change, ambivalence, drafting a plan; 3) High-risk situations, com-

mitting to the change plan, avoidance strategies. Both groups received the same educational materials. The primary endpoint was readiness to change methamphetamine use behaviors. The proportion of methamphetamine use differed between the groups: 60.9% MET versus 52.1% ED. The retention rate was 89.5%. The authors found significantly higher post-therapeutic scores on the "Readiness to change" and Contemplation subscales in the intervention group post-therapy compared to baseline, but no differences between the arms.

5.2.2.3 Contingency management

Method

Contingency management is an interventional method of traditional behavioral therapy, based on the theoretical principle of learned behaviors and rooted in operant and instrumental reinforcement. Accordingly, the frequency of a behavior (reaction probability) is influenced by its pleasant (appetitive) or unpleasant (aversive) consequences. Positive reinforcers (pleasant consequences), negative reinforcers (absence of aversive consequences), indirect punishment (absence of positive consequences) and direct punishment (aversive consequences) have been used in behavioral therapy for decades to modify behaviors in a large number mental disorders and problems. In contingency management, the types of reinforcement are used contingently, i.e. systematically, regularly, immediately and under defined conditions that have been agreed to with the patients. The aim is to reduce the frequency of adverse behaviors (e.g. drug use), while rewarding and incentivizing desirable behaviors (e.g. abstinence). The acceptance of material reinforcers by patients is co-determined by sociocultural attitudes and socioeconomic living conditions. It has not been verified whether study results obtained in the United States are applicable to the German system [168].

Evidence

A total of five RCTs are available on contingency management (CM) during the withdrawal treatment of methamphetamine-dependent persons: Two *efficacy studies*, two on the effects of various *reinforcement schedules* and one on different *reward durations*.

In a two-arm RCT conducted by Roll et al. (2006) in the USA, the effectiveness of CM was tested on 113 participants with methamphetamine abuse or dependence who were assigned to the following comparator groups: standard psychosocial treatment (ST) without CM versus psychosocial treatment plus CM (ST+CM) [169]. Patients with other substance-use disorders besides methamphetamine dependence were not excluded. Methamphetamine use was tested in a urine sample twice weekly; a missing test was rated as positive. The standard psychosocial treatment was based on the MATRIX model for methamphetamine-dependent individuals and was administered as a group intervention 3-times weekly for 16 weeks. CM followed the "fishbowl" technique with escalating rewards per week when the urine test was negative and resetting of the rewards back to baseline whenever the urine test was positive. The primary endpoint was use of illicit drugs tested in the urine and alcohol by breath test. Follow-ups took place after three and six months. At the end of the study, the retention rate was 38.7% in the ST group and 54.9% in the ST+CM group. The CM group produced significantly more negative urine samples and a longer duration of abstinence. Independently of the intervention, it was found that: If the urine samples of the past four weeks during the intervention were negative, then the probability increased that they also remained negative at the 3- and 6-month follow-up.

The second efficacy study (USA) was conducted by Shoptaw et al. (2006) on 229 methamphetamine-dependent participants and investigated the effect of a CM adjunct to pharmacological withdrawal treatment with SSRI in a placebo-controlled n RCT (4 arms): Sertraline + CM versus sertraline versus placebo + CM versus placebo [101]. In addition, a thrice-weekly intervention on relapse prevention (MATRIX) was offered. The primary endpoints were a) reduction in methamphetamine use and b) retention; the secondary endpoints: a) drug craving on a visual analogue scale (VAS), b) mood symptoms (Beck Depression Inventory), c) adherence and d) tolerability. The retention rate was 50.7%. Compared to all other conditions, the sertraline patients showed significantly lower retention rates. Moreover, they visited the relapse prevention significantly less often. In neither group, there was any significant reduction in methamphetamine use, albeit a significantly higher rate of patients on CM with three successive weeks of abstinence. There was no difference in craving, depression or adherence between the four arms. However, significantly more side effects were reported in the sertraline arms (mostly nausea, sexual dysfunction, gastrointestinal and anticholinergic adverse drug reactions).

Roll et al. (2013) investigated the effect of different durations of CM interventions in 118 methamphetamine-dependent individuals in the USA: standard psychosocial (MATRIX) treatment versus psychosocial treatment plus CM of varying duration (1, 2 and 4 months) [170]. The interventions, patient selection and endpoints (urine test) were the same as in the RCT by Roll et al. (2006) [169]. Follow-up took place after 6, 8, 10, 12 months. The overall retention rate for all treatments combined was 64.3% and correlated significantly with negative urine samples. The retention rates in the groups at follow-up were: Standard treatment (ST) (37%), ST + CM (67%), ST + CM2 (53%), ST + CM4 (76%). That produced a significant difference between ST and ST + CM4 after 16 weeks as well as at follow-up. As regards methamphetamine abstinence, there was likewise a significant difference between ST and ST + CM4 at follow-up: ST 3.4%, ST + CM1 13.3%, ST + CM2 20.0%, ST + CM4 34.5%. As regards negative urine tests (16 weeks), there were significant differences between all treatments apart from ST + CM1 and ST + CM2. At high "dose" and duration, the CM intervention thus increased the duration and continuity of methamphetamine abstinence.

The two studies on the efficacy of various reinforcement schedules in methamphetamine-dependent persons in the USA arrived at differential results ([171] and [172]). In the first trial, 18 patients received MATRIX treated plus two CM variants. The patients came to the clinic for a urine test 3 times a week for twelve weeks. If the test was negative, they received a reward (vouchers for goods or services worth $ 2.50 and an increase by $ 1.50 for each subsequent negative urine test). A missing urine test was counted as positive. In Group 1, a positive urine test led to the reward being reset to baseline. In Group 2, there was no reset, which meant that the value of the voucher remained and was upped with the next negative urine test. The two groups differed significantly with regard to the two clinical endpoints: negative urine tests: Group 1 (80%), Group 2 (38%); mean duration of abstinence: Group 1 (6.7 weeks) and Group 2 (2.8 weeks). The contingency regimen with reset, reward and punishment incentives combined appeared to be superior to the purely reward-based regimen in methamphetamine-dependent persons.

In the second trial, five different schedules were compared in 83 methamphetamine-dependent persons. The schedules 1-4 were based on clinical experience with the treatment of substance dependence, regimen 5 was conducted according to Higgins et al. (1994) [173]: slow continuous increase per visit by $ 1.25 (from $ 2.50 to $ 46.25 after 12 weeks), bonuses

remained the same. Variations: a) duration of the vouchers issued (8 or 12 weeks); b) differing voucher values (same value, increase or reduction in value to different levels); c) differences in the bonus system (always bonus, no bonus, same bonus, first bonus/then no bonus, different bonus amounts between the 5 arms). There were no significant differences between the five groups with regard to the total number of negative urine samples and the longest mean abstinence periods. The schedule according to Higgins et al. proved superior with regard to the time to the first negative urine sample, maintaining a 4-week abstinence during the intervention and, above all, the relapse rate after four weeks' abstinence. Accordingly, a slow, continually calculable increase in reinforcers with constant bonuses in methamphetamine-dependent persons appears most effective.

In conclusion, contingency management was well accepted as an interventional method in several studies (high retention rates). The evidence proves a marked add-on effect of CM as an intervention in multimodal withdrawal therapies (e.g. MATRIX), but not in SSRI treatment. The studies provide evidence that CM might also be effective as an intervention alone. The efficacy of CM is most striking with longer interventions and slow continuous calculable increase as well as in combination with positive reinforcement and withdrawal of reinforcers.

5.2.2.4 Cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT)

Method

Cognitive behavioral therapy (CBT) is rooted in psychological learning theories and cognitive psychological basic research. Today, CBT comprises that group of psychotherapeutic approaches which focus directly on systematically changing patients' dysfunctional patterns of perception, thoughts and attitudes (cognitive schemas, "cognitive distortions", "belief systems") alongside the classical methods of behavioral therapy involving conditioning and operant reinforcement. The cognitive perspective relies on a broad inventory of knowledge and methods from psychological basic and applied research and thereby encompasses all processes of perceiving, understanding, judging and deductive reasoning, including the executive functions and action control [174]. In the past decades, the cognitive perspective has spawned a variety of specific intervention techniques, extending from simple self-control procedures (self-verbalization, self-instruction, self-reinforcement, thought stopping) through four different modalities for the therapeutic change in patterns of interpretation and evaluation (cognitive restructuring, reframing, disputation, development of rational alternatives) up to complex therapeutic programs and models of self-therapeutic application (problem-solving training, self-management). Current CBT can be said to offer the most thoroughly studied and most effective psychotherapeutic methods for a broad array of mental disorders. Numerous meta-analyses and systematic reviews covering several thousand clinical studies attest to especially high levels of evidence for the efficacy of this intervention group in psychotherapy and addiction treatment [175-185]. Hence, it is not without reason that most of the psychotherapeutic guidelines issued by the relevant societies, including medical ones, list CBT as the method of choice for a variety of clinical pictures [174].

Acceptance and Commitment Therapy (ACT) is a "third-wave" further development of CBT, which combines classical techniques from behavioral therapy with mindfulness- and acceptance-based strategies and interventions for values clarification and includes the explanation of linguistic-thought-related processes (relational frame theory). ACT is administered to treat a number of disorders and problems and is increasingly being investigated with regard to its efficacy [186-193].

Evidence

The evidence on the efficacy of CBT in withdrawal treatment is astonishingly weak. There is only one RCT on CBT from Australia, which was conducted versus ACT.

Smout et al. (2010) investigated 104 treatment-seeking adults with methamphetamine abuse or dependence, who were randomly assigned to the CBT or ACT group [158]. All participants received 12 weekly 60-minute individual sessions of ACT or CBT. The primary endpoints chosen were a) reduction in methamphetamine use, b) reduction in severity of methamphetamine dependence, c) reduction in methamphetamine-associated negative consequences and d) improved participation in the intervention. Secondary endpoints were a) depressiveness, improvement in physical and mental well-being and b) reduction in the use of other narcotics (hair analysis). Post-intervention data were only available on 30% of participants in the two groups (retention rates after the twelve-week intervention: ACT 27.5%, CBT 32.1%). Treatment attendance in at least four CBT sessions or ACT was 61.1%. At the 24-week follow-up, both groups showed significant improvements in methamphetamine use and dependence severity. In the CBT group, there were significantly more methamphetamine-free hair samples after twelve weeks alongside a significant reduction in negative consequences of methamphetamine use at week 12 and 24. In the pre-post comparison, both groups showed a significant improvement in depressiveness and mental well-being.

5.2.2.5 Multimodal therapy regimens: MATRIX and FAST

Method

The Matrix Model Intensive Outpatient Treatment Program was developed in the 1980s at the MATRIX Institute on Addictions in California. It was designed to help in the withdrawal treatment of individuals affected by alcohol and other drug use and later expanded to include methamphetamine therapy. Based on a cognitive behavioral approach, the MATRIX Manual is a series of guides for delivering therapy. It includes interventions involving psychoeducation, motivational interviewing, contingency management, behavior modification, cognitive behavioral methods and family therapy and family care work [194; 195]. The program incorporates topic-specific individual and group therapy sessions (early recovery, relapse prevention, social support groups), family education, 12-step participation/peer group materials, relapse prevention and urine tests. The following topics are addressed: How substances affect the brain, aspects of relapse prevention, triggers and cravings, stages of recovery, relationship and convalescence, alcohol and cannabis, emotional regulation, 12-step participation, sex and convalescence, effects of addiction on family, medical effects of stimulant use.

Evidence

There are two RCT available on the efficacy of the MATRIX Model in the withdrawal treatment of methamphetamine-dependent individuals.

Rawson et al. (2004) conducted a multicenter two-arm RCT on 978 methamphetamine-dependent people at eight outpatient therapy centers in the USA, investigating the MATRIX model versus treatment-as-usual (TAU) [159]. The MATRIX treatment was given for 16 weeks with a maximum of 48 clinical sessions: cognitive behavioral therapy in groups (36 sessions), family therapy (12 sessions), social support groups (4 sessions), individual consultations (4 sessions). TAU was given for 8–16 weeks, differing somewhat in the implementation in the eight centers. All participants were tested weekly for methamphetamine and other drugs in the urine. Follow-up was conducted after six and twelve months. After six months,

the overall retention rate was 86%. In both groups, a significant reduction in methamphetamine use was achieved. In the MATRIX group, there were more clinical sessions and a better retention rate. Moreover, more patients participated in the intervention and completed the full regimen. The number of methamphetamine-free urine samples was also higher than for TAU. However, MATRIX was no longer superior to TAU after six and twelve months. The effect size in this trial was possibly underestimated given that the selection of the comparator (TAU with the same or higher dose and intensity of therapy) was not ideal.

In a two-arm RCT conducted in Thailand, Perngparn et al. (2011) compared the *outpatient* MATRIX model with another complex inpatient therapeutic model (FAST) in 135 male methamphetamine-dependent volunteers [147]. FAST (Family Alternative treatment activities, Self-help and Therapeutic Community) is a more intensive regimen than MATRIX. In order to determine the efficacy of the two models, interviews/questionnaires were used during the intervention and at post-interventional follow-up after 1, 3 and 6 months. During the Intervention, the FAST group showed a significant improvement in psychological and social functions as well as the assessment of treatment, whereas the MATRIX group showed a significant improvement in psychological and social functions. During follow-up, the FAST group had 11% relapses after three months and another 3.3% after six months (=8.6% overall). 50% of the patients in this group used alcohol up to 3 times per week. In the MATRIX group, the relapse rate after three months was 14% and another 7% (=21%) after six months. Here, the proportion of alcohol co-abuse (3 times per week) was 40–68%. At 6-month follow-up, the "survival rates" did not differ significantly between the two models. The 6-month retention rates were 65% and 51% in the FAST and MATRIX groups, respectively. Despite methodological weaknesses, the study results suggest that a more intense therapy in an inpatient setting may be superior to the MATRIX approach.

5.2.3 Psychotherapy in special settings: Stepped care, community-based approaches

Psychotherapeutic interventions for treating methamphetamine-dependence in different settings are consistent with the above-mentioned methods, but still co-determined by the respective circumstances. "Stepped Care" is a graduated system of interventional services that match treatment to the patient's needs; it starts by addressing the problem of use and extends through education/psychoeducation, encouraging a readiness to change up to the offering of singular or complex therapeutic services in outpatient, semi-inpatient or inpatient settings. "Community-based approaches" comprise care concepts that offer real-world prevention and therapy services appropriate to the life of those affected to support them in making changes in their everyday lives (e.g. local addiction counseling centers, street workers etc.).

Evidence

There is one prospective longitudinal analysis available on the efficacy of *community-based care options* for methamphetamine-dependent individuals, one observational study on s*tepped care approaches* as well as one pilot trial by Kay-Lambkin et al. 2010 [196].

McKetin et al. (2012) studied the efficacy of *community-based drug treatment* in 461 methamphetamine-dependent persons at 41 centers in Australia [197]. Intervention and control group showed significant differences with regard to duration and frequency of use, severity of dependence, proportion injecting methamphetamine, prison history and major depression. 112 participants received a community-based detoxification, 248 a residential rehabilitation,

and 101 methamphetamine users without therapy served as a quasi-control group. Detoxification consisted of approx. one-week's inpatient therapy with medical support of withdrawal symptoms, whereas the inpatient rehabilitation lasted weeks to months and consisted of an intensive multimodal treatment regimen. Endpoints were a) the frequency of drug use, b) continuous abstinence and c) the severity of dependence. Follow-up took place at three months, one year and three years' post-intervention. The follow-up rates were 80% after three months, 74% after one year and 66% after three years. There was no larger reduction in the detoxification therapy group compared to the quasi-control group, but a larger reduction in methamphetamine use when inpatient therapy was compared to control and detoxification (combined) after three months. The effect reversed slightly after one year. The abstinence rates for residential rehabilitation were 33% after three months, 14% after one year and 6% after three years versus quasi-control and detoxification (combined).

In another multicenter, one-arm observational study, McKetin et al. (2013) investigated the efficacy of a *stepped-care approach* that adapted the intensity and nature of the clinical intervention to the severity of each client's problem and goals. The sample comprised 105 methamphetamine-dependent persons in Australia [157]. The *Stimulant Treatment Program (STP)* applied approaches like motivational interviewing, CBT and mindfulness. The endpoints investigated were a) methamphetamine use, b) polydrug use, c) criminal involvement, d) sexual risk behavior and e) level of disability associated with poor physical or mental health, psychotic symptoms and hostility. Follow-ups took place after three and six months (by telephone). The participation rate in follow-up was 82% after three months and 79% after six months. In aggregate, a significant reduction in methamphetamine use was registered after three and six months alongside a significant reduction in mental disability, psychotic symptoms and hostility. There was no correlation between the number of counseling sessions or time spent in treatment and reduced methamphetamine use. No reduction in crime, sexual risk behavior and polydrug use was found.

5.3   Post-acute pharmacological therapy

5.3.1   Definition, setting, target symptoms

Post-acute pharmacological therapy can be administered by general practitioners or specialists on an outpatient basis, but also on a (partial) inpatient basis at acute hospitals or withdrawal facilities. It can support outpatient addiction-specific psychotherapy (addiction counseling centers, outpatient rehabilitation). Treatment during incarceration in a penal institution can also be considered.

To date, studies have investigated the following endpoints or main outcome measures:

- Reduction in the methamphetamine effect;
- Retention rates;
- Craving;
- Cognitive functions;
- Sleep quality;
- Mood improvement;
- Reduced use;
- Abstinence rates;
- Change in sexual risk behavior.

The ability to maintain an outpatient or inpatient rehabilitation during the prolonged post-acute withdrawal phase despite persistent cognitive and emotional limitations can be an important secondary objective of pharmacological management.

Almost all drug trials in the USA were conducted in combination with CBT psychotherapy according to the MATRIX manual [194]. The "retention rate" results in these trials are thus especially relevant in relation to the high drop-out rates reported at many sites.

Co-occurring disorders like persistent psychotic states or depressive episodes are covered in Chapter 6 Co-occurring organic diseases and mental health disorders.

5.3.2 General study data and guidelines

The systematic search identified a total of 58 studies on pharmacotherapeutic interventions in various settings (acute/post-acute). These mostly involve randomized controlled trials (RCT), with only very few study results being of sufficient methodological quality. To date, trials have investigated: Acetylcysteine, antidepressants, antiepileptics, atypical neuroleptics, calcium antagonists, muscle relaxants, opioid antagonists, psychostimulants, varenicline, cholinesterase inhibitors and citicoline.

The last US guidelines on substance abuse were published in 2006 and do not address amphetamine or methamphetamine. No guidelines from Australia, Canada or the UK are available on methamphetamine users in the stages of therapy considered here.

> **Every treatment decision must consider the fact that none of the drugs listed have a German marketing authorization for treating methamphetamine dependence (see Chapter 4 Acute therapy, Info Box 2).**

5.3.3 Individual drug classes

5.3.3.1 Antidepressants

Recommendations	Grade of recommendation
5-13 In patients with moderate, non-daily methamphetamine use, treatment with bupropion may be attempted in order to support them in achieving abstinence. LoE 2 [198-203] Vote: 100%	⇔
5-14 Sertraline should not be given to patients with methamphetamine-related disorder to achieve abstinence. LoE 2 [101] Vote: 100%	⇊⇊

Recommendations	Grade of recommendation
5-15 Imipramine may be administered to increase retention rates. LoE 2 [204; 205] Vote: 92%	⇔

Evidence

Among the drugs with dopaminergic and noradrenergic efficacy (selective reuptake inhibitors 2:1), the phenylethylamine derivative (cathinone) **bupropion** has been studied most intensively. Four RCT investigated the extent to which bupropion is suited to reduce use or increase abstinence rates [198-201]. The data from two of these studies was subjected to re-analysis [202; 203]. In summary, there was no significant effect with regard to the primary target variables abstinence and reduced use. In the 12-week trial conducted by Elkashef et al., it was not until a retrospective differentiation was undertaken between heavy (> 18 days per month) and light use (≤ 18 days per month) and gender that a significant effect was shown for the subgroup of men with light use, provided that they had achieved at least one MA-free week [198]. With these results as background, Heinzerling et al. (2014) focused their trial (n=84) on individuals with a use of ≤ 19 days of the past 30 days, i.e. with less than daily at baseline. However, the abstinence rates did not differ significantly in the last two weeks of treatment with bupropion versus placebo [201]. In light of these contradictory data, some study results suggest that individuals using methamphetamine not more than 18 days per month tend to be more abstinent on bupropion. A clinical trial lasting twelve weeks can be undertaken.

In their four-arm trial on 229 methamphetamine-dependent participants, Shoptaw et al. (2006) evaluated the efficacy of 100 mg **sertraline** and CM for twelve weeks [101]. The primary analysis did not show any efficacy for sertraline or CM. The negative effects of sertraline on retention rates and abstinence were revealed in a post hoc analysis. One explorative double-blind trial on **paroxetine** conducted by Piasecki et al. (2002) included a mere 20 subjects, with only three completing the trial [206].

Only one trial is available on **mirtazapine** versus placebo [207]. The authors investigated whether a 12-week trial of mirtazapine would reduce methamphetamine use and sexual risk behaviors in MSM (n=60). The success in this subgroup was significant. Patients with major depression were excluded. These results may be transferable to other subgroups (women, heterosexuals) (see also Section 7.3 Methamphetamine abuse among men who have sex with men (MSM)]).

In pre-tests of 150 mg imipramine for 180 days, the use of drive-enhancing **TCAs** like **imipramine** produced no significant differences besides a higher retention rate than in the 10-mg control group [204; 205].

5.3.3.2 Atypical antipsychotic drugs

Evidence

For the definition of this term, see Chapter 4.2.2 Pharmacotherapy. One trial is available on **aripiprazole** (n=37) over an observation period of eight weeks versus placebo that showed a superior effect on retention rates and cravings, but not on abstinence rates. Only patients

with psychosis in remission were enrolled [208]. Another trial on subjects without acute psychiatric disease in the medical history was negative [105].

A trial conducted by Newton et al. (2008) showed that aripiprazole at a dose of > 15 mg increased the craving for methamphetamine. Furthermore, a tendency emerged that aripiprazole potentiated the drug's effect. However, this finding was not significant [107]. One study on individuals with intravenous amphetamine dependence had to be terminated prematurely due to a higher relapse rate in the aripiprazole group [209].

Given the high drop-out rate, a low number of treated patients (n=12) and open-label, not-controlled setting, the strength of the findings of a manufacturer-sponsored trial with long-acting injectable **risperidone** is limited [210].

Positive case reports for **quetiapine** and **olanzapine** with regard to craving and drug use in patients with methamphetamine-induced psychoses do not yet permit any conclusive assessment [211; 212].

5.3.3.3 Muscle relaxants

Evidence

One controlled trial investigated **baclofen** versus gabapentin versus placebo in 88 methamphetamine users for 16 weeks, yielding no benefit for either baclofen or gabapentin [213].

5.3.3.4 Opioid receptor antagonists

Evidence

One experimental trial yielded a significant attenuation in cue-induced cravings (n=30) after four days' pre-treatment with **naltrexone**. Given the low number of patients involved and methodological weaknesses, no recommendation can yet be given based on these results [122].

5.3.3.5 Psychostimulants (analog treatment)

Recommendations	Grade of recommendation
5-16 Dopamine analog treatment attempts with **narcotic-classified** substances (e.g. amphetamine replacement with sustained-release D-amphetamine, sustained-release methylphenidate aimed at methamphetamine reduction/abstinence) that extend beyond acute withdrawal treatment should only be undertaken within the scope of registered clinical trials. LoE 2 [113; 114; 214; 215] Vote: 100%	⇓⇓⇓
5-17 Modafinil ought not to be used in the post-acute phase. LoE 2 [116; 118; 119; 216; 217] Vote: 83%	⇓⇓

Evidence

A smaller RCT on 110 mg sustained-release **D-amphetamine** in methamphetamine-dependent individuals (n=49) showed a reduction in withdrawal symptoms as secondary endpoint. However, the reduction in use after three months of sustained-release dexamphetamine was not significant versus placebo. Only the retention rate was higher on D-amphetamine (p = 0.014). Nevertheless, this effect had been mostly noticeable as early as the withdrawal phase [113]. In one small study (n=60) lasting eight weeks with 60 mg sustained-release D-amphetamine, Galloway et al. (2011) were not able to prove any significant influence on the number of drug-free urine tests despite significantly reduced craving scores [114].

In a 10-week treatment phase, the drug group receiving 18–58 mg/day sustained-release methylphenidate showed a lower frequency of use (10 of 30 days) with significantly fewer positive drug screening tests, lower craving scores and fewer depressive symptoms than the placebo group [214]. By contrast, Ling et al. (2014) found no significant difference in methamphetamine use at the 14-week follow-up after a similar 10-week therapy with 54 mg methylphenidate (combined with CBT). Nevertheless, methylphenidate did reduce cravings [215].

Mahoney et al. (2012), Kalechstein et al. (2010), Ghahremani et al. (2011) and Hester et al. (2010) found some positive influences on attention and cognitive abilities on modafinil therapy in the acute withdrawal phase [116; 118; 119; 216]. Whereas, Anderson et al. (2012) reported no difference in abstinence, retention rates or craving on 200–400 mg modafinil versus placebo over twelve weeks (in combination with CBT). Although, this trial enrolled a relatively large number of patients (n=210), the strength of its findings is limited by inadequate medication compliance and high drop-out rates in both study arms. Notwithstanding the above, patients with adequate medication compliance appeared to benefit more [217]. Overall, indirect stimulants like modafinil have been insufficiently studied in the post-acute phase; their risk of drug interactions is high (potentiation). Therefore, no recommendation for the post-acute phase can currently be made for this substance, which is not subject to the German Narcotics Law (BtMG).

No studies whatsoever are available on the efficacy of **caffeine**, although patients have clinically rated this freely available stimulant as helpful in preventing fatigue.

In patients at risk of developing dependence, **benzodiazepines** are not a suitable medication for achieving abstinence (see Chapter 6 Co-occurring organic diseases and mental health disorders).

5.3.3.6   Other medications

Evidence

One positive trial was conducted with **acetylcysteine** to determine whether it could reduce methamphetamine craving in a small, overwhelmingly male sample (n=32) [120]. Especially given its favorable side effect profile, this approach should be pursued. Current data from clinical trials do not yet justify recommending acetylcysteine for the post-acute management phase (for more on this subject, see Chapter Other pharmacological agents).

After encouraging preclinical trials, **ondansetron** was investigated in an RCT. Contrary to expectations, the drug group did not score better than placebo for any of the criteria [124].

An initial trial on **topiramate** showed positive effects in a re-analysis of the data. Prospective

tests should produce a confirmation before a recommendation can be issued (n=140) [218; 219]. Another placebo-controlled trial with a small number of cases (n=62) also produced evidence of efficacy. The administration of topiramate to methamphetamine users in the post-acute phase does not yet appear justified due to issues with side effects, including teratogenicity [123].

Two studies on a small number of methamphetamine users showed that **varenicline** can attenuate the positive subjective effects of methamphetamine [127; 128]. Larger RCTs will be needed to investigate whether these data will be associated with higher abstinence rates.

5.3.3.7   Pharmacological combination treatments

Recommendations	Grade of recommendation
5-18 Combined intravenous pharmacotherapy with flumazenil, gabapentin and hydroxyzine (PROMETA®) should not be given. LoE 2 [220] Vote: 83%	⇓⇓⇓

Evidence

The PROMETA® protocol consisted of flumazenil (a GABA antagonist with partially agonistic effects), the GABA agonistic antiepileptic gabapentin and the sedating anti-histamine hydroxyzine. This very complicated infusion combination therapy receives a high level of promotion in the USA. A 15-week trial with 120 methamphetamine users (n=120) conducted by Ling et al. (2012) yielded neither a significant effect for abstinence (drug screening) nor for self-reported abstinence, retention rates or craving scores versus placebo plus hydroxyzine [220]. There is a danger of severe side effects since epileptic fits be can triggered. The high placebo effect of infusion management and influence by the manufacturer in preliminary studies of Urschel et al. are pointed out. Urschel et al. (2011) still found positive effects on craving with higher abstinence rates compared to placebo; this was despite sponsoring by the manufacturer and insufficient study quality (complete failure to present the frequency of drug use in the study arms although such data were collected) [125].

A small (n=31) preliminary study (Grant et al. 2010) on the combination of **naltrexone and acetylcysteine** showed no advantages versus placebo [126].

5.3.4   Phytopharmacotherapy

No studies were identified on the efficacy of herbal medicines in methamphetamine users. If, however, they are administered, the potential for drug interactions should be considered. For example, this is the case with **St. John's wort**. Explicit mention must be made that simultaneous methamphetamine use is associated with the risk of serotonin syndrome. Metabolic interactions should also be watched out for.

Preparations or teas containing **ephedrine** and **pseudoephedrine** are not to be recommended. The ingredients are metabolized to d-amphetamine and are thus detectable in the urine.

5.3.5   General instructions on prescribing medications to drug users

Psychiatrists and general practitioners frequently feel "compelled" to prescribe medications although there is no evidence to support it. The demand from users for medication is consistent with their addictive dynamics; not least, the polydrug use had positively changed their mood in the past. On the other hand, many physicians have had clinical experience that prescribing a medication keeps the contact going (retention rates), enabling damage-minimizing interventions or building abstinence motivation.

To allow an estimation of the danger to patients from such non-evidence-based therapy, it is therefore recommendable to weigh their abstinence status:

Outpatient, non-abstinence-motivated: Medications should not be prescribed to make it easier for the user to "come down from a meth high", for example, to get them back on their feet for work on Monday or the likes ("go pill, stop pill"). The prescription of any added medications should best be refrained from unless an independent psychiatric indication has been established. Neuroleptic drugs being given to treat psychoses should be continued in an overdose-safe form according to clinical protocol (see Chapters 4 Acute therapy and 6 Co-occurring organic diseases and mental health disorders).

Outpatient, credible desire for abstinence, but unclear abstinence status: The patient should be comprehensively educated about the risks of drug interactions and adverse reactions of the "attempted therapy" and urgently recommended to take a drug holiday in the event of relapse or planned relapse.

Outpatient with verified abstinence, verified abstinence during inpatient rehabilitation: After the appropriate education about the risks and adverse reactions, and considering the approval status or the German law governing the prescription of narcotics (BtMVV), it is understandable when the treating physician undertakes therapy attempts (usually "off-label") within the scope his freedom of treatment when there is otherwise insufficient study data.

In patients with **sleep disorders** hypnotics ought to be avoided after withdrawal. Although there is no unequivocal evidence, the experts believe that "off-label" attempts with sedating TCAs or low-potency neuroleptic drugs can be undertaken after comprehensive education of the patient about adverse reactions and risks of drug interactions (serotonin syndrome etc.) for example to achieve sleep hygiene, see Section 6.10 Sleep disorders).

In clinical practice, low-potency neuroleptics like Melneurin or sedative TCAs like doxepin have proven helpful to counteract **cravings** in some cases. Doxepin is generally approved for the treatment of withdrawal symptoms and has been shown to confer benefit in clinical routine despite adverse cardiac reactions. In the outpatient setting, interactions, serotonergic syndrome and overdoses must be weighed in the balance.

5.4   Other therapies

In the daily practice of addiction medicine, supportive therapeutic methods like relaxation techniques, acupuncture, physical conditioning and naturopathic methods are used relatively frequently, both in the inpatient and outpatient settings, and mostly as adjuvants to standardized pharmacological, psychotherapeutic and psychosocial therapies. There are hardly any powerfully conclusive trials or post-marketing surveillance studies on the efficacy of these methods among users of stimulants, particularly not on the use of methamphetamine.

Recommendations	Grade of recommendation
5-19 As supportive treatment for alleviating withdrawal symptoms and to stabilize abstinence, methods of sports therapy (exercise therapy, physical conditioning) should be offered and provided. LoE 2 [221-223] Vote: 100%	⇑⇑⇑
5-20 Neurofeedback may be offered supplementing other therapies. LoE 2 [224] Vote: 82%	⇔
5-21 Auricular acupuncture (according to the National Acupuncture Detoxification Association (NADA) protocol) may be offered. Expert consensus (LoE 5), based on [225] Vote: 91%	⇔
5-22 The administration of such supportive therapies is predicated on the appropriate qualifications of the therapists. Expert consensus Vote: 100%	**Statement**

Three methodologically sound RCTs indicate that physical activity programs may be effective [221-223]. Accordingly, exercise therapy methods (exercise training, physical fitness) had a more positive effect than a health education program or education intervention in methamphetamine-dependent patients, as these exercise methods significantly improved methamphetamine abstinence symptoms like depressive moods and cravings. When exercise training programs were administered, the positive effects also applied not least to the [reduction in] weight gain that many patients subjectively perceive as negative (see also Chapter 6 Co-occurring organic diseases and mental health disorders and 8 Relapse prevention) [221-223]. Neurofeedback-supported and suggestive or hypnotherapeutic methods are administered occasionally, mostly in inpatient settings but have not become established. Among other reasons, this can be attributed to the fact that these methods are relatively complicated and also not suitable for all affected patients. This particularly applies to neurofeedback, whose efficacy is most thoroughly proven. In one randomized study on 100 male methamphetamine-dependent persons, neurofeedback in combination with a psychopharmacological therapy improved the severity of dependency, psychosocial complaints and quality of life compared to pharmacotherapy alone [224]. The method is only offered by a few (mostly inpatient) services and relies on specific equipment and human resources, both of which are not conducive to broader application.

Although there are no concrete scientific studies on its use in methamphetamine users, re-

ports on the benefits of using special auricular acupuncture methods ("according to NADA protocol") in addicts keep emerging. Positive experience has been gained in clinical practice with this form of acupuncture when given to stimulant users, especially during cocaine withdrawal. Isolated reports similarly suggest a potential benefit will be conferred to methamphetamine-dependent persons. Treatment with NADA auricular acupuncture is considered extremely low-risk in terms of potential adverse reactions and contraindications (www.nada-akupunktur.de) [225].

Notwithstanding isolated success stories in the popular media beyond the realm of science and medicine but even in a scientific context of more or less promising therapeutic trials on myriad methods within the "alternative medicine" spectrum (as opposed to conventional, mainstream medicine), experts are not convinced that there is sufficient evidence on the efficacy of alternative methods.

6 Co-occurring organic diseases and mental health disorders

Willem Hamdorf, Wolf-Dietrich Braunwarth, Roland Härtel-Petri, Heribert Fleischmann, Ursula Havemann-Reinecke, Peter Jeschke, Marco R. Kesting, Winfried Looser, Stephan Mühlig, Niklas Rommel, Ingo Schäfer, Katharina Schoett

6.1 General principles for treating co-occurring disorders

Co-occurring mental health disorders are common in both methamphetamine users and clients with methamphetamine-related disorders. In many of those affected, substance abuse is connected with their mental disorder insofar as they tend to self-medicate. They exploit the pharmacological action of methamphetamine to alleviate symptoms deriving from depressive disorders, anxiety or post-traumatic disorders [1; 226]. Over the clinical course of a methamphetamine-related disorder, it is often difficult to tell whether substance abuse occurred prior to mental disorder or vice versa.

Recommendations	Grade of recommendation
6-1 If there is a suspicion of any co-occurring mental disorders, specialty-specific diagnostics (differential diagnosis) should be performed or referrals made. Expert consensus vote: 100%	⇑⇑
6-2 To render a valid diagnosis of co-occurring mental disorders in methamphetamine users, the diagnosticians should be aware that the symptoms can be masked by drug-related effects or withdrawal symptoms. Expert consensus Vote: 100%	⇑⇑
6-3 In methamphetamine users, the indication for treatment of co-occurring mental disorders should always be reviewed repeatedly. Expert consensus Vote: 100%	⇑⇑

Recommendations	Grade of recommendation
<u>6-4</u> It is preferable to take an integrated treatment approach to methamphetamine-related disorder and co-occurring disorders. If this is not possible, treatment elements for both disorders ought to be coordinated appropriately. Expert consensus Vote: 92%	⇑
<u>6-5</u> To reduce symptoms of co-occurring mental disorders, affected patients should be offered disorder-specific psychotherapy methods. LoE 2 [147; 158; 159] Vote: 80%	⇑⇑⇑

6.1.1 Prevalence

In a study of Salo et al. (2011), the frequency of co-occurring mental disorders was documented by administering Structured Clinical Interviews (SCIDs). The lifetime prevalence for individual mental disorders shows considerable gender differences: Men suffered more from other addictions and psychoses, whereas women exhibited affective and anxiety disorders with a greater frequency. The proportion of anxiety disorders was 24.3%, with 12.2% thereof being due to post-traumatic stress disorder. Substance-induced psychotic disorders (23.8%) and affective disorders (32.3%) occurred frequently. Moreover, 81% of the study participants with methamphetamine-related disorder had at least one other substance-related disorder, e.g. cannabis and/or alcohol [227]. In many cases, the psychological symptoms caused the sufferers a high degree of impairment, requiring inpatient treatment. Many patients reported suicide attempts [228; 229]. A longitudinal study examining 563 methamphetamine users for 8–10 years showed that depressiveness, anxiety, psychotic symptoms and suicide attempts alongside heroin co-abuse and intravenous drug abuse are significant predictors for higher mortality. Overall, 8% of the methamphetamine users died during the study period; the most frequent causes of death were cardiovascular problems, HIV infection, overdose, suicide and accidents [25]. Treatment of co-occurring mental disorders can positively influence the course of a substance use disorder [230].

6.1.2 Diagnostics

As described above, it is often not possible to clinically distinguish the co-occurring psychological symptoms from the sequelae of methamphetamine abuse. It is not until the patient has been abstinent from their addiction that more comprehensive diagnostics and therapy are possible. Given these diagnostic problems, the indication for treatment of co-occurring mental disorders should be repeatedly reviewed in methamphetamine users. If it turns out that the co-occurring psychological symptoms persist, and treatment is indicated, the patient should be offered therapy or given the appropriate referral.

6.1.3   Treatment: Goals and settings

The treatment approach consists of a comprehensive, individualized, and at best, integrative treatment designed to put the two clinical pictures into remission. Disorder-specific and evidence-based psychotherapies have already been established for a number of psychiatric disorders (e.g. depression, PTSD, ADHD).

Over the further course of an addiction with co-occurring disorder, the selection of the right treatment settings plays a pivotal role. In principle, the choice covers outpatient, all-day outpatient and inpatient treatment settings. In healthcare reality, not only does the medical-psychotherapeutic indication for certain settings need to be considered, but also whether the settings are available or not. Not all treatment options are widely available, particularly in rural areas outside of urban centers; which means that inpatient treatment regimens may be necessary in such cases. Some integrative options already exist for the treatment of methamphetamine-related disorders and co-occurring mental condition.

These especially target patients with methamphetamine-related disorder (or drug-dependent persons) suffering from psychosis, ADHD, trauma or depression. They should fundamentally be preferred when planning treatment given that such options equally integrate both clinical pictures. If treatments for methamphetamine-related disorder and co-occurring mental disorders are given in parallel or sequentially, good liaison work and coordination of treatment content can make a major contribution to the therapeutic outcome.

6.1.4   Evidence

A systematic search was conducted on the treatment of co-occurring disorders in patients with methamphetamine-related disorder. Evidence was found for the following indications: Psychoses, depression, neurocognitive disorders and bipolar disorder. One systematic review of average methodological quality investigated 13 studies with pharmacological and psychotherapeutic interventions in patients with methamphetamine-related disorder and co-occurring depression. In these as well as in the other studies researched by AQuMed, co-occurring disorders were mostly only investigated as secondary endpoints. Since the number of studies is small and the robustness of the results is very limited, it is hard to derive evidence-based recommendations from them. Many are based on expert consensus. When making decisions about treatment, it is important to also be aware that none of the medications are approved for the treatment of methamphetamine dependence in Germany.

6.2   Co-occurring addictive disorders

6.2.1   Clinical relevance and epidemiology

The combined use of methamphetamine and other psychoactive substances is very commonly encountered in clinical routine. At least in the group of methamphetamine users with dependence syndrome and/or risky use ("heavy users", i.v. users), other substances were used regularly in addition to methamphetamine. Frequently, a substance-related co-occurring disorder will be manifest when a client contacts the addiction help services.

According to the results of the Statistical Report on Substance Abuse Treatment in Germany, the following additional abuse or dependence-related diagnoses are established in clients/patients with stimulant use disorders in connection with an indicated treatment: Cannabis (outpatient: 46%, inpatient: 70%), smoking (outpatient: 29%, inpatient: 85%), alcohol (outpatient: 26%, inpatient: 57%), cocaine (outpatient: 10%, inpatient: 26%), hallucinogens

(outpatient: 6%, inpatient: 21%), heroin (outpatient: 4%, inpatient: 9%) and benzodiazepines (outpatient: 2%, inpatient: 6%) [22].

The data and evidence on this subject are extremely sparse; the aspects presented here are overwhelmingly based on observations from clinical practice. Further research should be devoted to the gathering of data on co-occurring disorders, their clinical courses and on therapeutic options (see Chapter 10 Need for further research) [231; 232].

6.2.2 Management of substance-related co-occurring disorders

Recommendations	Grade of recommendation
6-6 The guidelines/recommendations specifically relating to the current, occasion-related withdrawal treatment apply whenever a patient develops a dependence on one or several other substances. The risks of interaction should be taken into account when selecting which medication to give. Expert consensus Vote: 100%	**Statement**

In principle, an integrated treatment of co-occurring disorders should be the aim (see Recommendation 6-4 in Chapter 6 Co-occurring organic diseases and mental health disorders). The experts are not aware of any conclusive studies on the Integrated simultaneous treatment of co-occurring substance disorders during post-acute therapy. Complex psychotherapeutic regimens like MATRIX specifically address multiple substance use [194]. It is currently not possible to judge which psychotherapeutic methods are the best for treating/managing polyuse patterns; this must be decided on a case-by-case basis.

For manifest opiate, benzodiazepine, alcohol or polydrug withdrawal syndrome, the authors recommend the respectively applicable substance-specific guidelines.

6.2.3 Methamphetamine co-abuse in patients on opiate replacement therapy

Recommendations	Grade of recommendation
6-7 The co-abuse of methamphetamine during replacement therapy in patients with opiate dependence is a serious complication of treatment and should be addressed by the physician administering the replacement therapy, who might get other therapists can be involved to work on it with the patient. The long-term objective is to achieve freedom from methamphetamine co-abuse. Expert consensus Vote: 91%	⇑⇑

6.2.3.1 Clinical Relevance

The experience from practices specialized in replacement has shown that opiate-supported treatment of opiate dependence (methadone/buprenorphine/diamorphine/sustained-release morphine replacement) is frequently associated with the co-abuse of psychostimulants. The patients want to enhance their drive with a higher replacement dose, medication-related loss of libido, increase self-esteem, for example, before contact with authorities, facilitate procurement prostitution and procurement criminality and especially in i.v. users desiring to experience a "kick".

Over the past years, the number of patients receiving replacement therapy has dropped remarkably in regions, where methamphetamine has a high availability and represents the predominant abuse and dependence pattern in drug users. These regions in Germany include Saxony, North Bavaria, Thuringia and increasingly also in Saxony-Anhalt and Berlin. By contrast, the number of methamphetamine users has clearly risen. In the federal state of Saxony, the total number of patients on replacement therapy declined by over 20% from 2011 to 2014 [21; 233; 234].

Similarly, there are reports from affected regions that previously achieved goals of psychosocial stabilization are all rapidly lost once methamphetamine is used again. That is the reason why physicians administering replacement therapy are repeatedly required to limit take-home prescriptions or initiate inpatient crisis interventions in patients with methamphetamine co-abuse, even if there is no acute threat to life.

Besides administering drug tests, the replacement therapy team should be watchful for the typical facial excoriations, weight loss or unusual drivenness as key indicators of acute relapses.

During methamphetamine intoxication, patients on replacement therapy, even those infected with hepatitis C or HIV, will tend to neglect the safer sex and safer use practices recommended as measures designed to protect both the patient themselves and others [235]. The hazards posed to minors by previously stabilized opiate-dependent persons on opiate replacement therapy who co-abuse methamphetamine must be re-reviewed constantly.

Unlike opiate, benzodiazepine or alcohol relapses, the direct life-threatening endangerment is caused less by respiratory paralysis than by potential cardiac interactions (QTC time).

6.2.3.2 Intervention

In patients undergoing replacement-supported therapy for opiate dependence, co-abuse of methamphetamine is therefore a complication that must be taken very seriously because it can pose a considerable impediment to the achievement of the objectives of the replacement therapy. Replacement therapy is subject to comprehensive legal regulations; therefore, its implementation and enforcement place requirements on patients and physicians alike. In the case of methamphetamine co-abuse, there is often no guarantee that these can be upheld:

- Regular, punctual presentation in the practice to receive administration of the replacement medicine under supervision;
- Psychosocial assistance;
- Compliance with the house rules and structural conditions;
- Concurrent treatments from other physicians;

- Compliance with social obligations (reliable care of children, adherence to deadlines set by the courts and authorities);

- Refraining from co-abuse itself.

This leads to the risk that methamphetamine co-abuse might cause premature discontinuation of replacement therapy (by the physician or the patient fails to present for treatment). As a consequence, those affected fall down the slippery slope into escalating polytoxicomania, dominated by the use of methamphetamine. This, in turn, can lead to a rapid decline in their physical and mental state, and can include the occurrence of life-threatening crises.

The dangerous co-abuse of methamphetamine as a "hard drug" in patients receiving replacement therapy is potentially associated with serious consequences like loss of driver's license, accidents on the job, complications within the criminal justice system up to arrest. That said, the authors nevertheless feel that an individual who occasionally takes methamphetamine should be viewed from a more nuanced perspective. Just because they used the drug must not necessarily lead an overly rushed decision to drop them from replacement therapy, but rather to keep them within the addiction help services system if justified.

The experiences at specialized replacement therapy practices moreover show that many patients receiving replacement therapy who have years of experience with drug use and with managing their own dependence can function as "opinion leaders" for new methamphetamine users. These "old hands" can convey warnings about the risks or pave the way for new users to access addiction help services.

6.2.4   Methamphetamine use and behavioral addictions (e.g. gambling addiction)

Recommendations	Grade of recommendation
6-8 When planning treatment, co-occurring behavioral addictions like e.g. gambling addictions should be taken into account. Expert consensus Vote: 100%	⇑⇑⇑

6.2.4.1   Epidemiology and risk factors

To date, only data from one a study is available on the occurrence of addictive or problematic gambling in methamphetamine users [236]. A comparison of 109 participants in an inpatient detoxification program in the USA showed that pathological gambling was 53% more likely to occur among the 32 methamphetamine users in the study group than in those abusing other substances (29%). The authors recommend routine screening of methamphetamine users for pathological gambling behavior [236].

Hayer (2012) classified risk factors for pathological gambling into individual, environmental (situational) and gambling-related [237].

Under the influence of methamphetamine, self-confidence is heightened, while chronic abusers develop a disturbed ability to assess risk [238]. Since users show binge-like substance use patterns with periods of continuous awakeness lasting several days, gambling halls with their virtually continuous opening times have a magical attraction for them. Moreover, the

stereotypical "one-armed bandits" arouse a huge fascination in individuals on a meth high. Whether this behavior promotes the development of a gambling addiction (even outside of meth abuse) is the subject of debate. There is a lack of robust data on this subject (see Chapter 10 Need for further research).

Treatment of the methamphetamine-related disorder offers a framework within which these sometimes existence-threatening behavioral addictions can be discussed and worked on with users.

6.3 Schizophrenia and methamphetamine-induced psychosis

Recommendations	Grade of recommendation
6-9 Pharmacotherapy of co-occurring psychotic disorders should follow the established principles of psychosis therapy. Expert consensus (LoE 5) Vote: 93%	⇑⇑
6-10 In patients with schizophrenia and co-occurring methamphetamine use, negative symptoms as a possible motive for drug use should be given special consideration when treating the psychosis. Expert consensus Vote: 93%	⇑⇑
6-11 In patients with methamphetamine-induced psychosis, the indication for antipsychotic therapy should be re-assessed after at least six months. Expert consensus (LoE 5), based on [87] Vote: 100%	⇑⇑

6.3.1 Prevalence

In 189 methamphetamine-dependent persons (33% women), Salo et al. (2011) found a lifetime prevalence for methamphetamine-induced psychoses of 23.8% [227].

6.3.2 Diagnostics

Co-occurring psychoses primarily manifest as drug-induced psychoses (ICD-10: F15.5) and as schizophrenia (F20.X). They are to be differentiated from psychotic symptoms during intoxication. The latter only persist as long as direct effect of the drug is expected to last.

Stimulant-related psychoses – termed "psychotic disorder" under ICD-10 code F10 "Mental and behavioral disorders due to psychoactive substance use" – are delineated from schizophrenia (F20) based on the following criteria [53]:

- Manifestation during or immediately following substance use (within 48 hours);

- At least partial recovery within a month;

- Full recovery within six months.

In practice, this differentiation is often not possible because the user is rarely abstinent long enough. Under all circumstances, regular toxicological tests should be performed over the course of the treatment.

A strict dichotomy cannot be assumed if the stress-vulnerability model of schizophrenia is applied [239; 240]. Nevertheless, a differentiation should be attempted to avoid unnecessarily long therapy regimens with neuroleptic drugs. A no longer indicated antidopaminergic therapy, involving effects like anhedonia and loss of drive, might promote relapses.

It is best to use the temporal relationship between use episodes and the development or resolution of psychotic symptoms for differentiation. Iwanami et al. (1994) investigated 104 subjects with methamphetamine-associated psychosis: 54 went into remission within a week of stopping use, 17 within the second week and six others within the first month. By the end of the third month, the symptoms had resolved in 10 additional participants. Nevertheless, 17 patients were psychotic for longer than three months [241]. Bramness et al. (2012) concluded that acute methamphetamine-induced psychoses resolve rapidly [239].

A clear differentiation based on the psychopathological cross-sectional clinical picture is currently not possible.

Patients who previously experienced methamphetamine-induced psychoses are at a higher risk of developing psychoses again. But also a history of schizophrenia and schizotypal personality traits are associated with a higher probability of psychotic symptoms in amphetamine users [239].

6.3.3   Therapy of schizophrenia and methamphetamine-induced psychosis

6.3.3.1   Pharmacotherapy of primary schizophrenia

In primary schizophrenia (F20.X), therapy according to published practice guidelines is recommended. The last S3 practice guideline that appeared in 2005 also recommended that **atypical neuroleptics** be preferred in patients with polydrug use (on this subject, see Info Box 2 in Chapter 4 Acute therapy | Section 4.2.2 Pharmacotherapy [112]).

Since methamphetamine counteracts typical negative symptoms like lack of drive and withdrawal, some cases can be assumed to involve self-treatment attempts. Under these circumstances, the patients can be offered other treatment options like antidepressants. In addition, other potential functional traits of abuse should be considered like a positive impact on anxieties or cognitive deficits.

6.3.3.2   Pharmacological management of methamphetamine-induced psychosis

If methamphetamine-induced psychosis is present, the aim should be to stop the abuse and initiate antipsychotic pharmacotherapy. There are no guidelines to follow for this situation. The "Guidelines for the medical management of patients with methamphetamine-induced psychosis" issued by government authorities of South Australia do not refer to methamphetamine psychoses in the aforementioned sense, but to rapidly resolving psychotic intoxication syndromes. They recommend that **olanzapine** should be given orally or i.m. at an initial dose of 10 mg after failed **benzodiazepine** administration [87].

What is discussed is whether the antidopaminergic effect of neuroleptic drugs can promote cravings and relapses in methamphetamine users. Volkow et al. (2001) described a lower level of dopamine D2 receptors in the orbitofrontal cortex in this population [242]. Bramnes et al. (2012) suggest that the D2 antagonism in neuroleptic drugs could lead to anhedonia and thereby increase the vulnerability for relapses [239]. Moratalla et al. (2014) note that methamphetamine reduces dopaminergic markers in the striatum, thereby resembling early stages of Parkinson's disease [243]. These considerations suggest giving preference to **atypical antipsychotics** (AAP). Moreover, the indication for continuing neuroleptic therapy should be re-assessed after six-months of treatment (see Chapter 4 Acute therapy | Section 4.2.2 Pharmacotherapy).

Evidence

The literature available to date on the pharmacological therapy of methamphetamine-induced psychosis produces the following picture:

Verachai et al. (2014) conducted a trial comparing **haloperidol** (up to 6 mg) with **quetiapine** (up to 300 mg) for the management of methamphetamine-induced psychosis (n=80) [109], in consideration of anhedonia and risks to the extrapyramidal motor system. Both substances achieved a high remission rate (84.1% and 88.9%, respectively), although there was no significant difference between the two. The strength of the trial's findings is limited by the fact that no clear delineation of acute psychoses during intoxication vis-à-vis drug-induced psychoses was made. It was striking that even very low doses (haloperidol 2.3 mg +/–0,8; quetiapine 112.2 mg +/–34) led to successful treatment and that the symptoms went into remission in the majority of patients after 8 days.

Leelahanaj et al. (2005) compared **olanzapine** vs. **haloperidol** in 58 patients with amphetamine-induced psychosis, diagnosed according to DSM IV. Both arms achieved high response rates, although differences in side effects were observed as expected: extrapyramidal motor side effects (EPMS) on haloperidol, weight gain on olanzapine [108]. Although this trial raised fewer doubts about the presence of substance-induced psychoses, the extent to which these were caused by amphetamine or methamphetamine still remains unclear.

For a period of six weeks, Farnia et al. (2014) investigated **risperidone** vs. **aripiprazole** in the therapy amphetamine-induced psychoses diagnosed according to DSM IV. Within the given context, it can be assumed that the 53 subjects were methamphetamine users. Both AAPs achieved a significant reduction in positive and negative symptoms on the SAPS and SANS. With regard to positive symptoms, risperidone was significantly superior. The advantages of aripiprazole in managing negative symptoms were not significant [110].

Wang et al. (2016) compared the same medicines for the same indication. Aripiprazole and risperidone did not differ in terms of good antipsychotic efficacy (n=42). However, aripiprazole showed a higher rate of adverse reactions and lower retention rates [111].

As a partial agonist of the D2 receptor, **aripiprazole** is a candidate for methamphetamine replacement during abstinence while also antagonizing its effect if abused again. Sulaiman et al. (2012) investigated the efficacy of aripiprazole versus placebo for the post-acute management of drug-induced psychosis in 37 methamphetamine users. Compared to placebo, aripiprazole lowered the PANSS score significantly over the further course. The retention rate was significantly better than with placebo, but the abstinence rate was not [244].

Seddigh et al. (2014) published two case studies on **clozapine** for therapy-resistant meth-

amphetamine-induced psychosis [245]. Their two patients remained relapse-free and abstinent for 8 and 9 months, respectively. The authors point to the low affinity of clozapine to D2 receptors, which are reduced among users and to its strong anti-serotonergic effect: "Regarding this profile, clozapine seems to overcome adrenergic and serotonergic arousal seen in methamphetamine abuse." The two theoretically well-justified positive case studies suggest that systematic studies on clozapine for methamphetamine-induced psychosis are needed; these may be difficult to conduct given the medication's known adverse reactions.

6.3.3.3 Other therapies (electroconvulsive therapy)

Evidence

In 2010, Grelotti et al. reported on a case of successful treatment of methamphetamine-induced psychosis with electroconvulsive therapy (ECT) after neuroleptics failed. They pointed out the neuroprotective and neuroplastic effects of ECT [246]. Additional positive case reports on ECT after failure of neuroleptic treatment were published by Ahmadi et al. in 2014 and 2015 [247; 248]. This intervention has not been investigated sufficiently to warrant a recommendation.

6.4 Depression

Recommendations	Grade of recommendation
6-12 To date, available studies have not revealed any efficacy of anti-depressants for co-occurring depression in patients with methamphetamine-related disorder. LoE 2 [97; 99-101; 198; 199; 207] Vote: 100%	**Statement**
6-13 Sertraline should not be administered for the treatment of co-occurring depressive symptoms in patients with methamphetamine-related disorder. LoE 2 [101] Vote: 93%	⇓⇓
6-14 To reduce the symptoms of depression, a symptom-oriented therapy attempt with quetiapine may be offered. LoE 2 [249] Vote: 89%	⇔

Recommendations	Grade of recommendation
6-15 To manage depression, supportive dietary supplements with citicoline or creatine may be considered. Citicoline: LoE 2 [250; 251] Creatine: LoE 3 [250] Vote: 100%	⇔
6-16 To reduce the symptoms of depression, affected patients should be treated with disorder-specific psychotherapy approaches, e.g. cognitive behavioral therapy. LoE 2 [158; 252] Vote: 100%	⇑⇑
6-17 Psychoeducation should be offered. LoE 2 [253] Vote: 100%	⇑⇑
6-18 Sport and exercise therapy should be offered to patients with co-occurring depression. LoE 2 [223] Vote: 100%	⇑⇑

6.1.1   Epidemiology

Psychiatric comorbidity is often seen in methamphetamine users or in patients dependent on it. In one trial on 526 methamphetamine-dependent patients, a concomitant Axis I disorder was present in at least 48%, with the proportion of affective disorders proving particularly high. Females were more frequently affected than males [254]. In numerous studies, the rate of depression in methamphetamine users was higher than 35% [100]. In a cross-sectional study on patients with methamphetamine-induced psychosis, the prevalence of depression was as high as 48% [255].

6.4.1   Clinical Relevance

Depression persists for more than a year after cessation of methamphetamine use [256]. This is possibly due to the diverse pharmacological and toxic effects of methamphetamine on the brain [242; 257]. The concurrence of methamphetamine use and depression interferes significantly with the success of the treatment for both depression and cravings. Here, according to various authors, there is no difference as to whether premorbid depression already existed or was caused by methamphetamine use [258]. However, in choosing the right type of treatment, it is important to consider whether the depression is intrinsic or methamphetamine-induced.

6.4.2 Interventions – Overview

In a review by Hellem et al. (2015), which was of average methodological quality, a total of twelve published studies were analyzed, eight of which were randomized controlled trials (RCT) for the treatment of the dual diagnosis "depression" and "methamphetamine-dependence" [100]. This included three studies of psychological interventions, six pharmacological therapies, two combined psychological and pharmacological interventions and one trial of the dietary supplement citicoline. The authors of this review concluded that the antidepressants investigated (5 RCTs with either mirtazapine, imipramine or bupropion) were ineffective for the treatment of depression. Modafinil (1 open trial) showed a significant reduction in depressive symptoms without reduced use. Depressive symptoms improved by 33% with citicoline (versus 13% with placebo), but no effect was observed on methamphetamine use (1 RCT). The studies of pharmacological and psychotherapeutic combinations with sertraline plus contingency management (CM) showed no effect on depression (1 RCT). Modafinil plus cognitive behavioral therapy (CBT) reduced depressive symptoms (1 single blind trial with HIV-positive participants) compared to placebo [100]. Two studies of psychological interventions in methamphetamine users showed signs of efficacy of CBT and/or a stepped care approach for coexisting depression [196; 252].

The different management options are presented in detail in the following:

6.4.2.1 Pharmacological management

For the pharmacological management of depression, see the systematic reviews by

For the pharmacological management of depression, see the systematic reviews by Brackins et al. (2011), Rajasingham (2012) and Hellem et al. (2015) [98; 100; 104]. It should be noted that the present trials made no general distinction between depression due to substance intoxication or withdrawal symptoms and genuine independent depression as per DSM-IV criteria [100]. Furthermore, none of the pharmacological studies for the treatment of depression verified medication intake by measuring plasma levels. Also, possible pharmacokinetic aspects such as, e.g. increased metabolism of mirtazapine or imipramine in concomitant tobacco smoking or medication interactions were not considered [99; 204; 205; 207; 259]. A meta-analysis by Christian et al. 2007 on 1,016 methamphetamine-dependent persons showed that approx. 65–70% smoke methamphetamine [260]. It is therefore very likely that they also smoke large amounts of tobacco. Overall, it appears that serotonin reuptake inhibitors (SSRI) in particular have no positive antidepressant effect and can even worsen the clinical symptoms in methamphetamine-dependent persons. Medications, on which studies are available, are presented in detail below:

6.4.2.2 Antidepressants

Bupropion

Bupropion is a selective dopamine and noradrenaline (also weak serotonin) reuptake inhibitor (NDRI) and needs the CYP2B6 enzyme to produce the psychoactive metabolite [259]. Bupropion vs. placebo was tested in three RCTs (two in the post-acute setting: n=73, n=151, one in acute therapy: n=26). Sustained-release bupropion 150 mg twice daily (300 mg daily) showed no improvement in depression and anxiety in diverse patient populations with different degrees of dependence. However, known side effects of bupropion such as insomnia, pain (headaches, back pain, muscular-skeletal pain), euphoria and depressive moods were

observed [97; 100; 198; 199]. In the trial by Shoptaw et al. (2008), additional participation in contingency management (CM) and CBT for twelve weeks was offered. On average, only 4–5 CBT sessions were attended and only approx. 35% of the participants continued up to week 12 in the placebo-controlled trial. There was no significant difference in depressive symptoms [199]. Neither did the combination of group therapy (MATRIX) three times a week with sustained-release bupropion 150 mg twice daily produce any improvement in depression, measured as a secondary outcome variable with a two-arm, twelve-week study design [198].

Duloxetine

An experimental human double-blind in-vitro and in-vivo laboratory study with crossover design conducted on 16 patients showed that duloxetine inhibited the release of serotonin and noradrenaline as well as the subjective feelings produced by MDMA (3.4- methylenedioxymethamphetamine) [261]. It is postulated that duloxetine can help in the management of psychostimulant dependence. To date, however, there are no trials of the management of depression with duloxetine in methamphetamine dependence.

Imipramine

Two double-blind RCTs by Galloway et al. (1994; 1996) in a total of 64 methamphetamine-dependent persons, taking different doses of imipramine up to 150 mg over 26 weeks, showed no effect on depression in these patients. However, neither study considered tobacco smoking as a variable that influences imipramine plasma levels [204; 205].

Mirtazapine

Mirtazapine was studied in two placebo-controlled RCTs. A larger RCT was carried out in a post-acute setting (n=60; exclusively MSM) for twelve weeks with 30 mg daily, a smaller RCT in the acute setting during the withdrawal treatment with 30 mg daily for 14 days (n=31). Both studies showed no symptom improvement (including sleep duration, anxiety, depression) as a secondary outcome [99; 207]. However, as patients with major depression were excluded, it is possible that the effects of comorbidities were not seen [207]. Also, the dose of 30 mg used in both studies is rather low. Moreover, it is not stated whether the patients were tobacco smokers. There were no significant differences in the prevalence of side effects and the number of treatment drop-outs due to adverse events. Common side effects of mirtazapine were documented as: Drowsiness, increased appetite and weight gain (see also [98]).

Sertraline (± contingency management)

The antidepressant sertraline inhibits the reuptake of serotonin, noradrenaline and dopamine. A randomized placebo-controlled trial (n=229) with a four-arm design over twelve weeks (sertraline 50 mg twice daily) with and without contingency management (CM) and with retrospective sub group analysis (n=18) in the post-acute setting showed that sertraline (± CM) did not lead to an improvement in the depression [101; 262; 262]. However, patients treated with sertraline vs placebo experienced significantly more side effects, such as nausea, sexual dysfunction, gastrointestinal and anticholinergic symptoms. It is possible that this is also the reason for the significantly poorer retention rates (p < 0,001) and lower utilization of relapse prevention programs (p = 0,014). The dose of sertraline was 50 mg twice daily. It is not clear whether a second sertraline dose was given in the evening. Increased side effects would be expected in this situation. In the post-hoc analysis higher methamphetamine

use and lower abstinence was found when taking sertraline. In all four groups, depression had significantly improved in week 14 by 9 points on the Beck Depression Inventory (BDI).

6.4.2.3 Neuroleptics

Aripiprazole

A small double-blind phase I trial by Newton et al. (2008) on oral aripiprazole given at 15 mg (n=16) and occasionally 30 mg in methamphetamine-dependent persons to evaluate its safety showed no significant difference in depression, mood and psychiatric symptoms compared to placebo [107]. Aripiprazole had no significant effect on (cue-induced methamphetamine) craving. Aripiprazole more frequently caused akathisia, tremor and restlessness (see also [104]).

Quetiapine

A randomized, double-blind trial on 96 patients with bipolar disorder and cocaine (62.5%) or methamphetamine-dependence (37.5%) compared treatment with quetiapine and risperidone over twelve weeks [249]. It should be noted that quetiapine, contrary to risperidone, is also licensed for the treatment and relapse prevention of depression in bipolar disorders. Detailed information on the study design and patient characteristics are provided in Chapter 6.5 Bipolar disorder. The primary outcome was a significant reduction in manic and depressive symptoms from baseline to the end of the study for both substances (p < 0,0005 respectively), however, no difference in mood improvement was found between both treatments. Long-term follow-up was not possible due to a high drop-out rate in the two groups. There were no treatment drop-outs due to adverse reactions. The trial was funded by AstraZeneca. There is no respective trial for the treatment of depression in methamphetamine-related disorders independent of bipolar disorders.

6.4.2.4 Psychostimulants

Modafinil

A randomized, double-blind, placebo-controlled trial on 71 methamphetamine- dependent persons assigned to modafinil (400 mg daily) for 12 weeks, CM and weekly CBT showed no significant difference in depressive symptoms as a secondary outcome variable with comparable retention rates (drop-out rate > 50%) compared to placebo [263]. A small pilot study (n=13) of modafinil (50 mg to maximum 100 mg/day) plus CBT over 18 months showed a positive trend of combined medication and psychotherapy on depression in patients with higher baseline BDI [264]. However, it is not possible to make general assumptions due to the small sample size.

Methylphenidate

In a randomized, double-blind, placebo-controlled trial (n=56), conducted in an outpatient setting in Iran, methamphetamine-dependent persons with a diagnosis of depression without other psychiatric comorbidities received sustained-release methylphenidate in escalating doses (week 1: 18 mg, from week 3: up to 54 mg daily) over 10 weeks. These patients showed a significant improvement in depression, measured as secondary outcome variable [214]. However, there were possibly also patients with opioid-dependence in this cohort, as taking methadone was not an exclusion criterion. Furthermore, the validity of the results is limited due to low patient numbers. The efficacy of taking methylphenidate beyond the dura-

tion of 10 weeks is not clear. Furthermore, in Germany the treatment with methylphenidate of patients with at least dual dependence (methamphetamine and opioids) is not allowed, particularly from a drug regulation perspective. On this topic, see also the detailed explanations in Chapter 6.9 Attention deficit hyperactivity disorder (ADHD).

6.4.2.5 GABAergic substances/anticonvulsants

Baclofen and gabapentin

A randomized, double-blind trial with a three-arm design looked at baclofen and gabapentin vs. placebo over 16 weeks in 88 methamphetamine-dependent persons in an outpatient setting (baclofen 20 mg three times daily; gabapentin 800 mg three times daily) [213]. All patients received additional psychosocial counseling (MATRIX) that was attended by approx. 55 – 60% of patients from all three groups. There was no effect on depression (trend in favor of baclofen), measured as a secondary outcome variable. There was one treatment drop-out due to dizziness with baclofen. The most frequent moderately severe side effects with baclofen were flu-like symptoms, pain, headaches, nasal congestion and toothache. The difference was not significant, however, detailed information about tolerability was not given. This is a trial with relatively low patient numbers, a high drop-out rate and inconsistent information on adherence (see also [98]).

Topiramate

A multi-center, randomized, double-blind, placebo-controlled trial by Elkashef et al. (2012) evaluated topiramate in 140 methamphetamine-dependent users over 13 weeks. The minimum dose was 50 mg daily and the target dose 200 mg daily, which was very often not achieved. A comparative compliance of approx. 70% (week 6) showed no significant effect on the secondary outcome variable "depression" [218]. There are no detailed data on tolerability, however, it was generally well tolerated up to a dose of 200 mg daily. Topiramate is a weak carbonic anhydrase inhibitor and can therefore influence the metabolism of methamphetamine and the excretion in the urine in the sense that methamphetamine plasma concentration increases slightly with topiramate.

6.4.2.6 Cholinesterase inhibitors

Rivastigmine

A small double-blind, placebo-controlled trial on 23 methamphetamine-dependent persons looked at the tolerability of rivastigmine in combination with methamphetamine, including the effect on mood, over 14 days. No effect on mood could be found under these trial conditions [265].

6.4.2.7 Dietary supplements

Creatine

In a multi-center pilot study by Hellem et al. (2015), 14 women with depression and methamphetamine-dependence were treated for eight weeks with oral Creatine monohydrate 5 g daily as nutritional supplement (minimum 50 mg daily) [250]. The background of the trial stems from data showing that reduced brain phosphocreatine concentrations are associated with treatment resistant depression and that these are also reduced in methamphetamine users [266]. The data of this small trial with low case numbers, spread over eight centers,

show significantly improved symptoms of depression and anxiety, measured using HAMD and BAI. Side effects were rare gastrointestinal symptoms and muscle cramps.

Citicoline

Citicoline is a naturally occurring compound, sold in the USA as well as in Germany as a dietary supplement. CDP choline, also known as citicoline, is an intermediate in the synthesis of phosphatidylcholine from choline. Choline is necessary for the synthesis of the neurotransmitter acetylcholine and the essential phosphatidylcholine and sphingomyelin of the cell membranes in the brain. Citicoline increases phospholipid uptake in the membrane, increases the synthesis of structural phospholipids as well as the noradrenaline, dopamine and serotonin levels in the different areas of the brain. Citicoline is said to have neuroprotective and cognition enhancing properties. A Cochrane review reported that citicoline, compared to placebo, significantly improved cognitive function in patients with vascular dementia [267; 268]. A randomized, placebo-controlled trial on 60 methamphetamine-dependent persons with bipolar or unipolar disorder showed that 2000 mg citicoline daily over twelve weeks significantly improved depression without improvement in cognitive functions [251].

6.4.2.8   Psychotherapy and psychosocial therapy

Psychotherapy

In their systematic review, Hellem et al. (2015) concluded on the basis of three psychological (brief intervention + MI/CBT; CBT versus CM versus CBT+CM versus gay-specific CBT; CBT/MI) and two combined psychological pharmacological studies (sertraline + CM versus sertraline versus CM versus placebo; modafinil + CBT) that these interventions are hardly effective in the concurrent diagnoses of methamphetamine-related disorder and depression [100; 101; 196; 252]. That said, the review does point out the considerable methodological limitations of the underlying individual studies which detract from the strength of their findings. The results of the individual studies are also presented in a misleading way: For example, the trial conducted by Peck et al. (2005) on 162 homo- and bisexual male methamphetamine users with overwhelmingly mild depressive symptoms showed that all four investigated interventions (CM versus CBT + CM versus gay-specific CBT) produced a significant improvement in depressive symptoms versus baseline over the clinical course, which was most pronounced in the first month. Nevertheless, the individual interventions did not differ in efficacy. The participation rates in the various interventions ranged between 41% and 74% [252].

Another RCT investigated CM as a psychotherapeutic intervention (sertraline plus CM versus sertraline versus CM versus placebo), but was not able to establish any differences among all four arms in terms of effect on depression [101].

However, it seems questionable to conclude on this basis that there is a lack of evidence for the efficacy of psychotherapeutic approaches in methamphetamine-related disorder and co-occurring depression.

Moreover, another two-arm randomized trial (by Smout et al. [2010]) that was not included in the review proved an effect of psychotherapeutic methods: In this trial, 104 methamphetamine-dependent outpatients (78% i.v. drug use) were treated with CBT versus ACT for twelve weeks to test the difference between ACT or CBT, both given weekly as 60-minute individual sessions. At 24-week follow-up, both arms showed a reduction and significant im-

provement in the self-reported symptoms of depression and of the physical and mental well-being. All data collected over the clinical course produced no significant difference between ACT and CBT.

6.4.2.9 Education

One Thai RCT investigated peer-based education in young subjects aged 18–25 years [253]; a detailed description of it can be found in sections 4.2.3 Psychotherapeutic methods and 7.3 Methamphetamine abuse among men who have sex with men (MSM). Seven 2-hour sessions were administered to small groups of 8–12 participants twice weekly. The contents of the education intervention included: teaching participants to think critically about their methamphetamine use, sexual behavior and sexually transmitted infections. The primary endpoint constituted depressive symptoms scored according to CES-D. Follow-up took place after three, six, nine and twelve months. At twelve months, a significant reduction in CES-D scores was found in the participants of the intervention group (intervention: 20.0 versus 15.7; p < 0.0001; control: 18.3 versus 17.9; p = 0.489), an effect that was less pronounced in the peer network intervention (sexual partners or partners from the drug scene).

6.4.2.10 Sports

In a two-arm randomized trial, 138 newly abstinent, overwhelmingly male methamphetamine-dependent individuals were treated with an 8-week exercise program or health education sessions (control) offered at their residential facility [223]. The structured exercise program, consisting of progressive aerobic and resistance exercise training was conducted three times weekly for 60 minutes. The structured health education control sessions also took place three times a week. Over time, both programs reduced depression and anxiety symptoms, measured by BDI and BAI (self-reported inventories). Compared to the control intervention, the exercise program had a more significant impact on reducing depression and anxiety symptoms. In both groups, the frequency of participation correlated with the improvement in depression and anxiety symptoms. Patients in the health education program were also taught about stress reduction, which might also have had an impact on reducing symptoms.

6.5 Bipolar disorder

Recommendations	Grade of recommendation
6-19 For the management of bipolar disorder, a therapeutic trial with quetiapine or risperidone may be recommended to treat both the depressive and the manic symptoms. LoE 2 [249] Vote: 100%	⇔
6-20 For the management of bipolar disorder, the nutritional supplement citicoline (or creatine) may be offered to treat depressive symptoms. Citicoline: LoE 2 [251] Creatine: Expert consensus (LoE 5), based on [250] Vote: 100%	⇔

Recommendations	Grade of recommendation
6-21 Patients with bipolar disorder should be treated with disorder-specific psychotherapy approaches, e.g. cognitive behavioral therapy, to reduce their symptoms of depression. LoE 2 [158; 252] Vote: 100%	⇑⇑
6-22 Psychoeducation should be offered. LoE 2 [253] Vote: 100%	⇑⇑
6-23 Sport and exercise therapy should be offered to patients with co-occurring bipolar disorder. Expert consensus (LoE 5), based on [223] Vote: 100%	⇑⇑

6.5.1 Risk factors

In a cross-sectional study conducted in Malaysia, risk factors and other factors were investigated that are associated with methamphetamine use in methamphetamine-dependent patients who suffer from psychoses. Here, key factors found were co-occurring depressive disorder with an odds ratio (OR) of 7.18, bipolar disorder with a OR = 13.81 as well as antisocial personality disorder with a OR = 12.61 [269]. Bipolar disorder is therefore not an insignificant psychiatric comorbidity in methamphetamine-dependent persons. In a trial conducted in Iran, among the 121 patients with a documented medical history of methamphetamine-induced psychosis within the last 6 months, 16.5% had a bipolar mood disorder [255].

There is evidence that patients with a bipolar disorder take stimulants to increase the symptoms of hypomania or even mania because they fear a potential drift into depression [270]. A further reason they use amphetamines might be in an attempt to "better control" the weight gain caused by the psychotropic drugs they are taking to manage the bipolar mood disorder, but also to increase the sexual experience. The combination of mania and methamphetamine use can lead to particularly risky behavior.

However, hardly any therapeutic trials have been conducted on the management of this high-risk patient group.

6.5.2 Pharmacological management

6.5.2.1 Neuroleptics

Quetiapine and risperidone

A randomized double-blind trial on 96 patients with bipolar disorder and cocaine (62.5%) or methamphetamine-dependence (37.5%) compared treatment with quetiapine and risperi-

done over twelve weeks [249]. Both drugs were given in escalating doses; the maximum daily doses were 600 mg quetiapine and 6 mg risperidone. Psychosocial therapy was allowed. Patients with bipolar I and bipolar II disorders, hypomanic and manic episodes or mixed states (YMRS) with methamphetamine-dependence were included. Patients with substance-induced mood disorder (DSM-IV) were excluded. 85% received CBT. One primary endpoint was the improvement the bipolar disorder (YMRS, IDS-C30). The majority of patients (approx. 85%) suffered from bipolar I disorder. Bipolar disorder had lasted for 24 years on average. The most frequent mental health comorbidities were posttraumatic stress disorders (PTSD) (36%) and obsessive-compulsive disorder (20%). 50% of the patients received concomitant psychiatric medication. The results showed a significant reduction in manic and depressive symptoms for both substances ($p < 0.0005$ respectively) from baseline to study completion; however, there was no difference between the two therapies regarding mood improvement ($p = 0.26$) and craving ($p = 0.69$). Long-term follow-up was not possible due to a high drop-out rate in both groups. No drop-outs were due to adverse reactions. The trial was funded by AstraZeneca.

6.5.2.2 Dietary supplements

Citicoline

In a randomized placebo-controlled trial on 60 methamphetamine-dependent persons suffering from bipolar or unipolar disorders, depression improved significantly on 2000 mg citicoline daily over twelve weeks with good tolerability. An improvement in cognitive function was not found [251]. (Detailed information on citicoline can be found in Section 6.4 Depression.)

Creatine

In a multicenter pilot study, 14 women with depression and methamphetamine-dependence were treated for eight weeks with a daily dose of 5 g creatine monohydrate p.o. (minimum 50 mg daily) [250]. Although the case number is small, the data show a significant clinical improvement in depressive and anxiety symptoms, measured with HAMD and BAI. Side effects were occasional gastrointestinal symptoms and muscle cramps.

6.5.3 Psychosocial therapy and psychotherapy

In a systematic review, different interventions were studied with regard to their efficacy in methamphetamine-dependence and co-occurring depression (see Section 6.4 Depression) [100; 196]. The applicability of the data to patients with methamphetamine-related disorder and co-occurring bipolar disorder has not been validated. This is also true for the results of a peer-based education trial; a detailed description can be found in Sections 5.2 Psychotherapeutic interventions and 7.3 Methamphetamine abuse among men who have sex with men (MSM) [253].

Weiss et al. designed a 20-hour program for the simultaneous psychotherapy of patients with bipolar disorder and co-occurring substance-use disorder that explicitly takes into consideration and focuses therapeutically on the specific problems of this dual diagnosis and on the interdependence between symptoms (e.g. substance use to balance depressive versus manic symptoms and manic symptoms as triggers for high-risk use). This program was successfully evaluated in a pilot study and an RCT [271-274].

6.5.4   Sports

A randomized trial with 138 recently abstinent, mostly male methamphetamine-dependent persons showed that a regular exercise program lasting 8 weeks significantly reduced depression and anxiety symptoms compared to a health education program [223]. Participation frequency was correlated to an improvement in depressive and anxiety symptoms. A detailed description of the trial can be found in Section 6.4 Depression. Although the trial did not include persons with bipolar disorder, the results seem to be transferable.

6.6   Anxiety disorders

Recommendations	Grade of recommendation
<u>6-24</u> Patients with methamphetamine-related disorder and a co-occurring anxiety disorder should be offered treatment according to the S3 practice guideline "Anxiety disorders". Expert consensus (LoE 5), based on [275] Vote: 93%	⇑⇑⇑
<u>6-25</u> Sport and exercise therapy should be offered to patients with a co-occurring anxiety disorder. LoE 2 [223] Vote: 93%	⇑⇑⇑

6.6.1   Prevalence

Anxiety disorders rank among the most frequently co-occurring mental disorders in patients with methamphetamine-related disorder [2; 276-278]. In the previously cited study by Salo et al. (2011), an anxiety disorder (lifetime prevalence) was found in 24.3% of the subjects. In addition to post-traumatic stress disorders (see Section 6.7 Post-traumatic disorders, post-traumatic stress disorder (PTSD)), the subjects suffered from generalized anxiety disorders (7.4%), coercive disorders (3.7%), panic disorders with and without agoraphobia (2.6% each) as well as conversion disorders (1.1%) [227]. Anxiety symptoms will be manifest in clients with methamphetamine-related disorder, among other conditions, as a component of intoxication or withdrawal (see Chapter 4 Acute therapy). Oftentimes, the anxiety symptoms will persist after stopping the abuse. In this context, anxiety disorders were associated with a poor response to addiction treatment, more frequent requests for treatment and greater burden from psychiatric symptoms [254; 279]. Successful anxiety management is linked to a deactualization of the addiction. Regarding the therapeutic approach to the diagnostics and management of anxiety disorders, reference is made here to the S3 Practice Guideline "Management of anxiety disorders" [275].

6.6.2   Therapy of anxiety disorders

6.6.2.1   Pharmacological management

Evidence

Within the scope of placebo-controlled twelve-week therapeutic studies, **mirtazapine** and **bupropion** were tested for their efficacy during withdrawal in subjects with a methamphetamine-related disorder [97; 99]. No reduction in anxiety was demonstrated. Besides their considerable methodological weaknesses, these studies investigated small numbers of cases and did not study anxiety symptoms as a primary study endpoint. Randomized, placebo-controlled trials, which investigated the efficacy of medications for anxiety diseases as primary endpoint in methamphetamine-related disorders are lacking to date. Pregabalin, approved for generalized anxiety disorder, has not been investigated in patients with methamphetamine-related disorder either. In the package leaflet, one restriction for administration is "a history of substance abuse". That is the reason that pregabalin should not be given to patients with methamphetamine-related disorder.

Finally, no literature-based recommendation for pharmaceutical substances can thus be given for the special indication for treating anxiety co-occurring in patients with methamphetamine-related disorder. That said, it can be presumed that the medications recommended in the S3 Practice Guideline "Management of anxiety disorders" will also have an analogous effect in patients with methamphetamine-related disorder [275]. Even if there is no evidence for this, treatment attempts with medications listed in the S3 Practice Guideline appear justified given that anxiety disorders in methamphetamine-related disorder go hand in hand with a substantial psychosocial burden for those affected and thus should be attributed with an extremely high clinical relevance.

6.6.2.2   Psychotherapeutic management

Evidence

Psychotherapeutic management of anxiety disorder (particularly using behavioral therapy approaches) is indicated. According to the S3 Practice Guideline "Screening, diagnosis and management of alcohol-related disorders" pharmacotherapy and psychotherapy can be combined in the event of poor efficacy [90].

In a randomized therapeutic study (n=217), intensive motivational interviewing plus cognitive behavioral therapy was tested versus a motivational standard therapy with regard to methamphetamine use (see Section 5.2 Psychotherapeutic interventions). Anxiety and depression status were secondary outcome measures. There was a reduction in self-reported methamphetamine use, although no significant differences between the two treatment groups were found with regard to anxiety [164].

One study by Rawson et al. (2015) evaluated an exercise program for patients with methamphetamine-related disorder [223]. The 135 study enrollees received an exercise program consisting of around 60 minutes of aerobic activity on a treadmill and weight training for the major muscle groups. The exercise sessions took place three times a week for eight weeks. The control group received theoretical health education. A significant decline in depressive status and anxiety were measured on the BDI and BAI.

6.7 Post-traumatic disorders, post-traumatic stress disorders (PTSD)

6.7.1 Prevalence

Individuals with substance-related disorders are found to have high rates of traumatic experiences like suffering physical or sexual violence. For example, a German sample of individuals with methamphetamine use had already suffered 34.6% physical violence and 14.4% sexual violence in their childhood [28]. Some international studies report even much higher rates of interpersonal violence in childhood (up to 70%), although these not rarely involve special groups like MSM populations [280].

A frequently co-occurring disorder after traumatic experiences is the post-traumatic stress disorder (PTSD). Their prevalence in individuals with substance-related disorders etc. is dependent on the setting and the substance used. Higher rates are found in harmful use or dependence on illegal drugs (compared with alcohol-related disorders) and in individuals on treatment (compared with those affected in the general population) [281]. One representative survey of the Australian population found that the point prevalence of PTSD in individuals with harmful use or dependence on amphetamine-type stimulants was 23.8% [282]. This was more or less consistent with the rates found by European studies in alcoholic patients entering treatment (15–25%) [283; 284], meaning that an even higher PTSD prevalence of individuals with methamphetamine-related disorders can be expected in treatment settings.

Different studies produced evidence of functional relationships between the symptoms of PTSD and substance abuse. For example, experimental studies showed that individuals with substance-related disorders have stronger cravings when presented with trauma-related cues [285]. Two studies on methamphetamine-dependent persons gave consistent reports that avoidance behavior and vegetative hyperarousal, but not the intrusive re-experiencing associated with PTSD, were related to increased abuse in individuals [286; 287]. A pre-existing PTSD diagnosis was correlated with a more negative therapy outcome after three years [288]. By contrast, studies in patients with methamphetamine-dependence, as well as other substance-related disorders suggest that a trauma-specific treatment can improve prognosis in addictions [289; 290].

6.7.2 Therapy

Recommendations	Grade of recommendation
6-26 Patients with co-occurring PTSD should be offered trauma-specific stabilizing integrative cognitive behavioral therapy. Expert consensus (LoE 5) Vote: 93%	⇑⇑
6-27 Patients with co-occurring PTSD and sufficient use-free phases should be offered exposure-based psychotherapy methods. Expert consensus (LoE 5) Vote: 100%	⇑⇑

As a therapeutic approach, the S3 Practice Guideline "Post-traumatic stress disorder" recommends the delivery of exposure methods while taking co-morbidities and any required stabilization into consideration [291]. Currently, cognitive behavioral therapeutic exposure management and Eye Movement Desensitization and Reprocessing (EMDR) meet the level of evidence Ia [184]. Meanwhile, studies have become available on patients with substance-related disorders and PTSD that integrate interventions with cognitive behavior therapy and elements from trauma and addiction treatment. This applies both to the administration of trauma exposure and stabilizing interventions, whereas the latter proved even more effective in patients with high stimulant use than in patients with low stimulant use [292-294]. The studies on stabilizing methods refer to "seeking safety", an integrative cognitive behavioral therapeutic regimen [295]. It has been shown that exposure-based therapy can also be conducted safely and effectively in heavily addicted patients, despite persistent abuse, when abuse is reduced or has stabilized and a certain degree of alternative coping strategies are available to the patient [292]. Sufficient use-free phases are defined as a minimum of several days around the date of the exposure session. This allows the exposure therapy to take effect in patients while they are not experiencing withdrawal symptoms. Moreover, it must be ensured that the psychosocial and physical situation is sufficiently stable and that a sufficient affect tolerance exists so that the exposure does not put the patients at risk of resorting to abuse as a coping strategy despite the potentially increasing stress they are put under [291]. To date, these two interventions have not been investigated in patient samples that exclusively exhibit methamphetamine-related disorder.

6.8 Personality disorders

6.8.1 Epidemiology

Substance-related disorders and personality disorders frequently co-occur. In 34–73% of patients with drug-related disorders, a co-occurring personality disorder is present [296]. Within the scope of the "National Epidemiologic Survey on Alcohol and Related Conditions" (NESARC) encompassing 43,093 individuals, 47.7% of the drug-dependent individuals had at least one personality disorder [297].

By means of the SCID II interview, Kranzler showed that over 70% of cocaine-dependent patients receiving inpatient treatment suffered from at least one personality disorder. Borderline (34%), antisocial and narcissistic (both 28%), avoidant and paranoid (both 22%), compulsive (16%) and dependent personality disorders (10%) occurred with the greatest frequency [298].

Similarly, high rates of a co-occurring personality disorder were shown in patients with methamphetamine-related disorder. In 70.2% of patients, at least on personality disorder was diagnosed. Borderline personality disorders (35.5%), antisocial personality disorders (6.6%) and their combination (16.5)% and depressive personality disorders (9.1%) were most frequent [255].

6.8.2 Clinical relevance

Patients with substance-related disorder and personality disorder exhibit addiction problems at an earlier age, are younger when they enter into an addiction-specific treatment and have lower psychosocial functioning than patients without co-occurring personality disorder [299; 300]. Premature drop-outs from treatment are common during management of a substance-related disorder. A trial on inpatient-treated drug-dependent persons showed that antisocial

and histrionic personality disorders, in particular, were associated with early attrition from treatment within the first 30 days. Over the entire nine months' treatment, the proportion of dropouts was higher in patients with borderline personality disorders [301]. The comorbidities "substance-related disorder", "borderline personality disorder" and "antisocial personality disorder" are strongly associated with a higher burden of symptoms and worse treatment outcome [302-305].

Besides personality disorders, certain personality traits were found to be linked to methamphetamine use. Studies on methamphetamine-dependent persons administered the "Neo Five Factor Inventory" showed them to have a higher degree of neuroticism, less social tolerability and less conscientiousness compared to a non-abusing control group [306; 307]. Moreover, an association exists between impulsivity, sensation-seeking and substance-related disorders [308]. The above-mentioned personality traits are frequently encountered; they often hold great significance for the development of substance-related disorders and can be triggers for relapses. During psychotherapy, an intensive analysis of the interaction of personality traits and the substance-related disorder is important for relapse prevention.

6.8.3 Treatment setting

For planning treatment strategies in patients with methamphetamine-related disorder and co-occurring personality disorder, it is necessary to select a suitable setting which is compatible with the integrative treatment of both disorders or which coordinates the different treatments. It is important to select treatment settings that enable crises and drop-out tendencies to be identified and therapeutically managed at an early stage. Given this background, the selection of an inpatient setting (e.g. as part of inpatient withdrawal treatment) appears to make sense in many cases.

6.8.4 Therapeutic management of personality disorders

Systematic literature search for drawing up this publication did not identify any RCTs on pharmacotherapy in patients with personality disorder and methamphetamine-related disorder. All attempts at pharmacological treatment, e.g. aimed at crises or co-occurring disorders are undertaken "off label", i.e. without the medication being approved for that indication. Potential interactions between medications and addictive substances (including alcohol) should be considered.

Psychotherapeutic management is deemed the method of choice. The S2 guideline for personality disorders issues recommendations on diagnostics, treatment strategies and therapies that appear to be transferrable to methamphetamine-related disorders and personality disorders in general [309]. One systematic review of the German literature cited dialectical behavior therapy for substance abusers (DBT-S), dual-focus schema therapy (DFST) and dynamic deconstructive psychotherapy (DDP) as efficacious psychotherapeutic techniques. These therapeutic studies were mainly conducted on patients with borderline personality disorder and substance-related disorder [310]. This psychotherapy technique appears to hold a general applicability to patients with methamphetamine-related disorder.

6.9   Attention deficit hyperactivity disorder (ADHD)

Recommendations	Grade of recommendation
6-28 The diagnosis of adult ADHD should be based on the criteria of the 2008 NICE Guidelines and the European consensus: 1. According to ICD-10 and DSM 5 2. Symptoms must be at least moderate, clinically pervasive, occurring in two or more settings (e.g. at home, work etc.) 3. ADHD must already have been present in childhood 4. Diagnosis rendered by two experts Expert consensus (LoE 5), based on [311; 312] Vote: 75%	⇑⇑⇑
6-29 Treatment should consist of a holistic concept including psychosocial, behavior therapy, psychoeducative and family therapy elements as well as pharmacotherapy for ADHD and addiction treatment. Expert consensus Vote: (93%)	⇑⇑⇑
6-30 When the indication for pharmacotherapy is established, first line therapy ought to consist of atomoxetine or antidepressants like e.g. bupropion, venlafaxine or duloxetine. Expert consensus (LoE 5) Vote: 93%	⇑
6-31 Methamphetamine-dependent persons ought to be treated with methylphenidate only in the event that the treatments described in 6-29 and 6-30 show poor efficacy; close monitoring and follow-ups are imperative. Methylphenidate must be discontinued immediately whenever improper use, abuse and misappropriation are suspected. Expert consensus (LoE 5) Vote: 100%	⇑

6.9.1   Prevalence

The prevalence of ADHD in Germany is estimated to be 4.7% of all adults [313]. The majority show co-occurring mental disorders. The most frequent co-occurring disorders alongside substance-related disorders include depression, anxiety, personality disorders [313; 313-315]. In one retrospective study, ADHD was diagnosed in 21% of patients with methamphetamine-related disorder. These overwhelmingly involved the hyperactive and combined subtype. In patients with methamphetamine-related disorder, an ADHD diagnosis was repeated-

ly associated with cognitive disorders and difficulties in everyday functioning [316].

6.9.2   Diagnostics

The diagnosis and management of patients suffering from ADHD and methamphetamine-related disorder should be performed by multi-professional teams. Diagnosis is based on DSM-5 or ICD-10 criteria during the use-free interval. Accordingly, the ADHD symptoms (hyperactivity, impulsivity and attention deficit) must have already been present in childhood and occur in at least two settings (e.g. at home, work etc.). Additional criteria are at least moderate clinical and/or psychosocial impairments (see also S3 Practice Guideline "Screening, diagnosis and treatment of alcohol-related disorders") [90; 311; 312].

The co-occurrence of ADHD and methamphetamine use often poses challenging problems for the attending physician. Many users have come to believe that a "minor" dose of methamphetamine improves their concentration and attentiveness. Over the course of their "self-medication", several of such users develop a methamphetamine-related disorder.

Acute use of methamphetamine and possibly even withdrawal symptoms can clinically resemble ADHD symptomatology. Hyperactivity, attention deficits and impulsivity are hallmarks of these disorders. A reliable differentiation is only possible over the clinical course of an abuse-free interval in consideration of the patient's medical history. (For a more detailed description and duration of withdrawal symptoms on methamphetamine, see Section 2.1 Symptoms.)

A holistic treatment strategy is pivotal to the management of ADHD in adults with methamphetamine-related disorder. Besides psychotherapy, medications can be prescribed as needed.

6.9.3   Therapy of ADHD

Evidence

The systematic search identified no studies on the management of methamphetamine-related disorder and co-occurring ADHD. Currently, **methylphenidate** and **atomoxetine** hold German marketing authorization as medications for adults with ADHD. When making decisions about treatment, it is important to also be aware that none of the medications are approved for the treatment of methamphetamine dependence in Germany.

In adults with ADHD and methamphetamine-related disorder, **atomoxetine** is the medication of choice. Caution should be exercised when co-administering atomoxetine and methamphetamine due to cardiac adverse reactions [317]. In patients with depressive syndromes, a **dual antidepressant** (e.g. bupropion, venlafaxine, duloxetine) can also be given (see also Section 6.4 Depression).

German guidelines are available on the diagnosis and therapy of ADHD in adults: Treatment with methylphenidate has been assessed as efficacious with a 1 B level of evidence (grade of recommendation A) and recommended as pharmacotherapy of choice [318]. Similarly, the frequently cited international NICE guideline recommends methylphenidate as medication of choice for ADHD in adults [311].

The treatment recommendations given in the S3 Practice Guideline on **methylphenidate** administration to adults with ADHD is not directly transferable to patients with methamphetamine-related disorder. There is a potential for tolerance to methylphenidate developing be-

cause its chemical structure is similar to methamphetamine. When these patients are treated with stimulants, the potential for abuse additionally exists, as does the risk that they will resell them on the black market. The prescribing information warns that methylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism because of the potential for abuse, improper use and them selling or giving away the drug.

Patients with methamphetamine-related disorder and ADHD should be treated with methylphenidate only if the above-mentioned treatment approaches and psychotherapy yield poor efficacy. Treatment with methylphenidate should only be attempted under close monitoring of both medical prescriptions and drug abstinence.

If possible, the pharmacological adjustment of a patient to methylphenidate is best undertaken in an inpatient setting. Methylphenidate must be discontinued immediately whenever improper use, abuse and misappropriation are suspected.

In light of the inherent abuse and resale potential of methylphenidate, sustained-release dosage forms should be prescribed and their maximum dosage not exceeded. Additionally, there is a risk of adverse reactions, e.g. cardiac, serotonergic syndrome and even sudden death, when a patient uses methamphetamine on methylphenidate medication [319]. It is necessary to continually review and weigh the risks and outcomes of treatment at close intervals.

6.10   Sleep disorders

Recommendations	Grade of recommendation
6-32 Patients with sleep disorders that persist for more than four weeks after completing withdrawal treatment ought to be offered further diagnostics and any treatment necessary. Expert consensus Vote: 100%	⇑
6-33 Medications with known dependence potential should only be given in justified isolated cases to patients with methamphetamine-related disorder and sleep problems. Expert consensus (LoE 5) Vote: 100%	⇓⇓

6.10.1   Clinical Relevance

Sleep disorders are a major problem for many methamphetamine users. A substance abuse binges with waking phases of several days followed by rebound sleep counts as one of the most common substance use patterns. As part of these patterns, smaller doses of methamphetamine are taken over days to experience the drug's effect and ward off impending fatigue. Over time, the drug's effect wears off and the user "crashes", i.e. they breakdown physically from exhaustion and lack of sleep. In one study on over 900 patients with methamphetamine-related disorder, one third of the subjects suffered from major sleep disturb-

ances measured by the Pittsburgh Sleep Quality Index [320].

Both the use of and withdrawal from methamphetamine influenced objective sleep parameters: After methamphetamine administration, the time required to fall asleep was longer and the total number of hours slept shorter [321]. In patients with substance-related disorders, it has been shown that the relapse risk is elevated when sleep disorders are present [322; 323]. Furthermore, the reoccurrence of sleep disorders may announce a relapse event [324; 325].

During methamphetamine withdrawal, the time required to fall asleep and the total number of hours slept are longer. Furthermore, the subjects wake up more often and complain about diminished sleep quality [326]. During withdrawal, there is additionally more REM sleep [327]. As a result of diminished sleep duration and quality, stimulant users suffer from tiredness during the day, this was found to be linked to cognitive disorders (see Section 6.11 Neurocognitive disorders) [328-330]. It was shown that poor sleep quality was associated with more days of use per month. Multiple usage variables affect sleep quality and daytime sleepiness [331].

During withdrawal, there is often an increased need for sleep; by contrast, sleep disorders with increased time required to fall asleep and sleeping through the night occur during the post-acute treatment phase; this can lead to daytime sleepiness and performance deficits. During methamphetamine abstinence, sleep disorders usually improve within a few weeks. Measures to help users structure their daily routine e.g. during inpatient withdrawal treatment, are often experienced as being helpful.

In some patients with methamphetamine-related disorders, however, all types of sleep problems may persist over a longer period of time. This may serve as reason to seek specialist sleep and psychiatric diagnostics. Oftentimes, sleep disorders are a symptom of co-occurring mental disorders. For example, post-traumatic stress disorders, depression, anxiety disorders, (drug-)induced psychotic disorders and ADHD are associated with a higher incidence of sleep disorders.

6.10.2   Management of sleep disorders

6.10.2.1   Pharmacological management

Evidence

In a double-blind, randomized, placebo-controlled trial on 20 subjects with methamphetamine-related disorder, retention rates, sleep quality etc. were investigated during withdrawal after one week's administration of modafinil. The sleep quality was documented on St. Mary's Hospital Sleep Questionnaire. There was no difference between the modafinil and the placebo groups [115].

Mirtazapine was tested in a double-blind, placebo-controlled trial on 31 study participants with methamphetamine-related disorder during withdrawal for its effect on retention rates and sleep, among other parameters. The results suggested an improvement in sleep disturbances as well as an overall longer sleep duration on mirtazapine [99].

In aggregate, the data and evidence on the pharmacological management of sleep disorders is insufficient, specifically in methamphetamine-related disorder. At present, no evidence-based recommendations can be derived therefrom. Nevertheless, there is a substantial need

for the psycho- and pharmacotherapeutic management of sleep disorders in patients with methamphetamine-related disorder, both during withdrawal treatment and for post-acute management. Therefore, medications should be chosen that do not have any dependence potential (e.g. no benzodiazepines, no benzodiazepine analogues, i.e. Z-drugs, no clomethi-azole). Chapter 4 Acute Therapy discusses the administration of benzodiazepines in patients with methamphetamine-related disorder in more detail. In severe co-occurring mental diseases (e.g. psychoses), benzodiazepines represent one treatment option. In clinical practice, sedative antidepressants (e.g. mirtazapine, TCAs) are given temporarily. In patients currently using methamphetamine, the drug interactions with sleep medication to be prescribed should be critically reviewed and the efficacy of such a prescription evaluated.

6.10.2.2   Other therapeutic options

Oftentimes, options like calming teas, acupuncture, aromatherapeutic applications and sleep hygiene measures are used. There are hardly any data available on these options in the context of patients with methamphetamine-related disorder, although they play a substantial role in therapeutic routine.

Additional information can be accessed in the **Practical guide for patients** on the website of the German Society for Sleep Research and Sleep Medicine (schlafmedizin.charite.de/patienten/ratgeber).

6.11   Neurocognitive disorders

Recommendations	Grade of recommendation
6-34 The presence and extent of neurocognitive disorders ought to be considered when planning treatment. Expert consensus Vote: 100%	⇑
6-35 Medications for neurocognitive disorders can currently not be recommended in patients with methamphetamine-related disorder. LoE 2 [117-119; 127; 210; 216; 251; 332] Vote: 100%	**Statement**

6.11.1 Clinical Relevance

After chronic methamphetamine use, neurocognitive disorders are of great relevance to counseling and treatment. Impulsivity, attention and concentration deficits, disturbances of information processing speed along with disorders of executive function can diminish the treatment outcome and lead to therapy drop-out. Current reviews of scientific studies on cognitive disorders in patients with methamphetamine-related disorders reveal the myriad treatment-relevant aspects of this heterogeneous clinical picture [333; 334]. The ability of these patients' return to work after unemployment is encumbered. Weber et al. (2012) showed that cognitive disorders were associated with unemployment in subjects with meth-amphetamine-related disorder [335].

Chronic high-dose abuse is particularly associated with cognitive disorders. It is notable that individuals with executive function disorders of other origins also are at a higher risk for starting illicit drug use (e.g. ADHD) [336; 337].

In a meta-analysis of 17 studies on the occurrence of cognitive disorders in patients with methamphetamine-related disorder, these patients scored much worse on "learning", "executive functions", "memory" and "information processing speed" compared to non-drug-using control groups [329]. Compared to the other domains, "verbal fluency" is less impaired [338]. It is very difficult to clinically judge the presence and extent of cognitive impairments during a consultation with clients/patients. When the impact on "verbal fluency" is rather small, the impairments may be underestimated. In general, the cognitive functions of patients with cognitive disorders who achieve abstinence from their addictive substance markedly improve during several months' addiction treatment (e.g. as part of inpatient withdrawal treatment) [339]. By contrast, a brief abstinence of up to a month does not lead to any major improvement [340]. Whether a full recovery can be achieved through abstinence from the addictive substance cannot be answered in light of the insufficient study data on the clinical course of abstinence. The effects of frequently co-occurring mixed use (methamphetamine, alcohol, cannabis) on cognitive function should be considered. As part of any therapeutic strategy, multidimensional test diagnostics can make sense to estimate the extent of damage and personalize the planning for the treatment setting (e.g. referral to inpatient treatment).

6.11.2 Therapy of neurocognitive disorders

6.11.2.1 Pharmacological management

Evidence

In placebo-controlled therapeutic studies with respectively small numbers of cases, various active substances have been tested in subjects with cognitive deficits and methamphetamine-related disorder: These included **citicoline**, **donepezil**, **modafinil**, **risperidone**, **rivastigmine** and **varenicline** [117-119; 127; 210; 216; 251; 332]. In aggregate, the results produced no markedly positive effects. Several studies yielded contradictory results. Most studies only diagnostically tested individual domains of cognitive functions, e.g. attention, working memory and reaction time, which limits the strength of the findings and narrows the inter-study comparability. Ultimately, larger therapeutic studies are required to enable an assessment of the therapeutic effects on cognitive function domains exerted by individual substances (as well as their role within patients' everyday life).

6.11.2.2 Cognitive training methods

In terms of therapeutic methods, many therapy centers are already working with different types of cognitive training. In their review, Rezapour et al. describe methods of neurocognitive rehabilitation especially tailored for methamphetamine-addicted individuals [341]. Therein, they determined 1. Memory and Learning, 2. Motor Functions, 3. Social and Emotional Processing, 4. Attention and Working Memory, 5. Impulsivity, Inhibition and Self-Control as the main targets of neurocognitive rehabilitation. Cognition-promoting methods (cognitive stimulation therapy) including both "paper and pencil" testing, but also computer-based retraining are recommended. In Germany, there are several cognitive training programs sold on the market. Moreover, memory strategy training, e.g. with memory aids are used to compensate for deficits. Reminder techniques and electronic reminder and memory aids (e.g.

smartphone) are also used. Another approach to neurocognitive training is meditation and mindfulness-based therapeutic approaches. These techniques can be used to train attention performance and practice interference control. Sport and exercise therapy is similarly administered as supportive methods [341]. A scientific evaluation and standardization of the individually applied methods is desirable.

6.12   Oral and dental hygiene problems – Warning signs for dentists and dental hygienists

Long-term methamphetamine use can affect oral health and hygiene. Typical symptoms of the advanced stage include marked tooth erosion, significant caries and periodontitis, subsumed under the term "meth mouth". In a matched-pair analysis with 100 German methamphetamine users (1 g/week over ≥ 12 months) showed that they had a significantly higher prevalence of caries, gingivitis and periodontitis compared to the control group. At the same time, oral hygiene was markedly worse among the methamphetamine users [44]. In methamphetamine users, the individual risk for oral diseases is affected by other factors besides the stimulant itself. These include oral hygiene and dental care, saliva quantity and quality, dietary habits, use of additional potentially pathogenic substances and socioeconomic status [44; 45].

No systematic literature search was conducted on therapeutic interventions against oral manifestations of chronic methamphetamine use. The cited publications are not based on clinical studies; rather, they merely present the problem and issue recommendations for therapy. When preparing the herein-contained instructions for dentists and dental hygienists, this was considered as much as was experience from clinical practice [342-346].

Recommendations	Grade of recommendation
6-36 Special aspects ought to be accounted for in the dental care and management of methamphetamine users (see list below). Expert consensus Vote: 100%	⇑

• Suspected methamphetamine dependence

A methamphetamine-related disorder should be weighed into the differential diagnostic balance especially in young patients, who complain about dry mouth, extreme bruxism and exhibit unexplained changes in the oral cavity and symptoms of nutritional deficiency. If this suspicion is confirmed, the following measures are recommended:

- Critically evaluate the patient's general health status, particularly the infection status (HIV, hepatitis).

- Moreover, a detailed medical history about the co-abuse of any other addictive substances should be taken.

- If the patient is receptive to medical counseling, a physician qualified in addiction medicine or a clinic specialized in addiction therapy and withdrawal should be consulted.

- See Appendix/addresses

Prophylactic measures

- Topical fluorides, remineralizing products and chlorhexidine should be prescribed for caries prevention.

- Due to the elevated risk of xerostomia, methamphetamine users should be recommended to drink 8–10 glasses of water daily and avoid diuretic substances like caffeine, tobacco and alcohol.

- Additionally, they should stimulate salivation with pilocarpine (5 mg t.i.d.) and frequently chew sugarless chewing gum. Before administering the cholinergic pilocarpine, however, a judicious review of the potential contraindications should be undertaken.

- Due to the risk of reduced buffer capacity of saliva and the associated increased risk of erosion, restrictions should be placed on acidic foods and abrasive toothpaste while more-gentle brushing should be recommended.

- A mouth guard therapy should be prescribed concomitantly to protect the enamel and dentin, and prevent temporomandibular joint problems [347; 348].

Dental treatment

- If an invasive dental measure is required, paranoia, anxiety and paradoxical painful sensation should be taken into consideration when planning the therapeutic strategy.

- In general, a local anesthetic without vasoconstrictor action should be used since the vasoconstrictor proportion in the local anesthetic can cause abnormal sympathicotonic triggering in the patient. If a local anesthetic with vasoconstrictor is urgently indicated, the patient should be made to abstain from methamphetamine for not less than 24 hours before any dental intervention.

- In patients with advanced caries, tooth extraction is recommended.

- In an early stage of dental caries, glass ionomer cements and copolymers can be used as filling materials with the advantage of fluoride release.

- Intubation anesthesia should be considered within the scope of any extensive restoration. It is advisable to consult a maxillofacial or oral surgeon.

- During the postoperative phase, opioid analgesics should not be prescribed because of the potential for abuse and respiratory depression; therefore, non-steroidal anti-inflammatory represent the medication of choice.

- Other organic diseases that can co-occur with harmful methamphetamine use are described Chapters 2.1 Symptoms and 4 Acute Therapy .

7   Special situations

Stephan Mühlig, Henrike Dirks, Janina Dyba, Michael Klein, Jeanine Paulick, Norbert Scherbaum, Jan-Peter Siedentopf

7.1   Pregnant women, young mothers and prenatal harm

The highest prevalence of problematic methamphetamine use in women can be found in the age groups between 20 and 30 years [29]. One special problem with these methamphetamine-using young women of reproductive age—also compared to other drugs—lies in the fact that they have sexual intercourse without contraception with an over-proportionately high frequency, which leads to unwanted pregnancies [349; 350]. Some of the reasons for this include the specific, sexually disinhibiting and experience-enhancing pharmacological effect of methamphetamine, i.e. heightened intensity of sexual arousal and experiencing orgasm. This sexualizing effect in conjunction with the drug-induced loss of executive control and self-control tends to be associated with other risk behaviors, i.e. frequently changing sexual partners extending to excessive promiscuity, unprotected intercourse, procurement prostitution. With long-term methamphetamine use, menstrual cycle disorder can occur, preventing the women from knowing when their last period stopped or started. These factors are presumed to substantially elevate the risk for pregnancies that are unplanned or noticed too late in addition to delayed or insufficient prenatal preparation [77; 78; 351].

7.1.1   Prenatal methamphetamine exposure due to maternal abuse during pregnancy

Recommendations	Grade of recommendation
7-1 Methamphetamine use during pregnancy and nursing causes considerable harm to the unborn fetus or neonate. LoE 2 [352] Vote: 100%	**Statement**
7-2 Physicians and other healthcare staff who treat or care for pregnant women at inpatient and outpatient centers providing obstetric, prenatal care, neonatology and pediatric services ought to be continually educated about the problems potentially posed by continuing methamphetamine use during pregnancy, sensitized to the high risks for mother and unborn child and trained in dealing with this problem (including brief interventions). Expert consensus Vote: 100%	⇑

Recommendations	Grade of recommendation
<u>7-3</u> Pregnant women who use methamphetamine should receive early instructions about the associated risks to the embryo, fetus and clinical course of pregnancy. This particularly applies to educating them in an understandable manner about the increased frequency of prenatal growth disorders, defects, learning and behavior disorders in addition to the potential for early onset of labor and premature placental detachment. Expert consensus Vote: 100%	⇑⇑⇑
<u>7-4</u> Pregnant women with a medical history of drug abuse or suspected of currently abusing drugs should be motivated to undergo voluntary drug screening tests. Expert consensus Vote: 100%	⇑⇑⇑
<u>7-5</u> Pregnant methamphetamine users should be supervised by an interdisciplinary team, at best consisting of a close cooperation between outpatient and inpatient facilities of addiction medicine/help services, obstetrics, neonatology departments as well as family / youth help services. Expert consensus Vote: 100%	⇑⇑⇑
<u>7-6</u> Pregnant women with pre-existing methamphetamine use should be encouraged to achieve abstinence as fast as possible and be referred to the corresponding needs-appropriate counselling and therapy services. Expert consensus Vote: 100%	⇑⇑⇑
<u>7-7</u> If abstinence cannot be achieved immediately, measures of harm reduction should be recommended and organized (see Chapter 9 Harm reduction). Expert consensus Vote: 100%	⇑⇑⇑

Recommendations	Grade of recommendation
7-8 When encountering pregnant women with a medical history of drug abuse or suspected of currently abusing methamphetamine, pre- and perinatal precautionary measures ought to be taken to prevent complications during birth. Expert consensus Vote: 100%	⇑
7-9 Methamphetamine-using pregnant women should be urgently advised to deliver in a perinatal medical center. Expert consensus Vote: 100%	⇑⇑
7-10 The neonates of methamphetamine-using women should be examined for possible prenatal harms and provided needs-appropriate medical, therapeutic or pedagogical services to compensate for potential harms over the further clinical course. Expert consensus Vote: 85%	⇑⇑
7-11 If a neonatal abstinence syndrome (NAS) is presumed, the approval of the mother should be obtained to screen for the specific substance in mother and child. Expert consensus Vote: 91%	⇑⇑
7-12 If NAS is suspected, a standardized Modified Finnegan Neonatal Abstinence Score Sheet should be administered to prepare for and accompany therapy. Expert consensus Vote: 100%	⇑⇑
7-13 Upon the onset of a NAS, supportive care measures should be initiated. Expert consensus (LoE 5), based on [353] Vote: 100%	⇑⇑

Recommendations	Grade of recommendation
7-14 Upon the onset of a severe NAS, suitable, symptom-related pharmacological treatment ought to be given. Expert consensus (LoE 5), based on [354; 355] Vote: 100%	⇑

7.1.1.1 Prenatal methamphetamine exposure due to maternal abuse during pregnancy

As with other psychoactive substances, when expecting mothers abuse drugs (alcohol, illicit substances) during pregnancy they run a high risk of causing potentially very serious harms to their unborn child [150; 356]. It should be assumed that all psychoactive substances diffuse readily across the placenta to the fetus. This was documented for methamphetamine in animal studies and hair analyses [357; 358]. Substance exposure leads to prenatal dependence in the embryo or fetus, growth impairment, congenital malformations, organ damage, withdrawal symptoms after birth and increased susceptibility of neonates to infections. Developmental delays and behavioral anomalies can persist beyond adolescence (see Section 7.1.2 Postnatal consequences and late sequelae).

Depending on the pattern of use and route of administration, there is a risk of infectious diseases (sexually transmitted diseases, STD), such as HIV or hepatitis, that potentially can complicate the pregnancy [359; 360].

The prevalence of drug-exposed neonates is estimated at 7–18% [361]. A substantial proportion of women using methamphetamine continue to abuse drugs during pregnancy as they notice too late, repress the thought of being pregnant or cannot or do not want to stay abstinent. Existing data and reports indicate that the proportion of methamphetamine-using pre- and peripartum women is higher than for other illegal drugs: In one monocentric observational study conducted by the Department of Neonatology, Clinic and Polyclinic for Pediatrics and Adolescent Medicine, University Hospital Dresden, urine drug screening tests in known methamphetamine-using mothers and their newborns were carried out peripartum, after obtaining consent from the mothers. In more than half of the mothers and/or neonates, urine screening performed immediately after birth was positive for methamphetamine. This suggests that drugs were used immediately before delivery and contradicts claims by pregnant women frequently heard in clinical routine that they stopped drug use once they knew they were pregnant. It remains unclear whether pregnant methamphetamine users at least reduce their methamphetamine use or not.

7.1.1.2 Harms due to methamphetamine use during pregnancy

Statement of the problem

During pregnancy, methamphetamine crosses the placenta and enters into the unborn child; this can lead to miscarriages, premature births alongside a broad range of malformations and deficiency syndromes [362-366]. Furthermore, methamphetamine use weakens the mother's body (lack of fluids and nutrients, disturbs the sleep-wake cycle, causes severe cardiovascular strain, weakens the immune system), which, in turn, can lead to further developmental problems in the child. Growing evidence shows that serious prenatal damage (e.g. micro-

cephalus, vertically transmitted infections) and the resulting potentially unfavorable courses of development in the child (e.g. intrauterine growth retardation) is caused by maternal methamphetamine use during pregnancy [367-369]. Prenatal damage can occur either due to the primary pharmacological effects of methamphetamine (neurotoxicity) or to secondary stresses to both the mother's body (e.g. risk of premature placental abruption) and the unborn or neonate (asphyxia and respiratory distress syndrome, danger of respiratory arrest, dyspnea, hyperexcitability, severe agitation and increased susceptibility to stress).

A systematic review of evidence from international studies on the effects of prenatal methamphetamine use on the child [352] identified 27 publications from a total of 12 studies. In these published studies, the effects of prenatal methamphetamine use were investigated in the following areas of childhood development (see Guideline Report): health (e.g. infant and child mortality, premature birth), cognitive (e.g. neuropsychological and impairment of executive function), motor (e.g. movement, gross and fine motor function, coordination), neurobehavioral (e.g. attention, stress and arousal regulation), neuronal (e.g. structural and metabolic changes) as well as physiological development (e.g. gestational age, head circumference, height and weight). Among the harm domains investigated by the studies, problems in physiological development (23 publications) led the list, ranking in dominance over damage to neurobehavioral (11 publications) and health development (9 publications). The study results respectively referred to significant differences in methamphetamine-using mothers compared to a parallel group of mothers not using drugs. The most frequent significant differences found were in gestational age (15 publications with and 5 studies without significantly lower gestational age in methamphetamine-exposed children) [363-367; 369-378]. Five of a total of six publications with the outcome "premature birth" (before the 37th week of gestation) showed a significantly higher probability of premature birth in methamphetamine exposure, compared to the unexposed control group [13; 14; 17; 18; 29; 37]. In three of the six studies, a two to three times higher risk of premature birth was found for prenatal methamphetamine exposure compared to mothers with no drug use [13; 14; 17].

A retrospective cohort study [14] identified a risk of very early premature birth (before the 32nd week of gestation) 4.5 times higher in methamphetamine exposure. Forrester et Merz (2007) found that prenatal methamphetamine use is associated with an increased risk (22%) of birth defects. The most frequent harms were found mainly to the central nervous system (e.g. microcephalus) and the cardiovascular system. With regard to weight and head circumference, the study results were inconsistent: A significant difference was only found in around a third of the studies [369; 372; 374; 377; 378]. Chang et al. (2004) detected significantly lower brain volumes in methamphetamine-exposed children, with significant changes additionally being found in the white matter [379-381]. The two publications investigating metabolic changes yielded significant differences in striatum, thalamus and white matter [371; 382]. Four of six publications on the cognitive development of methamphetamine-exposed children reported significant differences in executive functions [21; 32], neuropsychological problems (e.g. significant impairment of continuous attention as well as verbal and spatial long-term memory) [30] and cognitive problems (e.g. significantly impaired learning progress compared to unexposed children of the same age, difficulties in completing tasks besides inattentiveness; OR = 2.8 for cognitive problems in methamphetamine-exposed children) [15; 32]. All six publications on motor abnormalities reported significantly unfavorable differences for children with prenatal methamphetamine exposure: Impairment of grasping movements and fine motor function [377], coordination [381; 383], quality of movement [25; 37] and gross motor function as well as motor performance [384]. Ten of 11 publications on neurobehavior-

al development showed significant differences, for example, with regard to attention problems and ADHD [373], impaired inhibition control [365] as well as significantly higher stress and significantly lower arousal regulation [372; 374; 385-387].

To date, no German data are available on this topic. In the aforementioned monocentric observational study by the Department of Neonatology, Clinic and Polyclinic for Pediatrics and Adolescent Medicine, University Hospital Dresden, it was noted that methamphetamine-using pregnant women attended their first prenatal check-up late in their pregnancy: About 21% of the affected women did not present until they were in the advanced stages of pregnancy (after the 20th week of gestation). 14% of methamphetamine-using pregnant women did not attend any pre-natal check-ups prior to delivery at all [388]. According to this survey, between the years 2007 and 2015, 129 neonates required post-natal treatment for intrauterine methamphetamine exposure. The number of fetuses affected by maternal use of drugs of addiction (ICD-10 P04.4) (here: methamphetamine) increased between 2007 and 2015 in the University Hospital Dresden from 2 to 34 cases [389]. An underestimation of prenatally exposed children and therefore an underreporting of cases can be assumed here. For one, this is because the drug screening tests conducted as part of this routine data collection were only ordered in suspected cases. Another reason is that, unlike opioid-exposed, methamphetamine-exposed neonates can initially remain clinically unremarkable. The rate of neonates with microcephalus in methamphetamine-using mothers increased three-fold (22.1%). Morphological abnormalities were found particularly in the brain (approx. 26%), heart (approx. 12%) and kidneys (approx. 9%) [388].

Awareness and diagnostics

To date, there are no studies available on the practicability, acceptance or efficacy of diagnostic screening measures for the detection or early detection of maternal methamphetamine use during pregnancy.

In light of the available findings on the risks of complications and harms for the unborn children of methamphetamine-consuming mothers, it is nevertheless, ethically and clinically imperative to encourage pregnant women to undergo drug screening tests whenever there is a medical history of or a current suspicion of drug abuse (see Sections 2.2 Diagnostics and 3 Awareness and early intervention). Given that the performance of drug screening tests against the will of those affected is a) not possible and b) could be associated with the risk that drug-consuming women will refrain from contacting obstetric care services, such measures are generally predicated on the consent of the affected patient. The detection of maternal methamphetamine use during pregnancy as well as the provision of appropriate assistance and supportive options aimed at achieving the fastest possible drug withdrawal in the methamphetamine-using mother first requires an awareness and a sufficient mindfulness of the problem on the part of professional groups working in this healthcare sector – alongside the availability of expertise in addiction medicine. In some regions (e.g. Saxony, Berlin), networking liaisons currently exist or are emerging between obstetrics, youth and addiction help services as well as other stakeholders within the healthcare system. These networks coordinate expertise in medicine, social medicine, social pedagogy and addiction therapy and organize effective assistance options for the affected neonates and their families.

Interventions

Currently, the data and evidence are still very rudimentary when it comes to prevention measures against methamphetamine use in pregnancy or targeted interventions aimed at

achieving fast withdrawal and withdrawal management of methamphetamine-using pregnant women and thereby on the prevention of prenatal harms due to maternal methamphetamine use.

The systematic evidence searches only turned up one clinical efficacy study on targeted interventions in the high-risk group of methamphetamine-using females. Jones et al. (2014) tested the acceptance a *women-specific intervention* (Reinforcement-based Treatment plus Women's Health CoOp; RBT+WHC) versus a psychosocial education (PE) in a two-arm RCT on 36 *pregnant* methamphetamine-dependent women of color (duration of use: 31.7 months) in South Africa (age: > 18 years old; currently pregnant; methamphetamine use in the past 30 days; regular methamphetamine use in the past 6 months; unprotected sexual intercourse in the past 30 days; HIV-negative) [390]. Sessions for both interventions occurred four times before the expected due date on four consecutive days. On each intervention day, either the two-hour specific intervention (RBT+WHC) or the PE were carried out. The intervention (RBT+WHC) contained modules addressing pregnancy and parenting, drugs and alcohol, HIV prevention and planning the future; the PE consisted of simply imparting information with the same scope as frontal presentation. Endpoints were: a) Methamphetamine use in the past 6 months, b) Sexual risk behavior (unprotected sex with changing partners) in the past 30 days, c) number of prenatal appointments attended and d) Neonatal outcome (neonatal length of hospital stay; birth weight and gestational age at delivery). Acceptance of the intervention was high: 33 of 36 participants attended all four sessions. In both groups, a significant reduction in methamphetamine use was found over the course of the study. There were no differences determined between the groups with regard to the frequency of drug use, unprotected sex, number of antenatal appointments attended and neonatal outcome (neonatal hospital stay; birth weight and gestational age). *Limitations*: Small sample size; the study primarily focused on feasibility and acceptability and not on demonstration a difference in efficacy; the overwhelming proportion of women were in stable relationships with main sex partner, detracting from the strength of findings on condom use; and a control group without intervention was lacking.

Insofar, the recommendations in this Chapter are based primarily on clinical experience and clinical consensus. It is urgently recommended that pregnant women with current methamphetamine use be encouraged to achieve abstinence as fast as possible and be put them in contact with the appropriate needs-aligned counselling or therapeutic services (see Overview: Chapter 2.3.2 Supportive and therapeutic services). Qualified inpatient withdrawal treatment is a suitable method or a needs-aligned therapeutic service for achieving this purpose. If abstinence cannot be attained immediately, harm-mitigating measures should be initiated as quickly as possible (see Chapter 10 Research needs). If the affected pregnant woman is not willing to take any harm-mitigating measures, she should not be put off by a rigid adherence to protocol. Rather, it is imperative that she be kept in the folds of addiction help services and repeatedly and caringly encouraged to take the necessary measures to protect the unborn child.

7.1.1.3 Methamphetamine-related complications of delivery

Statement of the problem

Mothers who continue to take drugs during pregnancy have a higher rate of perinatal complications and of maternal and neonatal mortality [362; 363; 391]. The organic sequelae of chronic drug abuse, maternal withdrawal syndromes or later mental disorders (craving, anx-

iety about repression or return to drug milieu, financial or judicial problems can cause pregnant women to be less able to cope with stress and feel greater stress as mothers before the birth and during the delivery. For example, these stress reactions are associated with elevated adrenalin secretion and a narrowing of the blood vessels in the umbilical cord; this in turn, can constrict the blood flow, nutrient supply and oxygen getting to the fetus. As a consequence, there is a significantly higher risk of premature labor, hemorrhaging, possible premature placental detachment alongside a markedly increased risk of miscarriage or premature delivery [376; 388]. In the monocentric observational study conducted by the Department of Neonatology, Clinic and Polyclinic for Pediatrics and Adolescent Medicine, Dresden University Hospital, the rate of premature births (< 37 gestational week) among the pregnancies of mothers with identified methamphetamine use was 32%, i.e. four times higher than average; whereas the proportion of hypotrophic children with a birth weight < 10th percentile was three times (24.2%) higher than average. Moreover, the rate of neonates with too low head circumference (22.1%) was similarly three times higher than the average for the Federal State of Saxony [388].

Awareness and diagnostics

Given these significantly higher risks for complicated deliveries, early detection of maternal drug abuse is critically important.

Interventions

Empirical studies on the efficacy of appropriate measures could not be found. Based on clinical experience, however, the following measures are urgently recommended:

In methamphetamine-using pregnant women who have not managed to achieve timely abstinence during pregnancy or perinatal care or who are physically and mentally impaired as a result of their chronic abuse or substance withdrawal (e.g. increased aggressiveness), appropriate precautionary measures need to be taken before and during birth. In light of the elevated risk for a premature placental detachment, the delivery should take place under continuous CTG monitoring.

Additionally, affected patients might be infected with previously undiagnosed infectious diseases. Beside the possibility of perinatal transmission (e.g. HIV, hepatitis) to the child, the healthcare staff must protect themselves in this regard as well. Given the often lacking or insufficient prenatal care, the presence of previously undetected growth disorders, congenital birth defects or diseases (e.g. congenital rubella syndrome, cytomegaly, infections, syphilis) must be expected.

7.1.1.4   Neonatal withdrawal symptoms or neonatal abstinence syndrome (NAS)

Statement of the problem

Maternal methamphetamine use can result in a neonatal abstinence syndrome (NAS). For 30 years now, NAS has been classified as a separate clinical diagnosis (ICD-10 code P96.1) that manifests as neurological (e.g. tremor, irritability, hypotension and somnolence), gastrointestinal (limited sucking, reduced fluid uptake, poor weight gain) and autonomic nervous symptoms (tachycardia, trembling, vomiting, tendency to seizures, pain). The time of NAS manifestation depends on the last drug intake (chronic abuse versus acute intoxication), total dose, route of administration, but is also affected by the pharmacokinetics and dynamics of the substance used by the pregnant woman.

The onset of the neonate's clinical symptoms mostly occurs immediately postnatally (amphetamine abuse), but may take up to 36–72 hours or with a delay of as many as 7 days to four weeks in the case of co-abuse with sedating psychotropic drugs. The severity and course of NAS are apparently independent of gender, race, APGAR score, gestational age or substance levels in the child.

As a function of the type and number drugs used during pregnancy, the NAS incidence is estimated to range from 4–95% [354; 361]. It most frequently occurs from polytoxicomania. In hospitals in Saxony, methamphetamine-induced NAS has been occurring with a dramatically rising tendency since 2010 (2010: approx. 25 cases, 2011: approx. 45 cases, 2012: approx. 80 cases, 2013: approx. 115 cases, 2014: approx. 168 cases, 2015: approx. 186 cases), whereas opioid-induced NAS has been stagnating with numbers approaching 20 cases annually. The data collected by the Saxony Neonatal Survey in the Dresden University Hospital in 2013 produced 146 neonates in total with withdrawal symptoms due to the mother taking addictive drugs during the pregnancy.

The most frequent symptoms include hyperexcitability/irritability (38%), hypotension/somnolence (35%), poor feeding and suck (24%), excessive sucking (17%), Vomiting/spitting up (8%), seizures (4%), sweating (4%) and hypertension (3%) [388].

Awareness and diagnostics

The diagnosis of NAS is relatively simple when the mother has a known medical history of drug abuse (opioids). Besides drug screening of the mother and newborn, it is recommended that the diagnosis be validated by determining the time of NAS manifestation, its clinical course, the need for pharmacological therapy and the response, but also to use NAS scoring starting at birth (e.g. Loretta Finnegan) [392]. If it the mother's drug and substance abuse status is unknown and the symptoms in the neonate are unclear, substance screening tests cannot be dispensed with in order to establish a differential diagnosis to rule out other diseases with similar symptomology.

A suspicion of NAS is always to be equated with suspicion of substance abuse in the mother. In principle, she has the right to refuse to diagnostic measures that would yield a result that she is already aware of (proof of substance abuse). In order to enable a more nuanced therapy of the neonate, the intrauterine substance exposure of the fetus needs to be known [393]. Given this background, the mother should be instructed about the importance of giving a truthful account of her medical history as well as having it underpinned by a maternal drug test. Supplementally, urine, blood and meconium tests (rarely hair analyses) can be used to postnatally diagnose the child's prenatal substance exposure. The results only represent the cumulative findings of the last weeks of pregnancy and therefore might even be irrelevant to the current situation. Since these tests affect the ill neonate, it is also possible to perform testing against the mother's/parents' will in the interests of the child; sometimes this involves obtaining a court order [394; 395]. Since such a measure can irreparably destroy the mutual trust between patient and doctor, it should only be resorted to in exceptional cases or after the failure of an attempt to obtain consent.

Seeing as the most common symptoms of methamphetamine NAS cannot be measured by the classic Finnegan score, it appears advisable to adapt the score. The table depicted below takes account of this adaptation. Such a score is predicated on cross-sectoral interdisciplinary cooperation wherein all stakeholders work towards the goal of determining and describing the child's clinical symptoms more exactly. The previously collected data from a clin-

ical observational study show that methamphetamine withdrawal contrasts with the classic opiate withdrawal; it is more heterogeneous in nature, exhibiting a diversity of unspecific symptoms. This might be caused by two things: the very commonly observed co-abuse (including, but not limited to nicotine, alcohol, cannabis, psychotropic drugs) and secondly, by whether methamphetamine was taken immediately prior to delivery [388].

The Finnegan score is measured between meals with the patient at rest.

Table 10 Neonatal abstinence syndrome after methamphetamine use during pregnancy (adapted from [355; 388; 392])

Neurological symptoms	Gastrointestinal symptoms	Autonomic nervous system symptoms
38% Hyperexcitability	24% Poor feeding and suck *(2)*	35% Hypotension
35% Somnolence	17% Excessive sucking *(1)*	4% Sweating *(1)*
4% Seizures *(5)*	8% Vomiting *(2/3)*	3% Hypertension
High-pitched crying *(2/3)*	Diarrhea *(2/3)*	Fever *(1/2)*
Tremors at rest *(3/4)*	Poor weight gain	Respiratory rate *(1/2)*
Tight muscle tone *(2)*		Mottled skin *(1)*
Myoclonic jerks *(3)*		Excoriation *(1)*
Hyperactive Moro reflex *(2/3)*		Frequent yawning *(1)*
Tremor when disturbed *(1/2)*		Nasal flaring *(2)*
Sleep after feeding *(1/2/3)*		Stuffy nose *(2)*
		Sneezing *(1)*

The numbers in italics represent the weighting on the Finnegan score, percentages of the symptom frequency are based on Dinger. All Items without weighting in italics are scored with two points, making 57 the maximum achievable score.

If symptoms of the upper part of the table are mainly manifest, methamphetamine withdrawal is likely. Whether this first attempt to modify the Finnegan score is practicable will not be seen until further data are collected and analyzed, at best on a multicentric basis. Given this background, it cannot be emphasized enough that co-abuse might play a—or perhaps even THE decisive role—in the development of symptoms in the child. What frequently remains unknown is the extent to which such symptoms are due to intoxication or withdrawal.

Interventions

Evidence

The standard measure for treating NAS should be non-pharmacological "supportive care" and, if possible, include admitting the neonate to a level I or II inpatient neonatal center for monitoring and therapy [354; 355; 361; 392].

Supportive care includes:

a) Low-stimuli environment (remove nociceptive stimuli such as light, noise, commotion etc.),

b) Close spatial boundaries (swaddle or snugly wrap baby in blanket and cradle, "kangarooing"),

c) Early feeding (frequent high-calorie formula feedings with smaller amounts),

d) Adequate electrolyte and volume replacement.

Severe withdrawal symptoms require pharmacological therapy. Adequate pharmacological management targets the control of severe withdrawal symptoms within 48–72 hours after medication induction and should be closely monitored by NAS scoring [354]. In severe cases, a symptom-related inpatient therapy of the neonate should be initiated immediately.

With a frequency reported at 2-49%, NAS requiring treatment after maternal methamphetamine use occur much more rarely than in persons with opiate or mixed use and lasts on average much shorter than withdrawal from methadone or buprenorphine [354; 366].

Whereas an opiate or opioid is the therapy of choice for NAS after opiate exposure during pregnancy and phenobarbital or clonidine are only added on in severe treatable abstinence syndrome, no evidence-based therapy recommendations could be identified for methamphetamine NAS. In non-opiate-related NAS, the current recommendation is primary symptomatic therapy with phenobarbital: Initially give 16 mg/kg body weight, followed by maintenance therapy with 5 mg/kg/day, distributed over two doses, then reduced commensurate with the NAS course by 10% or 1 mg every 24-48 hours [354; 355].

7.1.2   Postnatal consequences and late sequelae

Recommendations	Grade of recommendation
7-15 In addition to the tests within the early detection program ("U tests"), the neonates, infants and small children of methamphetamine-using mothers should be systematically examined and diagnosed for any neurocognitive damage, delayed development or late mental sequelae. Expert consensus Vote: 91%	⇑⇑⇑

Recommendations	Grade of recommendation
7-16 As needed or indicated, the appropriate fostering or therapy services should be recommended and organized for the children of methamphetamine-using mothers. Expert consensus Vote: 100%	⇑⇑⇑

Statement of the problem

The data and evidence on the postnatal consequences and late sequelae of prenatal fetal exposure in these children is still rudimentary. The long-term sequelae exhibited by approx. three-quarters of all affected children included developmental deficits like delayed speech and motor development due to the permanently tight muscle tone with restricted mobility, difficulties crawling, overextended joints and the avoidance of bending movements [371; 372; 377; 385; 388]. Additionally, learning, attention and memory disorders, a heightened reactivity to stress alongside specific behavioral anomalies (aggressiveness, anxiety, depression, reclusiveness) have been observed up to primary school age [364; 365; 372-375; 378; 379; 383; 384; 387; 396]. The neurocognitive harms presumably resemble those of fetal alcohol syndrome (FAS/FASD) [356]. Nevertheless, the data and evidence on long-term sequelae emerging during childhood development post-methamphetamine exposure are still insufficient.

Postnatally, drug exposure due to breast-feeding as well as neglect or domestic violence often endanger the welfare of the child (see Section 7.1.3 Nursing and 7.2 Methamphetamine abuse in the family context). In the 2014 statistics published by the Children's Protection Group of the University Hospital Dresden, 63% of the children whose well-being was endangered by parental drug abuse were between the age of 0 and 3 years [397]. Ambivalence of the mother, rejection of the neonate and avoidance of communication with the progeny represent the postpartum complications in the mother-child bonding caused by methamphetamine abuse#. Other risk factors include polytoxicomania, low socioeconomic status, malnutrition, inadequate medical care and viral infections.

Awareness and diagnostics

The available findings underpin the importance of systematic examinations of neonates, infants and small children of methamphetamine-using mothers for targeted diagnosis of any neurocognitive damage, delays in development or late mental sequelae [398]. The conventional "U tests" are not sufficient for this purpose and should be supplemented by neuropsychological and neurological developmental diagnostics and supplemental radiological examinations (MRI) conducted by specialists#.

Interventions

Currently, no studies are available on the efficacy of fostering or therapy measures for the children methamphetamine-using mothers.

It nevertheless appears indicated to offer the appropriate general fostering or therapy services that are available for neonates, infants and small children to methamphetamine-using mothers to help them deal with their ills and symptoms.

(See also Section 7.2 Methamphetamine abuse in the family context.)

7.1.3 Breast-feeding

Recommendations	Grade of recommendation
7-17 Breast-feeding should be recommended to mothers who have achieved stable abstinence. Expert consensus (LoE 5), based on [399] Vote: 91%	⇑⇑⇑
7-18 Mothers who have recently achieved abstinence should breast-feed their babies no earlier than 24 hours after a negative specific drug test (see Section 2.2 Diagnostics). Expert consensus (LoE 5), based on [400] Vote: 100%	⇑
7-19 A pregnant woman who does not achieve abstinence or cannot maintain stable abstinence by the time of the delivery ought to be advised not to breast-feed. Expert consensus Vote: 100%	⇑

Statement of the problem

Methamphetamine-using mothers breast-feed their babies less frequently than drug-free mothers. In a trial by Shah et al. (2012), 204 methamphetamine-using mothers were compared with 208 drug-free mothers; the breast-feeding rate among the drug-using mothers was found to be only half as high (38% versus 76%) [401].

Methamphetamine reaches very much higher concentrations in the breast milk than other amphetamines (around 20 times higher), whereas methamphetamine levels in breast milk are even 3 to 7 times higher than the levels in the mothers' blood [402]. Methamphetamine taken by the smoking or intravenous route leads to comparable concentrations in breast milk [403]. Breast-fed children are exposed through breast milk and can suffer life-threatening intoxications [400; 404; 405]. In one pharmacokinetic study, methamphetamine was no longer detectable in breast milk samples as early as 24 hours prior to a negative urine screen; this is one reason why breast-feeding 24 hours after a negative urine screen should allow a sufficiently long safety interval to recommend breast-feeding in mothers with stable abstinence. In this context, the method of methamphetamine production would also appear relevant because contamination with potentially toxic chemicals is to be expected [403; 406; 407].

Awareness and diagnostics

If there is a known medical history of drugs or methamphetamine use is suspected, specific drug screens and, if necessary, breast milk testing can be performed.

Interventions

Methamphetamine transfers in relevant doses into the breast milk; this is one reason why habitually methamphetamine-using mothers who have recently given birth should be advised to not breast-fed [402; 403]. For example, the benefits of breast-feeding appear to outweigh the harms if a reliably maintained abstinence during the breast-feeding phase can be assumed on the part of the mother after she has been appropriately educated about the risks and shows compliance. Breast-feeding is thus to be recommended if stable abstinence is achieved (repeatedly negative screens during pregnancy and the breast-feeding phase) [399].

The WHO recommends mothers with sporadic methamphetamine use to not breast-feed 24 hours after use. Moreover, they should be educated about the fact that methamphetamine can be transferred into the breast milk and cause harm to the child [400].

Mothers who take additional illegal drugs and/or are administered psychoactive agents should not breast-feed because these drugs may be "cut" with other substances and therefore contain impurities that can accumulate in the breast milk [354; 360; 361].

Because HIV viruses can be transferred into the breast milk, HIV infection is a contraindication for breast-feeding (observe the current guidelines) [360].

Recommendations on breast-feeding by mothers with hepatitis C infection are discussed elsewhere; therefore, reference is made to the current recommendations issued by the National Commission on Breast-Feeding: "The National Commission on Breast-Feeding had already issued its position on the subject of hepatitis ("HCV-positive mothers and breast-feeding") in its recommendation dated 19 March 2001 [408] and in a supplementary recommendation dated 8 January 2004 [409]. The position of the National Commission on Breast-Feeding in HCV-infected mothers has since been controversially debated. Because the body of evidence has not changed, it can still be assumed that no case of HCV infection resulting from breast-feeding has been demonstrated. There remains, however, a theoretical, residual risk that, in the presence of high viral load, infection of the infant can occur via bleeding wounds (e.g. nipple injuries). When counseling mothers, the following aspects should therefore be taken into account:

- HCV-positive mothers can be encouraged to breast-feed following appropriate counseling.

- HCV -positive mothers should be referred to seek and be supported by professional help to avoid bleeding injuries of the nipples. [410]

Hepatitis B infection is not an absolute contraindication if the newborn is actively and passively immunized at birth. Despite immunization, infection of the child cannot be ruled out with certainty in the presence of high maternal viral loads based on currently available data. The respective AWMF guideline is currently being reviewed, in particular with regard to reducing the viral load during pregnancy. An update on the breast-feeding recommendations can also certainly be expected [411].

7.2　Methamphetamine abuse in the family context

To further an understanding for the family circumstances of methamphetamine users, greater focus here is placed on aspects of the couple's relationship and parenthood.

No systematic literature review was carried out on this topic. The recommendations are based on the results of a selective study review and clinical experience. Furthermore, another important source derives from the results from the German Federal Ministry of Health's project "Crystal Meth and Family" that collated information about the family situations of methamphetamine users and the psychosocial living environment of affected children in Saxony. In this context, case records from the Saxony Addiction Support Service were analyzed and qualitative interviews carried out with parents who were (former) drug users. In addition, a standardized psychological assessment of the children was carried out [412].

7.2.1　Partnership

As yet, very little is known about how methamphetamine users form partnerships, although it must be assumed that partners and sexual contacts change frequently and that violent confrontations occur [40; 412; 413]. Moreover, both partners often use methamphetamine [412].

Recommendations	Grade of recommendation
7-20 If required, couple counseling ought to be offered, particularly regarding drug use-related conflicts between partners, violence and sexuality. Expert consensus Vote: 100%	⇑
7-21 If domestic violence is suspected, the situation should be evaluated and documented and victim protection measures instigated, as required. Expert consensus Vote: 100%	⇑⇑

Regular methamphetamine use by one's partner can also work as a motive for starting to take the drug oneself [28]. A records analysis of the clientele of Saxony addiction counseling centers revealed that more than half of the documented partners also showed substance abuse, which, in most cases, also involved methamphetamine [412]. Qualitative interviews conducted by the "Crystal Meth and Family" project showed that methamphetamine-using parents reported an increase in conflict and confrontations in their relationship mainly due to drug use [412]. The use of methamphetamine is often associated with an increased occurrence of violent behaviors, mainly interpersonal violence. Domestic violence in particular seems to play a key part with 80% of methamphetamine-using women reporting the experience of abuse or violence at the hand of their partner. On the contrary, men report experiencing more violence from friends or strangers [414].

However, the direction of the correlation between interpersonal violence and methamphetamine use is unclear and inconclusive [415]. The use of methamphetamine is considered as a

risk factor for interpersonal violence, just as persons affected by interpersonal violence use substances as a way of developing individual coping strategies [416].

7.2.2   Parenthood

Methamphetamine-using parents have been classified as belonging to a special subgroup of methamphetamine users [1; 417]. In Germany, these are often young families or single parents with multiple problems [412].

7.2.2.1   (Un)planned parenthood

Recommendations	Grade of recommendation
7-22 Methamphetamine users should be educated about the interrelationships between the drug effects and sexuality, the risks of unplanned pregnancies and a prenatal substance exposure for the child. Expert consensus Vote: 100%	⇧⇧⇧
7-23 Methamphetamine-using parents should be offered parental competency training courses. Expert consensus Vote: 100%	⇧⇧⇧
7-24 Methamphetamine-using parents should be informed about the services offered by the youth and family assistance agencies. Expert consensus Vote: 100%	⇧⇧⇧

The sexually disinhibiting effect of the substance and the resulting negligence to use contraception in a high proportion of (younger) women users can lead to unplanned pregnancies and early parenthood, coinciding with an already challenging living situation in these individuals [1]. Undetected and unplanned pregnancies are associated with a major risk that mother continues to abuse methamphetamine despite her pregnancy. Prenatal substance exposure in children poses a risk to their health and development; parents should be educated about these risks and harms (see Chapter 7.1 Pregnant women, young mothers and prenatal harm). The analysis of documents from the "Crystal Meth and Family" project showed that pregnancies and biological children are very meaningful motives for methamphetamine users to achieve abstinence and should be given consideration as part of addiction therapy [412].

Attainment and stabilization of parental abstinence, as much as the fostering of parental (parenting) competencies are central issues for both expecting and existing parents, irrespective of the location at which the children may have been involuntarily committed. For example, this can happen by offering training interventions on parenting competency, whereas in the ideal case, the substance-related special features (e.g. behavioral changes caused by methamphetamine use) and the clinical courses of addiction therapy should be taken into

consideration. Such a program is currently being developed at the German Institute for Addiction and Prevention Research in Cologne.

7.2.2.2 Risks for children of parents using methamphetamine

Recommendations	Grade of recommendation
7-25 Supervision for families where one parent abuses methamphetamine ought best to be undertaken at close intervals in cooperation with the family, youth and addiction help services. Expert consensus Vote: 91%	⇑
7-26 The first signs of developmental or behavioral problems in children whose parents are methamphetamine users should trigger expert diagnostics and risk assessments. Expert consensus Vote: 100%	⇑⇑
7-27 Appropriate support an d therapeutic services should be recommended and organized for children whose parents are methamphetamine users. Expert consensus Vote: 100%	⇑⇑

Children whose parents are methamphetamine users or addicts frequently grow up in an environment which harbors many potential risks to the child's development [412; 418]:

- Ambivalent behavior on the part of the parents;
- Neglect or insufficient care/supervision;
- Discontinuity in the relationship (repetitive separations due to children being put in foster care and parents undergoing hospitalizations, rehabilitation stays and incarcerations);
- Lower socioeconomic status;
- Co-occurring mental disorders in the parents (depression, personality disorders, psychoses);
- (Early) traumatization;
- Exposure to parents using drugs and/or to substances.

In one American study, 29 children whose parents were addicted to methamphetamine (aged between 6 and 15 years) received psychodiagnosis. The children were clearly emotionally challenged exhibiting behavioral problems in terms of elevated externalizing and internalizing behaviors. A number of children also showed signs of traumatization [418]. Another study yielded comparative results for children from homes where parents used methamphetamine.

Compared to a control group, behavioral problems and mental vulnerability were greater [419]. The results from the German research project "Crystal Meth and the Family" are consistent with these findings.

Once again, about half of the children were emotionally challenged, exhibited behavioral disorders and had social problems. Moreover, some children showed signs of depression [412]. The small sample sizes in the existing studies are a limiting factor. Similarly, prenatal substance exposure, for example, can have a potential impact that affects the child's behavior over the long term [420].

The families should be supervised according to existing collaborative agreements between the youth and addiction help services under the German Child and Youth Welfare Act that provides the legal basis for ensuring a suitable living environment for all affected children. Fundamentally, a low threshold for access to support services for affected children is relevant in addition to offering help to drug-using parents. As an example, self-help groups or group programs for the children of addicted parents can be mentioned here. The aim of group programs like "Trampoline" [421] is to mobilize resources and empower the children to learn coping strategies, thereby preventing them from developing mental or addiction disorders themselves (www.project-trampolin.de). Comprehensive psychodiagnostic tests and risk assessments can be useful when psychological difficulties or behavioral problems manifest themselves in children, thereby allowing pediatric and adolescent psychotherapy to be offered as needed

7.3   Methamphetamine use among men who have sex with men (MSM)

7.3.1   Prevalence

Men who have sex with men (MSM) represent a subgroup with a high prevalence of methamphetamine use [422; 423]. Methamphetamine is often used among MSM in the context of sexual activity [424].

There is a large body of evidence indicating that methamphetamine use is highly correlated with sexual risk behaviors, e.g. for acquiring or transmitting HIV or other sexually transmitted infections (STIs). One systematic review identified 61 studies that analyzed methamphetamine use in HIV-positive and HIV-negative MSM [104]. The overall results showed that methamphetamine use was significantly more prevalent among HIV-positive than HIV-negative MSM. HIV-positive methamphetamine users exhibited significantly greater sexual risk behaviors. They were more likely to engage in unprotected anal intercourse with serodiscordant partners compared to HIV-positive MSM who do not use methamphetamine. Compared to MSM who do not use methamphetamine, HIV-positive methamphetamine-using MSM had significantly higher rates of anal sex without condoms, multiple sexual partners, multiple sexual partners whom they met over the Internet, more frequent sex with partners injecting drugs and higher rates of STIs (specifically gonorrhea, syphilis and chlamydia).

A study of 475 HIV-positive MSM who received specialized outpatient treatment at the university hospitals in Essen and Bochum showed a lifetime prevalence of 2.9% for methamphetamine use on at least one occasion. The 12-month prevalence for use that was regular, but no more than three times a week, was 0.6% [425].

Prospective longitudinal studies even suggest a causal relationship between methamphetamine use and sexual risk behaviors. In a prospective cohort study, 8,950 HIV-negative MSM were questioned repeatedly over a twelve-month period about their self-reported metham-

phetamine use and sexual risk behaviors [37]. Methamphetamine use was reported by 8.5% of the participants. 82 individuals had just started their methamphetamine use during the interview period. In this group, sexual risk behaviors increased significantly after drug use started. Methamphetamine use was the strongest predictor for unprotected intercourse with a partner of unknown or negative HIV status, compared to all other illegal drugs [37]. Older longitudinal studies also prove that both regular and occasional methamphetamine use is associated with an increase in sexual risk behaviors [426].

7.3.2   Therapy

Recommendations	Grade of recommendation
7-28 Due to the close interconnection between methamphetamine use, sexual activity and risk behavior in the group of MSM, management should be specific to the target group and oriented towards the sexual life-worlds of these men. Expert consensus Vote: 100%	⇑⇑⇑

The subgroup of MSM methamphetamine users is a population that is exposed to multiple health risks, particularly to HIV and other sexually transmitted infections. Health risks increase considerably in individuals injecting drugs intravenously. Existing interventions focus on this topic because of the close relationship between methamphetamine use and sexual risk behaviors among MSM. This close interconnection between methamphetamine use, sexual activity and risk behavior in the group of MSM requires a target-group-specific treatment approach, oriented towards the sexual life-worlds of these men.

Evidence

All available studies on the therapy of MSM with a methamphetamine-related disorder from the year 2000 onwards were recorded as part of a systematic review. One review including but not limited to 15 therapeutic studies showed considerable methodological limitations [104]. The literature on evidence-based interventions is still very sparse. Many studies have low case numbers, are more like pilot studies and there is a lack of randomized controlled trials with higher sample sizes. When designing interventions, established treatment approaches for substance-related disorders were used and adapted to the target group of MSM. Some authors suggest that Methamphetamine-using MSM be seen as a specific risk population and be offered the pre-exposure prophylaxis with antiretroviral drugs for HIV-prevention already licensed in the USA [37].

7.3.2.1   Evidence of psychotherapeutic interventions

Evidence

Current findings suggest that contingency management is not the first-choice method of treating MSM with a methamphetamine-related disorder. Peer group-based approaches and innovative online-based interventions are showing the first positive results; nevertheless, there is a lack of randomized controlled trials on this subject as well.

Adapted Motivational Interviewing

In a pilot study (n=39), Zule et al. (2012) chose motivational interviewing that is a proven approach in addiction therapy [427; 428]. Following a one-off session, the number of days of drug use reduced from nine to three per month. Moreover, episodes of unprotected anal intercourse with a casual partner reduced from 81% to 25%. Mimiaga et al. (2012) incorporated 10 sessions of a combined behavioral activation therapy to stabilize mood and reinforce positive activities with integrated risk reduction counseling on sexual risk behaviors [429]. After three months, methamphetamine use, depressive symptoms and sexual risk behaviors decreased significantly. However, this was similarly a pilot study with a small number of participants and no control group.

Contingency management

Contingency management in the therapy of substance-related disorders is an evidence-based behavioral therapeutic intervention that provides tangible rewards as positive reinforcement (e.g. shopping vouchers, take-home prescriptions for opiate substitution) and looks at the achievement of desired outcomes, e.g. urine screening confirming abstinence from an addictive substance or regular attendance at treatment sessions [430]. Carrico et al. (2015) compared contingency management only with contingency management plus affect regulation training in a small sample population (n=21 as part of a twelve-week program) [431]. Although positive affect regulation in patients improved with both interventions, substance use was, however, not significantly reduced. Shoptaw et al. (2005) similarly selected a contingency management approach [432]. They investigated 143 methamphetamine-using MSM, of whom 77% were HIV-positive. Over a twelve-week period, the participants turned in a urine sample three times a week. They received a shopping voucher for every methamphetamine-negative urine sample. A total of 42% of urine samples were negative for methamphetamine, only 8% of the participants provided 36 methamphetamine-negative urine samples, 52% managed 12 and a further 17% managed 24 methamphetamine-negative urine samples. In a randomized controlled trial of 127 MSM, Menza et al. (2010) found no significant benefit of contingency management [433]. There was even a tendency that participants from the contingency management intervention were highly likely to provide methamphetamine-positive urine samples during follow-up. Moreover, they reported a significantly higher methamphetamine use once or more than once weekly.

Peer group-supported interventions

In a public campaign against drug abuse in Thailand, a total of 983 methamphetamine-dependent users were assessed [253]. The authors describe methamphetamine use in Thailand as an epidemic. They report a three-fold increase to 2.5 million users between 1999 and 2002. The comparability of the sample with the German population is not guaranteed. Sexually active methamphetamine-using MSM, who could bring at least one other participant from their sexual network or another drug user into the trial, were included. Only the 415 "Index participants" received the intervention, not the "network partners". The intervention involved 7 two-hour peer-based psychoeducation sessions on the topics of "methamphetamine use", "sexual behavior" and "sexually transmitted infections". An equally significant reduction in self-reported methamphetamine use in both the index and the network group was observed in the follow-up tests. In both groups, the use of condoms increased significantly between baseline and follow-up. Both groups did not differ significantly with regard to reduced methamphetamine use and increased condom use, thereby supporting the theory of a multiplicative effect of peer-based interventions.

New perspectives are offered by interactive interventions that are communicated via the Internet or social media. In this way, young, tech-savvy target groups in particular can be reached. Reback et al. (2012) developed a total of 400 different texts based on different health-psychological models that were sent to participants (n=52) by text message [434]. The text messages were aimed at reducing substance use and sexual risk behaviors. Every participant created a personal profile. Based on this information (e.g. about typical times of sexual activity or substance use situations) the participants received the most appropriate text messages. Participants were given the option of texting with a study investigator if they needed further communication. Therefore, trained peers were available as part of the trial. The participants reported significantly lower use of methamphetamine, less intravenous use and less frequent unprotected anal intercourse. As a virtual social support in potential risk situations, text messaging seemed to be a suitable and innovative approach to reaching individuals who were not in regular personal contact with the health- and counseling system.

MSM target group-specific interventions

Some psychotherapeutic interventions supplemented cognitive behavioral therapy approaches (CBT) with MSM-target group-specific subcultural aspects. In a four-arm, randomized controlled design, 162 MSM with methamphetamine-related disorder, of whom 60% were HIV-positive, were assessed 432]. The participants received either CBT or contingency management or CBT plus contingency management or CBT plus MSM-target group-specific elements. Target variables were reduction in methamphetamine use tested by urine screening and reduction in sexual risk behaviors over a follow-up period of six and twelve months. The participation rate in the four interventions varied considerably: Contingency management (32.4%) and CBT (40.8%) showed the lowest participant rates, MSM-specific CBT (55.8%) a medium rate and contingency management plus CBT (73.8%) showed the highest rates. Also, with regard to retention rates in weeks, contingency management plus CBT scored highest (13.3%), followed by contingency management (12.0%), MSM-specific CBT (11.3%) and CBT (8.9%). Contingency management plus CBT proved superior in other parameters: The longest abstinence duration defined as negative urine tests and reported methamphetamine use in the last 30 days. During the intervention phase, CBT scored significantly worse than all other interventions. However, this outcome was reversed at 6- and 12-month follow-up. At both follow-up endpoints, CBT showed particularly high rates of negative urine samples and fewer days of use, based on self-reports.

In a two-arm randomized, controlled trial of 128 participants with methamphetamine-, cocaine- or alcohol-related disorders, Shoptaw et al. compared an MSM-target group-oriented CBT (*gay-specific* CBT, GCTB) to an MSM target group-specific approach with the focus on social support (*gay-specific* social support therapy, GSST), that also included group therapy for HIV-risk behavior [435]. Both interventions were conducted three times per week over 16 weeks. The primary outcomes were defined as reduction in methamphetamine use, reduction in sexual risk behavior and participation rate. The participation rate (16 weeks completed) was 62.5% for GCBT and 50% for GSST. This difference was not statistically significant. Both groups showed a significant reduction in methamphetamine use and sexual risk behaviors between baseline and follow-up after 52 weeks.

7.3.2.2   Pharmacological interventions

Recommendations	Grade of recommendation
7-29 Mirtazapine may be offered to MSM to reduce methamphetamine use and sexual risk behavior. LoE 2 [207] Vote: 83%	⇔

Evidence

A double-blind randomized controlled trial investigated the effect of mirtazapine vs. placebo on methamphetamine use and sexual risk behaviors [207]. Sixty methamphetamine-dependent, sexually active MSM participated in the trial. They were randomized to either a daily oral dose of 30 mg mirtazapine or placebo and 30 minutes of weekly substance use counseling. Urine tests were performed weekly. Current major depression and severe organic disease were some of the exclusion criteria. Mirtazapine was chosen because it rarely causes erectile dysfunction (< 1%) and would therefore be presumed to have greater acceptance among the male target group than other medications.

The number of methamphetamine-positive urine tests in the mirtazapine arm after twelve weeks was significantly lower compared to baseline. After twelve weeks, various sexual risk behaviors were reported significantly less in the mirtazapine arm (number of partners with whom methamphetamine was used, unprotected anal sex with HIV-serodiscordant partners, insertive anal sex with HIV-serodiscordant partners by ITT analysis). Medication adherence was low to moderate (48.5% measured by a masked medication event monitoring system and 74.7% self-reported). The authors assume that mirtazapine could be even more efficacious with better adherence.

8   Relapse prevention

Norbert Wittmann, Sascha Milin

8.1   Statement of the problem, definition, goals

Relapse prevention takes place at different levels and, when it applies to drug dependence, covers includes a wide range of individual and group interventions, manualized approaches, practical case-by-case support services, medical interventions, structured aid services and crisis intervention programs. Studies on this were not systematically searched. This chapter looks at methods derived from clinical evidence on and social work experience with other substance use disorders that the experts believe are transferrable to methamphetamine-related disorders. Given the diverse range of interventions available, practical examples of therapeutic, social work-based, self-help and individual and/or group interventions are presented to improve an understanding for each type. Obviously, other modalities can also be used, depending on each individual situation.

Recommendations	Grade of recommendation
8-1 Methamphetamine users should be encouraged to utilize the relapse prevention services offered by established stakeholders within the system of addiction help services. Expert consensus Vote: 100%	⇑⇑
8-2 In order to choose the appropriate services, clients should receive individual counseling or be referred to specialized drop-in centers. Expert consensus Vote: 100%	⇑⇑

Relapse prevention in drug dependence plays an important role for long-term treatment outcomes and its merits have also been incorporated into inpatient therapy [436]. Since drug dependence is a chronic disorder, treatment is complex and lengthy; relapses are seen as part of the recovery process. Accordingly, there are differences between general and specific modalities for relapse prevention and/or relapse management. The range extends from relapse prevention programs and substantive content during (ongoing) (inpatient) therapy, through post-therapeutic relapse prevention programs up to individual interventions and group programs in the context of everyday supervision and follow-up care of former drug users. Professional therapeutic and social work-based interventions are as integral a part as are structural assistance and self-help services. Appropriate interventions are offered by established stakeholders within the addiction help services. These are recognized institutions, which are part of regional and national professional help networks that apply evaluated and proven methods and concepts.

The recommendations in this chapter refer to the period after the completion of medical therapy and/or social work-based interventions for withdrawal or abstinence from methamphetamine, respectively.

Methamphetamine use has specifically inherent problems in that the group of people involved is particularly heterogeneous both with regard to motives for use (needs/function) as well as sociodemographic characteristics. Meaningful relapse prevention must consider the different groups of people and their motives, for instance, as determined by the ZIS study (see Chapter 1 Epidemiology) [1].

By taking these categories of user groups into account, motives and/or need sets can be delineated and used as a basis to propose individually tailored relapse prevention programs. These assumptions are evaluated and verified with the person involved during individual consultations and/or counseling sessions.

8.2   Therapeutic strategies for relapse prevention

Recommendations	Grade of recommendation
8-3 Standardized, addiction-specific group or individual therapy for relapse prevention should be offered and organized by qualified stakeholders in the addiction help services. Expert consensus Vote: 100%	⇑⇑⇑

A variety of methods and concepts are conceivable as professional therapeutic strategies for relapse prevention. In general, it is therefore recommended to rely on regional addiction support experts and counseling services and/or integrate them into the treatment process (see Appendix 4).

Furthermore, it is important to check whether group interventions or more individualized programs would be more effective and acceptable for that patient. Group interventions usually prescribe specific structures in terms of time and content. They focus on group dynamic motivation and empowerment techniques and promote opportunities for contacts and communication. Individual counseling sessions have the advantage that anonymity can be maintained and that the therapeutic structure can be precisely tailored to the individual situation of the affected person.

8.2.1   Therapeutic group training programs

Recommendations	Grade of recommendation
8-4 Group therapy is particularly suitable for individuals who require clear structures. Expert consensus Vote: 82%	**Statement**

Example: Relapse prevention training – RPT

The aim of RPT is to influence the treatment of drug-dependent persons through early systematic and psychoeducative interactions and, in addition to relapse prevention and management, to turn those affected into experts on their own condition. The group context creates a bond and can be supportive and motivating in managing critical phases.

The RPT manual offers a structured training program for relapse prevention in drug dependence (RPT). Methodical key aspects of relapse are discussed during 15 group sessions [437].

Table 11 Primary objectives of RPT program

- To turn drug-dependent persons into experts on their own disorders;

- To prepare for and prevent relapses in a targeted manner;

- To develop appropriate means for handling relapses (relapse management).

Furthermore, individual aspects such as personal risk profile, coping strategies and resources are developed jointly to prepare affected individuals adequately for immanent or current relapses. In addition to education and the development of a better self-assessment, training aims to formulate a realistic self-efficacy expectation, to improve the ability of anticipation, to reduce abstinence injury effects as well as to practice coping strategies [437].

In general, RPT and similar modular training programs (e.g. KISS, SKOLL, controlled drinking; see Appendix 4) are suitable for all groups of people. However, group options are usually less attractive for individuals, to whom anonymity is important and/or for those who need flexible options due to professional or family reasons.

8.2.2   Individual treatment training programs

Recommendations	Grade of recommendation
8-5 Individual therapeutic options are particularly suitable for those seeking help whose anonymity is important or who cannot or do not want to be considered for group offers for other reasons. Expert consensus Vote: 82%	**Statement**

Example: Mindfulness-based relapse prevention – MBRP program

Individual training programs are particularly suitable for those who have already undergone and completed inpatient treatment. The aim is to maintain and develop perspectives and approaches that have already been acquired as an inpatient. A mindfulness-based model is presented here as an example of a suitable type of individual training.

MBRP is a comparatively new treatment approach for former drug-dependent persons that was developed in 2010 at the *Addictive Behaviors Research Center* of the University of Washington [438]. This method was originally used to treat patients with depression.

The program was adapted for individuals, who suffer from the consequences of a dependence. It is helpful to sensitize those affected to personal triggers and recognize when damag-

ing addiction mechanisms affect them and automated behavioral patterns limit their lives. Mindfulness-based exercises should give individuals the ability to master classic challenges, to be become aware of the situations, to develop an awareness of the choices available for reacting differently in critical situations. It helps individuals make appropriate decisions consciously instead of reacting in an automated, damaging way. In the end, the overall goal of this approach is to break free of old habits and behavioral patterns that are often deeply rooted. The aforementioned modular training program (KISS, controlled drinking etc.) can also be used to compliment or supplement an individual setting. The advantage of individual settings is that the speed and content of modules can be individually adapted and accentuated.

Table 12 Primary objectives of the MBRP program

- To develop an awareness of personal triggers and automated behavioral patterns and

- techniques for "paused reflection" when automated behavioral patterns are triggered;

- To detect and cope with emotional and physical challenges;

- To build self-esteem towards oneself;

- To develop a mindful and healing lifestyle.

This program, as well as similar approaches, is considered suitable for a broad spectrum of different groups [438]. It could also be suitable for specific methamphetamine user groups such as single parents, young parents or persons with primary sexually orientated use. Moreover, mindfulness-based models can be well integrated into an individual's daily routine.

8.3   Participation-oriented services

Recommendations	Grade of recommendation
8-6 Participation-oriented support and assistance services like outpatient supervision, accommodation services and outpatient sociotherapy ought to be considered whenever patients are observed to have problems with structure and daily routine and appear incapable of resolving these problems on their own. Expert consensus Vote: 91%	⇑
8-7 Social worker-related support and assistance ought to be considered when other dependent persons could be affected a potential relapse. Expert consensus Vote: 100%	⇑

Example: "Assisted single living" as single intervention

"Assisted single living" is defined as professional, individualized social work service where persons seeking help are directed and guided in daily life, depending on their needs. Assisted single living is often considered after inpatient withdrawal treatment but, irrespective of this, can also be requested by appropriate expert agencies. The primary objectives of assisted single living are to support autonomous living as well as to (re-)establish a daily routine pattern. Assisted single living is appropriate where individual direction and guidance are required and where individuals appear unable to resolve problems related to this by themselves. In particular, complex social and/or everyday stress situations (such as childcare/schooling) are scenarios in which assisted single living should be considered. This form of support can usually be requested for a specific time when a need for it has been officially established and may be funded by extra-regional social welfare authorities as a standard service provision. In doing so, it is necessary to liaise with and/or involve regional providers. Furthermore, regional providers can make referrals to other regional participatory services such as occupational or education projects, training options and joint problem-solving groups, self-help initiatives, recreational and cultural initiatives etc.

Table 13 Key effect factors of assisted single living

- Maintain a structured daily routine and sensibly organize leisure activities;
- Provide assistance in looking for and keeping housing accommodations, sticking to a healthy diet;
- Provide assistance with bureaucratic matters, financial and debt management;
- Build and restore social and family networks;
- Provide assistance in parenting issues, family and help relating to pregnancies.

Depending on the presented heterogeneity of the affected persons, very different individual problems and stress scenarios can arise once abstinence has been achieved. This should always be established on a case-by-case basis and discussed openly with those affected. If necessary, other options such as e.g. participation-oriented support and accompanying offers such as outpatient care, housing and outpatient sociotherapy can also be considered.

Under certain circumstances, where other vulnerable persons are affected by relapse, a professional support contact to social service is urgently needed (e.g. families with young children, single parents, pregnant women; see Sections 7.1 Pregnant women, young mothers, and prenatal harm and 7.2 Methamphetamine abuse in the family context).

8.4   Self-help

Recommendations	Grade of recommendation
8-8 All users should be made aware of regional self-help groups or self-help options. Expert consensus Vote: 100%	⇑⇑⇑

Recommendations	Grade of recommendation
8-9 Online-based self-help services such as "Breaking-Meth.de" designed specifically for the target group of individuals with a methamphetamine-related disorder, ought to be introduced during post-acute inpatient therapy and recommended as a possible resource for the post-treatment phase. Expert consensus Vote: 100%	⇑
8-10 Sports activities, especially eventful community-based activities, ought to be recommended for relapse prevention. Expert consensus (LoE 5) Vote: 100%	⇑

Self-help activities are considered particularly important in methamphetamine dependence after completion of addiction therapy. Preparing patients for and educating then about the transition to self-help after therapy is an important building block of the MATRIX therapy manual applied in the Unites States (see Section 5.2 Psychotherapeutic Interventions) [194]. 12-step programs as well as alternative forms of self-help are included in this manual. Results from the ZIS trial suggest that affected persons in Germany also place great importance on self-help Among others, Narcotics Anonymous (NA), which uses a 12-step program, was named by those surveyed. However, there were also strong indicators that barriers still exist to users taking advantage of regional self-help groups. This included a lack of acceptance of the 12-step approach, having to travel too far to attend and fear of loss of anonymity. Several of those surveyed did not really believe that they belonged in heterogeneous groups together with alcoholics or heroin addicts [1].

Self-help services should be offered like the online-based "Breaking-Meth.de" and the not-for-profit group self-help association "Mountain Activity Club e.V." in Germany. Here, it is important to be aware of regional availability, to inform oneself appropriately or to consult specialized contact points for advice.

Example: "Breaking meth" – Online-based self-help for methamphetamine users

With funding from the German Federal Ministry of Health, a self-help portal is being operated and developed for individuals with methamphetamine experience, into which scientific knowledge of the characteristics of the diverse target groups in Germany flows. "Breaking-Meth.de" considers itself as offering guided self-help. It is supported scientifically and supervised by a prevention project with links to the scene [21]. The portal is accessible via computers with internet access as well as via mobile devices/smart phones and features appealing and amusing graphics. Facilitators contribute to it on a regular basis. Via the members' forum, which requires registration, different target groups can communicate with each other in virtual environments. One audience includes users who have remained "under the radar", but are starting to realize that they have a problem and are not in contact with support services yet. In addition, those individuals *during* and *after* addiction therapy are also targeted in

the context of aftercare or those who want to take advantage of online addiction self-help services after their treatment or as adjunct relapse prevention. Content that could trigger cravings or lead to retraumatization of individuals who have experienced violence and abuse are hidden using a special function ("trigger warnings") in the communication flow. They are only shown if, after having been made aware of the warnings, members consciously choose to make the content "visible". Thanks to the specially designed structure of the members' forum (Table 4), it can be recommended both for current users who wish to quit and for those who have already achieved abstinence.

Table 14 Essential communication sector of the Self-help portal "Breaking Meth" (breaking-meth.de) [439]

- Introductory area ("entrance hall");
- Options for organizing leisure activities ("Experience – Meet – Exercise");
- Provide assistance during relapses;
- Sharing experiences with long-term abstainers ("I'm clean and going to stay clean");
- Use following release from inpatient detox/addiction rehab therapy ("Out of rehab");
- Sexual motives to take meth as reasons for relapse and appropriate coping strategies ("Sex").

Example: "Mountain Activity Club e. V."

The Mountain Activity Club (MAC) in Nuremberg has been developed from the "Spotting" project that is funded by the German Federal Ministry of Health, whose aim includes the development of peer-supported help for young and adolescent drug users. Peer involvement (in this case: former drug-dependent persons) has a long tradition in self-help (cf. Alcoholics Anonymous, Narcotics Anonymous etc.) and is usually one of its main characteristics [194].

The Mountain Activity Club is a self-help group that focuses on younger affected persons, who share a passion for climbing. Climbing offers both individuals and teams a highly intensive range of experiences, rich in real potential for "thrills" and motivating feelings of self-empowerment [440]. Sport can help to reduce depressive symptoms in abstinent methamphetamine-dependent persons [223]. A trial at the University Hospital in Erlangen documented the promising use of "bouldering" as a therapeutic intervention against depression [441]. Former users suffer from depression or depressive moods, particularly after withdrawal from methamphetamine (on this subject, see also Section 6.4 Depressions).

Sporting events that offer intense experiences can play an important role in strengthening and developing social and self-competence. Participants of bouldering training at the MAC name "kicks" and "community" as the two factors of most benefit on a personal level. Empowerment, self-effectiveness, recognition and pride constitute further benefits that are helpful in leading a stable and drug-free life after dependence [442-444].

Table 15 Essential factors of the self-help project "Mountain Activity Club" (www.mountain-activity-club.de)

- Drug-free "Kicks" (intensive flow climbing adventures) and the joy of living;
- Alternative drug-free community (friendships based on shared experiences and mutual trust);
- Self-efficacy/self-empowerment (direct confrontation between objective barriers and personal ability);
- Recognition/acknowledgment (mutually cheering each other on, motivation and celebration of surmounting climbing challenges; being part of the climbing community);
- Pride (the good feeling remains > > self-confidence; solving problem through one's own personal abilities);
- Health (sports and athletic activities create make one feel good about one's body > creates a sense of meaningfulness).

Unlike other self-help concepts, the problem of drug use is not the focal point of the meetings. Instead, it is more about celebrating the shared enjoyment of climbing and fostering social contacts. The joint experience of "getting kicks", the intensive moments of flow that climbing offers, but also taking responsibility for each other's safety, "depending on one another", are essential factors that deepen trusting relationships. As a result, the sense of community assumes great importance in promoting a drug-free lifestyle. On the one hand, peer guides serve as role models and, on the other, as trusted partners with their own experience of use and dependence.

9   Harm reduction

Benjamin Löhner, Antje Kettner, Roland Härtel-Petri

9.1   Aim

The aim of harm reduction is to limit the extent of health and psychological damage that can result from methamphetamine use. The target audience are all those who do not want to or cannot stop their long-term methamphetamine use. Good education can play an important role in creating awareness of the causes of undesired effects and appropriate measures. It should be seen as an offer of advice and formulated accordingly in a neutral and objective way.

9.2   Basic principles of these recommendations

Primary studies on the question of harm reduction were not systematically searched. These principles mainly derive from long-term clinical experience gained in the context of addiction aid as well as from users of other illegal drugs. They are bolstered by international literature and recommendations from systematically searched guidelines on the management of methamphetamine-dependent persons [445-447].

Recommendations	Grade of recommendation
9-1 Methamphetamine users/dependent persons, who do not want to or cannot stop long-term use, should be recommended appropriate harm reduction behaviors. Expert consensus (LoE 5), based on [445-447] Vote: 92%	⇑⇑⇑

Further information on the topic "Harm reduction in methamphetamine use" is available from the following websites:

- www.drugscouts.de
- www.mindzone.info

A general note: The following behavioral instructions are no replacement for qualified drug counselling. An overview of liaisons who can arrange contacts to specialized drug counseling centers is provided the Appendix 4.

General

- Methamphetamine users should be encouraged to consult a specialist when psychiatric or physical health problems persist or recur instead of trying to treat themselves.
- It is recommended that adequate information materials (e.g. flyers, brochures, posters) on methamphetamine-specific topics be provided (see Appendix 4).

Routes of administration

- The addiction potential of methamphetamine increases in relation to how it is used in the following order: oral use, snorting, smoking, injection (i.v.).

- Intravenous users should be made aware of regional syringe provision/exchange programs.

- When injecting methamphetamine, it is advisable to use only personal and, if possible, sterile injection sets/equipment (filter, spoon etc.), so that the transmission risk of infectious diseases can be minimized In order to avoid damage to the veins through frequent puncture, it is advisable to vary between both arms/legs and/or femoral areas.

- Anal application without cannula ("up your bum") creates a similar effect to i.v. injections, but is much less damaging to the veins.

- When methamphetamine is smoked, only personal smoking devices should be used to prevent transmission of infectious diseases. In order to avoid burns it is recommended a mouthpiece is used.

- In nasal use, each person should use their own snorting tube to prevent transmission of infectious diseases. In order to minimize damage to the nasal mucosa, it is recommended that the methamphetamine crystals be crushed as much as possible, prior to use. Furthermore, it is advantageous to thoroughly clean the nasal mucosa after use and ensure they remain intact (e.g. using nasal creams, nasal flushes).

- Oral intake of methamphetamine is thought to be the lowest-risk route of administration.

Dosage and use patterns

- Crystal methamphetamine, compared to other illegal drugs such as amphetamine ("Speed"), usually has a higher potency and therefore should be planned and taken in as low a dose as possible ("How long do I want to stay awake"?)

- In order to reduce the risk of dependence, methamphetamine should not be used over several consecutive days.

- Keeping a use diary can be helpful to keep an overview of an individual's own use pattern.

- Methamphetamine should not be combined with other psychoactive substances (incl. alcohol) to avoid as far as possible unpredictable effects and side effects. If methamphetamine is nevertheless combined with other drugs, the potential risk of different substance combinations should be considered. The potential risks for different combinations are described below www.drugscouts.de.

- The concomitant intake of prescribed drugs and methamphetamine needs to be discussed with the prescribing doctor, because of possible interactions.

- To avoid a life-threatening Serotonin-syndrome, methamphetamine should, under no circumstances, be taken together with antidepressants and MAO-inhibitors [448], (see Chapter 5 Post-acute management).

- The young and very young in particular should urgently be made aware of the potential consequences of methamphetamine use and be encouraged to stay abstinent. The earlier drug use is started, the higher the risk of developmental impairment, development of dependence and/or long-lasting consequences (sequels??) and side effects.

Prior physical and mental conditions

- Individuals with cardiovascular problems, hypertension, epilepsy and cramps, liver and kidney damage hyperthyroidism and cardiac diseases should be advised extensively about the danger of life-threatening complications from methamphetamine use and encouraged to stay abstinent.

- Individuals with a history of mental health disorders in particular should be urgently advised about potential consequences of methamphetamine use and encouraged to stay abstinent (see Chapter 6 Co-occurring organic diseases and mental health disorders).

Diet

- Methamphetamine use causes the body to loose fluid, important minerals and vitamins, it also suppresses appetite. Food cravings can occur after use. Therefore, users should make sure that they eat a balanced diet as regularly as possible and drink plenty of non-alcoholic drinks to avoid and/or correct deficiencies.

- Methamphetamine is not suitable as a means of dieting. Although a relatively large amount of weight can be lost in a short time (in a very unhealthy way), the risk of weight gain is high after stopping methamphetamine use. This can easily lead to re-use. It is recommended to mutually discuss a healthy diet and possibly set up individual nutritional plans.

Oral hygiene [44; 449]

- In order to counteract mouth dryness (xerostomia), methamphetamine users should drink 8–10 glasses of water daily. Additionally, sugar-free chewing gum can be chewed.

- Due to the risk of reduced buffer capacity of saliva and the associated increased risk of erosion, restrictions should be placed on acidic foods and abrasive toothpaste while more-gentle brushing should be recommended.

- Dental braces can be helpful in order to protect the dental enamel, to prevent jaw joint problems and to relax chewing muscles.

- Other measures: See Chapte6 Co-occurring organic diseases and mental health disorders.

Pregnancy/breast-feeding

- Methamphetamine users should protect themselves from unwanted pregnancy by using condoms or other non-hormonal contraceptive devices.

  o Methamphetamine use can worsen menstrual symptoms, disrupt the monthly menstrual cycle and may damage fertility. A possible pregnancy cannot be excluded [77; 78; 351].

  o If users take oral contraceptives and use methamphetamine frequently, the contraceptive effect of the pill can potentially be reduced. For example, an irregular sleep - wake cycle and a changed perception of time can lead to taking the contraceptive pill at random times with the consequence that contraception can no longer be guaranteed.

- During pregnancy and breast-feeding, female users should always give up using methamphetamine (see Chapter 7.1 Pregnant women, young mothers and prenatal harm).

Sexuality

Users very often report a strong sexual stimulation, high desire and prolonged, partially very uninhibited sex.

- Users should have available and use lubricants and condoms when having sex [450].

  o Methamphetamine use dries out the mucosa and suppresses the pain sensation. Therefore, (particularly in anal intercourse) injuries such as small fissures can occur unnoticed and pathogens can be transferred easily in this way.

  o There is an increased willingness for unprotected sex and high-risk sexual practices. When "shooting up" (intravenous use), etc. during Sex parties, sometimes users (deliberately) abandon safe sex. If this is the case, it should be recommended to users to undergo frequent tests for HIV and other sexually transmitted diseases. If methamphetamine use is kept secret from a long-term male or female partner, the use of condoms in the relationship should also be recommended .

- There is a risk that frequent sex under the influence of methamphetamine can develop a dependence, become stronger or become dependent on sex with simultaneous drug use. Quite a number of users, who have frequently sex under methamphetamine influence, have reported that, over time, they have lost the pleasure of sex when abstinent and find it later quite difficult to re-learn to enjoy and appreciate sex without methamphetamine. This can be very frustrating and distressing and can lead to recurrent use. Even if this is a sensitive topic for many users, it is recommended to talk about it, to inquire and, if necessary to offer further help.

10   Need for further research

While drawing up this guideline, it became apparent that, from an expert viewpoint, relevant questions had not been addressed sufficiently to date. In order to provide more professional confidence in the future and to be able to design appropriate therapeutic offers for particular interactions, the participating authors are of the opinion that research into the following areas would be desirable (listed in order of the guideline chapters):

Prevention:

- Impact of depicting methamphetamine as "performance enhancing" in the information- or entertainment media on the perception and use by the general population
- Evaluation of education campaigns and transferability of findings from nicotine education [451], video and image campaigns such as the "Montana Meth Project" to German target groups

Epidemiology:

- Monitoring systems for documenting difficult to reach users (not reached by addiction support services)
- Prevalence of low-dose methamphetamine use (e.g. students preparing for exams, doping in amateur sport, occasional party-"preloading" in juveniles)
- Psychometric identification of personality characteristics of methamphetamine users compared to the general population and/or users of other substances
- Long-term observation and documentation of methamphetamine users with regard to co-occurring disorders and circumstances surrounding use

Care structures:

- The benefit and feasibility of flexible long-term therapies with outpatient and inpatient components
- Determining the current level of professional knowledge and information needs of general practitioners and internists working primarily in general practice regarding awareness, diagnostics, treatment options and specialists who offer further treatment and concepts for targeted approaches, while addressing potential barriers to access

Therapeutic strategy:

- Merits of integrated treatment concepts and the combination of different therapeutic approaches
- Development and evaluation of an integrated methamphetamine-specific approach on the basis of (cognitive) behavioral therapy

Pharmacotherapy:

- Merits of outpatient management with oral dopamine analogue ("amphetamine substitution") in acute- and post-acute management (ideally: a multicenter RCT with at least one arm that offers no intensive psychosocial intervention)
- Merits of acetylcysteine [120] and naltrexone [122] in reducing craving and as relapse prevention in post-acute management and rehabilitation

Psychotherapy:

- Applicability/options and barriers for the utilization of contingency management in Germany ("rewards" in the form of shopping vouchers/reductions when urine screens are drug-free)

Psychosocial therapy:

- Benefits of ergotherapy and occupational therapy in withdrawal and rehabilitation (correlation to the employment status of those affected?)

Alternative therapeutic approaches

- Benefits of caffeine (coffee) and drinks containing taurine or Guarana tablets in withdrawal and rehabilitation
- Merits of the NADA-acupuncture in the context of methamphetamine-detoxification

Self-help:

- Benefits of intensive education in online-self-help during or after the inpatient post-acute management

Family members:

- Support need in family members and the efficacy of psychoeducation

Co-morbidity:

- Co-occurring addictive disorders: Motive for using substances/co-abuse
- Risk factors for co-occurring gambling addiction such as age, gender, ethnic and cultural origin, socioeconomic or demographic variables as well as (other) psychiatric diseases [236]
- Psychoses: Relationship between establishing the diagnosis (F1x.5) and the emergence of methamphetamine in Germany since 1990 (healthcare research)
- ADHD: Efficacy of methylphenidate vs. placebo or vs. atomoxetine in methamphetamine-dependent adults with a confirmed diagnosis of ADHD both in an outpatient setting and when starting inpatient rehabilitation

Late sequelae in children of mothers with methamphetamine use during pregnancy:

- Relationship between prenatal fetal exposure to methamphetamine and late sequelae in those children (long-term observation), with the aim of develop suitable therapeutic interventions

List of Tables

Glossary

Axis I/II disorder	The multiaxial system of the → DSM-IV categorizes all psychiatric disorders into five axes (categories): Axis I: all clinical disorders (psychological disorder) and other clinically relevant problems excluding personality disorders and mental disorders (impaired intelligence, mental disability) Axis II: Personality disorders and mental disabilities
Acidification	Acidification
Anosmia	Severely impaired or complete loss of sense of smell
Binge	Excessive, uncontrolled self-indulgent activity,; crystalline methamphetamine is used concomitantly for several days with the aim of achieving a high
Body packer	Individuals who smuggle multi-layer packaged drugs, hidden in their body cavities (swallow, vaginal, anal)
Body stuffer	Individuals, who "stuff" drug packages into their mouths, i.e. swallow them, when suddenly approached by police
Coping	Styles, mechanisms, behaviors and/or usually unconscious mental processes enacted to relieve conflict and anxiety
Craving	Powerful longing, desire; urge to pursue an addiction
Diaphoresis	Excessive sweating
Dyskinesia	Kinetic disorder
Entactogens	Psychoactive substances that cause one's own emotions to be perceived with enhanced intensity
G-AEP criteria	Criteria of the German appropriate evaluation protocol: Basis for assessing the need for inpatient treatment
Hyperexcitability	Excessive stimulation of the central nervous system
Hyperthermia	Overheating of the body
Hypotrophy	Subnormal growth, underdeveloped
Insertive	To place, fit or push (something) into something else
Intrusion	Reliving traumatic events
Laparotomy	Abdominal incision
Logorrhea	Pathologically excessive volubility, "verbal diarrhea"
MAC	Mountain Activity Club, a not-for-profit self-help association in Germany
Monovalent	Having a valence of one
MSM	Men who have sex with men
Mydriasis	Dilated pupils
Nociceptive	Sensitive to pain
Peer	Someone of the same age or like-minded

Peripartum	The time around birth
Polyvalent	having a valency of three or more
Prevalence	The number of cases in a defined population at a specific point in time
Promiscuous	Sexual contact with frequently changing partners or at the same time with several partners
Punding	Behavioral disorder, characterized by complex, purposeless movements
Rhabdomyolysis	Destruction of striated muscle cells, death of muscle fibers
Serodiscordant	One partner is HIV-positive, the other is HIV-negative
Sympathetic adrenergic system	Involved in the regulation of the cardiovascular system and the energy metabolism, the effects are mediated by adrenaline and noradrenaline
Tachycardia	Excessively rapid heart rate
Tachyphylaxis	Rapidly decreasing response to a drug
Teratogenicity	Effect of external factors that cause malformation in the embryo
Toxidrome	toxic syndrome; symptoms associated with exposure to a poison

Appendix

Appendix 1: Explanations and comments on the diagnostic criteria synthesized from the "Research criteria of ICD-10"

Other stimulant dependence (ICD-10, F15.2)

According to the definition in ICD-10, the diagnosis of **stimulant dependence** is reached if **at least three** of the following criteria have been **present simultaneously** for **longer than a month** during the **past year**:

1. A **strong desire** or sense of compulsion to use the stimulant substance.

2. **Impaired capacity to contro**l substance use in terms of onset, termination or levels of use. Persistent but unsuccessful efforts to reduce or control substance use. Substance use over a longer period than planned (e.g. *binge/speed run with use over several days, inability to leave supplies unused, use contrary to plans/intentions*).

3. **Physical withdrawal symptoms** at the time of cessation or use reduction, demonstrated by the presence of substance-specific withdrawal symptoms or by the use of the same or similar substances to reduce or avoid withdrawal symptoms.

4. Evidence of tolerance to the substance, in terms of increased doses required to produce the original effect achieved by lower doses. *More of the substance is being used than initially, or the same amount no longer produces the desired effect.*

5. **Preoccupation with substance use.** Progressive **neglect** of other pleasures or interests in favor of substance use, as well as more time being spent using, obtaining or recovering from the consequences of drug use.

6. **Persisting substance abuse** despite proof of **clearly** harmful **consequences**, even though those affected are or could be aware of the extent of the harm.

Acute intoxication (ICD-10: F15.0)

Stimulant use typically causes **one** of the following symptoms:

- Euphoria and sensation of increased energy

- Hypervigilance

- Grandiose beliefs or actions

- Abusiveness or aggression

- Argumentativeness

- Lability of mood

- Repetitive, stereotypical behavior

- Impacting personal circumstances (sociability or social withdrawal)

- Paranoid ideation

- Auditory, visual or tactile hallucinations, usually with preserved orientation.

Physically recognizable symptoms in drug use and particularly in an overdose
(**2 symptoms required to reach a diagnosis**):

- Increased heart rate (also reduced in intoxication)

- Cardiac arrhythmias

- Raised blood pressure (also reduced in intoxication)

- Perspiration and chills

- Nausea/vomiting

- Psychomotor agitation (or slowness in intoxication)

- Muscular weakness

- Chest pain

- Convulsions

- Loss of appetite (weight loss)

Clinically, dilated pupils, increase intrinsic reflexes, kinetic disorders, muscle cramps (including muscle weakness during intoxication) may be present. In the case of more severe intoxication, hyperthermia, respiratory regulation disorder with respiratory depression, cardiac arrhythmias, confusion and impaired level of consciousness with coma also occur.

Other stimulant abuse (ICD-10: F15.1)

Use of psychostimulants that damage health. The damage may be physical, e.g. due to *massive weight loss, tooth loss, skin excoriations or hepatitis from the self-administration of injected psychoactive substances or mental e.g. episodes of depressive disorder, psychotic disorder, inability to recognize or describe emotions (alexithymia), cognitive disorders, violence.*

*The **post-use syndrome** manifesting after occasional use is the opposite of the original effect. Depressive mood with anhedonia, fatigue, lack of motivation, weakness and irritability normalizes within 2–3 days. This term is not included in the international classification systems.*

Stimulant withdrawal syndrome (ICD-10: F15.3)

Withdrawal syndrome starts within a few hours to days after ceasing chronic use and *lasts for longer than 3–4 days*.

Besides the affective disorder in conjunction with anhedonia or sadness, **two** of the following symptoms are present:

- Psychomotor retardation or agitation

- Cravings for stimulating substances

- Increased appetite

- Insomnia or hypersomnia

- Bizarre, unpleasant dreams

The symptoms last for 4 days to 3 weeks, in individual cases for several months, when reclassification in ICD-10: F15.7 should be considered.

Clinically, depressive symptoms with anhedonia and suicidality, fatigue (lethargy, "weariness"), irritability with emotional instability and, as somatic symptoms, bradycardia and weight gain are frequently seen during withdrawal. Sleep after the "crash-phase" is often subjectively ineffective, typically with disturbing dreams. At the start of withdrawal, cognitive ability is subjectively significantly reduced.

Psychotic disorder F15.5

A cluster of psychotic phenomena that occur during or following psychoactive substance use but that are not explained on the basis of acute intoxication alone and do not form part of a withdrawal state. The disorder is characterized by hallucinations (typically auditory, but often in more than one sensory modality), perceptual distortions, delusions (often of a paranoid or persecutory nature), psychomotor disturbances (excitement or stupor), and an abnormal affect, which may range from intense fear to ecstasy. Consciousness is usually clear but some degree of clouding, though not severe confusion, may be present.

Only after proven abstinence, including from cannabis, and with persistent symptoms of methamphetamine-induced psychosis (MAP) over a six month period, should the diagnosis of F15.5 (previous psychotic symptoms clearly caused by stimulant use), be changed to F20.x (schizophrenia).

F15.7 Residual and late-onset psychotic disorder

A disorder in which alcohol- or psychoactive substance-induced changes of cognition, affect, personality, or behavior persist **beyond** the period during which a direct psychoactive substance-related effect might reasonably be assumed to be operating.

Onset of the disorder should be directly related to the use of the psychoactive substance. Cases in which initial onset of the clinical picture occurs later than episode(s) of such substance use should be coded here only where clear and strong evidence is available to attribute the state to the residual effect of the psychoactive substance.

This includes:

- Dementia and other milder forms of persisting impairment of cognitive functions
- Residual affective disorder
- Residual disorder of personality and behavior
- Late-onset psychoactive substance-induced psychotic disorder
- Flashbacks
- Post-hallucinogen perception disorder

Symptoms such as brief paranoid thoughts ("everyone sees that I once took drugs", "they talk about me"), increased sensitivity to noise as well as a "180 degree-view" (unfocused) can persist and are only reported shamefully when asked directly. Also, an aggressive, non-empathic change is often reported by family members, when asked, even when abstinence has been achieved. The DSM-IV classified this diagnosis as a stimulant-induced anxiety disorder.

F19.2 Other psychoactive substance dependence

The diagnosis of polytoxicomania (ICD-10 F19.2) should only be used when three or more psychoactive substances are used in a chaotic and random way or when the exact identity of some substances being used is uncertain or unknown. It is impossible to assess which substance is contributing most to the disorder. Dependency criteria must be met for all substances used.

Many of those affected take several substance classes in order to self-medicate undesired effects or withdrawal symptoms. Currently benzodiazepines, synthetic opioids, opiates and pregabalin are used.

The primary diagnosis is coded according to the substance or substance class used that causes the clinical picture at the time or is preferred substance contributing most to the disorder.

According to the DSM-V, this diagnosis should only be used for unknown or otherwise unnamed substances. The term polytoxicomania (Greek for "madness") or "polysubstance abuse" originating from ICD-9 is not included in DSM-V.

References

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Appendix 2: Interview checklist/items for initial assessment in amphetamines-type stimulant (ATS) users

1. Have you used the following substances in the past?

If yes: more detailed questioning and assessing whether these are relevant; only if they are relevant, enter the following into the table:

Route of substance administration (only in relevant use more detail right)	No relevant use	Age at first use	Days of use over the past 30 days	Main routes of administration oral, nasal, i.v., smoking, other	Time interval **since last** use: H D W M Y	**Withdrawal** syndrome in the past? Yes
☐ Alcohol	☐			O		☐
☐ Cannabis	☐			O—R		☐
☐ Synthetic (cannabinoids) smoker mixture (spice etc.)	☐			O—R		☐
☐ Amphetamine (speed)	☐			O—N—IV		☐
☐ Crystal meth/("C", "crystal speed")	☐			O-N-IV-R-A		☐
☐ MDMA, MDE, ("XTC")	☐			O—N—IV		☐
☐ Newer amphetamine-like substances ("research chemicals", "bath salts", bong cleaner like mephedrone, MDPV etc.)	☐			O—N—IV--R		☐
☐ Cocaine	☐			O—N—IV--R		☐
☐ Crack	☐			O—N—IV--R		☐
☐ Liquid ecstasy (GBL, GHB)	☐			O—N—IV		☐
☐ Hallucinogenics (LSD)	☐			O—N—IV		☐
☐ Inhalant solvents ☐ Lighter gas	☐			N –Inh--A		☐
☐ Biogenic substances (datura [jimsonweed], angel's trumpet, mushrooms, nutmeg etc.)	☐			O—N—IV--R		☐

Route of substance administration (only in relevant use more detail right)	No relevant use	Age at first use	Days of use over the past 30 days	Main routes of administration oral, nasal, i.v., smoking, other	Time interval **since last** use: H D W M Y	Withdrawal syndrome in the past? Yes
☐ Opioid analgesics (tramadol, fentanyl, codeine)	☐			O—N—IV--R		☐
☐ Methadone, buprenorphine and other substitutes	☐			O—N—IV--R		☐
☐ Heroin	☐			O—N—IV--R		☐
☐ Benzodiazepines ("Downers"/"benzos/bennies") ☐ Barbiturates	☐			O—N—IV--R		☐
☐ Ketamine ☐ Poppers (amyl nitrite)	☐			O—N—IV--R		☐
☐ Other substances (prescribed / not prescribed) (free text)	☐			O—N—IV--R		☐
	☐			O—N—IV--R		☐
	☐			O-R-A		☐
☐ Medically prescribed (methylphenidate, modafinil and other psychostimulants)	☐					☐
☐ Nicotine	☐			O—N—IV--R		☐

2. Are you **currently** under the influence of a substance?

☐ Yes   ☐ No   Describe?_____

3. Which substance do you **mainly** use?_____

4. Which substance has given you a **craving**?

_____

5. Which substance have you noticed **withdrawal symptoms** from? (detailed below)

_____

6. Have you had **physical** symptoms from the **use of stimulants**?

e.g.: Tooth damage and decay, scratched skin ("speed bumps"), phases of emaciation during use or uncontrollably enhanced appetite with adverse weight gain during withdrawal above the "ideal weight", lost sense of smell, increased nosebleeds?

☐ Yes   ☐ No   ☐ N/A

Other?_____

7. Did you experience unpleasant psychological effects when using stimulants? e.g.: Persecutory delusions, anxiety, "tweaking", outbursts of aggression, depression etc.

☐ Yes   ☐ No   ☐ N/A

Other?_____

From which other substances? _____

8. Have you had psychotic phases (paranoia/"tweaking, tripping")?

☐ Yes   ☐ No   ☐ N/A

e.g. seen people or things that other people could not see (hallucinations), or heard noises and e.g. thought that the police or others want to break in? Do you have the feeling of being stared at, that others are talking about you or you are being monitored?

If yes, when? How long did it last (resolved after 3 days of abstinence?), with/without treatment? What medication was helpful, side effects?

9. Have you had psychotic phases without substance use?

☐ Yes   ☐ No   ☐ N/A

If yes, optional: when? How long did they last? Treatment with medications?

10. Do you have these kind of symptoms currently?

☐ Yes   ☐ No   ☐ N/A

Which ones?_____

11. Have you ever become aggressive when using drugs?

☐ Yes   ☐ No

If yes, …

☐ towards individuals close to you/family members

☐ towards acquaintances

☐ towards friends

☐ towards unknown individuals

☐ towards myself

Which substances did you use?

_____

_____

12. Have you ever been so desperate that you wished you were dead?

☐ Yes   ☐ No

13. Have you ever tried to take your own life?

☐ Yes   ☐ No

14. In the last 30 days, have you had thoughts, made plans or tried to take your own life?

☐ Yes   ☐ No

15. Do you have such suicidal thoughts now? Concrete thoughts, concrete plans, how you could kill yourself?

☐ Yes   ☐ No

Describe?_____

16. Life-threatening complications occurred when using (substances)

☐ Never   ☐ Yes _____ Repeatedly _____ Relevant details _____

Life-threatening complications when using _____

☐ Never   ☐ Yes _____ Repeatedly _____ Relevant details _____

17. Has your drug use caused social problems for you?

e.g.: Loss of driving license, separation, loss of job, loss of custody etc.

☐ Yes   ☐ No   ☐ N/A

18 Are there any currently severe psychosocial problems?

_____

19 Are there any severe physical pre-existing diseases?

_____

20 Who are living together with? (legally dependent children?)

☐ Yes_____ ☐ No

21 Are you **already** in contact with an addiction counseling center, self-help group, psychiatrist or other addiction-specific setting?

☐ Yes, _____ ☐ No (regularly? N. appointment?)

22. Have you ever tried to reduce your drug use and failed?

☐ Yes   ☐ No (C)

23. Does it annoy you when relatives talk to you about your use of drugs?

(For which substance? _____)

☐ Yes   ☐ No (A)

24. Do you feel guilty about your drug use?

(Which substance?_____)

☐ Yes   ☐ No (G)

25. Have you taken the stimulants (Speed, Cocaine, Crystal Meth, not medically pre-scribed, without coffee/tea) in the morning in order "just to be able to function"?

(Which substance?_____)

☐ Yes   ☐ No (E)

26. Observation

Seems confused, disoriented, forgetful	☐ Yes	☐ No
Seems anxious,misinterprets situations (paranoia?)	☐ Yes	☐ No
Seems ataxic, risk of falling	☐ Yes	☐ No
Looks physically neglected, heavily emaciated or similar	☐ Yes	☐ No
Acts threateningly agitated	☐ Yes	☐ No
Makes threats	☐ Yes	☐ No

From here on, relevant questions about rendering/confirming a <u>diagnosis</u>

27. To which substances has tolerance developed, meaning, for example: Have you noticed that you need more methamphetamine for the same effect or that the same dose has less of an effect? _____

28. In methamphetamine/amphetamine tolerance development?

☐ Yes   ☐ No (**ICD-10 criterion)**

typical dosage of the current main substance _____

dose when last used _____

typical dosage of the current main substance II _____

dose when last used _____

typical dosage of the current main substance III_____

dose when last used _____

29. Typical /current use patterns of psychostimulant used:_____

☐ Episodic _____(Frequency)

☐ Occasional use ☐ Yes   ☐ No

_____

☐ "Binges" _____(Use until the supply is exhausted or the user suffers complete exhaustion followed by a short break)

☐ chronic _____

    (daily, more than once daily)

30. In the past 12 months, have you used more stimulants, such as Crystal Meth (Speed, Cocaine), or used them longer than planned?

☐ Yes   ☐ No (**ICD-10 criterion**)

31. Have you spent much of the past 12 months using drugs, getting stimulants like Crystal Meth, or recovering from drug use? Have you neglected other important things?

☐ Yes   ☐ No (**ICD-10 criterion**)

32. In the last 12 months, have you tried unsuccessfully to stop or restrict the use of stimulants?

☐ Yes   ☐ No (**ICD-10 criterion)**

33. Have you taken stimulants such as Crystal Meth to prevent withdrawal symptoms (the "down")?

☐ Yes   ☐ No (**ICD-10 criterion)**

34. What were the withdrawal symptoms? (Check ICD-10-criteria, see Appendix)

35. What were your initial and what were your later motives for psychostimulant use? (e.g. party fun, sexuality, primary performance improvement at work, weight regulation, to manage everyday life, other)

Initially _____

Later _____

36. Indications of other functionality such as self-medication of depressive disorders ("taken for depression?")

☐ Yes   ☐ No_____

37. What substances have you used to "come down from" to crystal meth or speed?

☐ None

☐ The following: _____

38. Have you ever sought treatment for any substance use?

39. If   ☐ yes, which drugs?

_____

What therapy produced which outcome? (How detailed depends on the setting! see below)

_____

40. Has it led to any substance-related sexual acts that you regret?

Yes ☐   ☐ No   ☐ N/A

41. Do you enjoy sex? (Multiple answers possible!)

☐ Only with drugs

☐ Also without drugs

☐ Not at all

☐ Only without a condom

☐ With frequently changing male/female partners

42. Was sex a means to an end for you in order to get **drugs**?

☐ Yes   ☐ No

43. Do you regularly watch movies or websites with pornographic content?

☐ Yes   ☐ No

If yes, how many hours a week?   Hours

44. How many time do you spend per day with …   **hours**

    a. Console games (XBox, Playstation, Wii etc.)

    b. General surfing on the internet (news, music, e-mails, etc.)

    c. Social networks (Facebook, WhatsApp, Google+, Twitter etc.)

    d. PC online games with gambling (poker, skat, sports betting…)

    e. PC multiplayer games (WoW, EvE, Counter Strike, Modern Warfare ...)

    f. PC online/smartphone browser games (Farmville, Aion …)

    g. Visits to amusement arcades

    h. TV series (more than 2 episodes in a row)

45. Has stimulant use led to increased gambling losses?

    ☐ Yes   ☐ No

46. Relevant medication?

    _____

47. Psychiatric co-treatment with

    _____

48. Please describe your main problems at the moment in addition to your dependence.

    _____

    _____

49. How can I / we / the service help you?

    _____

    _____

Additional questions for help (and therapy) planning (self-documentation/free text)

50. Visits to addiction counseling? How regularly? Currently?

51. Self (general practice) detoxification? (How often? How successful? How long was it successful? What were the reasons for relapse? Medication attempts?)

52. Inpatient detoxification (Where? When? How often? Completed? Reasons for cessation? How successful? How long was it successful? What were the reasons for relapse? Medication attempts)

53. Outpatient therapy (Where? When? Completed? Reasons for cessation? How successful? How long was it successful? What were the reasons for relapse?)

54. Inpatient therapy (Where? When? Completed? Reasons for cessation? How successful? How long was it successful? What were the reasons for relapse?)

General questions for <u>comprehensive </u>treatment planning (use self-documentation):

- Current abstinence motivation, goals, plans

- Social repercussions (forfeiture of driver's license, loss of job, separations, court cases, proceedings under the German Narcotics Law (BtMG).

- Are social help services used? Information need? Initiation required?

- Social situation, profession, marital status, relationship, non-drug-using acquaintances, supportive environment/endangered environment?

- Children/family members who need to be taken care of?

- Are somatic sequelae treated adequately?

- Are psychiatric sequelae treated adequately?

- Psychiatric pretreatments

- Duration of and reasons for abstinent phases

- Reasons for ending such abstinent phases

- Addictive disorders in the parents?

- Get more detail for relevant substances:

    State the periods in your life you used the substances:

Substance   **from age – to**

| Daily use |
| Weekly use |
| Monthly use |

References

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  http://www.ncbi.nlm.nih.gov/pubmed/11188499

- Schippers GM., Broekman TG. MATE. Measurements in the Addictions for Triage and Evaluation. Development of an instrument assessing patient characteristics in substance abuse treatment. Final report. ZonMw/Resultaten Scoren-project nr 31000068. Amsterdam, AIAR, AMC-Amsterdam & Bureau Bêta, Nijmegen, 2007

- http://www.mateinfo.eu/pubs/31000068.pdf

- European Addiction Severity Index:
  http://www.emcdda.europa.eu/html.cfm/index3647EN.html

Measurements in the Addictions for Triage and Evaluation (MATE):

- Buchholz A, Friedrichs A. ICF in der Suchttherapie. Die Anwendung des MATE-ICN zur Erfassung von Leistungseinschränkungen und Hilfebedarf bei Patienten mit substanzbezogenen Störungen. Konturen Sucht soz Fragen 2013;27(2):27-31

- Manual and protocol for assessment, scoring and use of the MATE:
  http://www.mateinfo.eu/pubs/MATE-de%202.1%20Manual%20and%20Protocol-D.pdf

- German explanation of "Measurements in the Addictions for Triage and Evaluation (MATE)":
  http://www.mateinfo.eu/german/index.html

- WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction 2002;97(9):1183-94

Appendix 3: German appropriate evaluation protocol (G-AEP) criteria

(German appropriate evaluation protocol

= Basics for assessing the necessity for inpatient treatment)

A Severity of the disease

A1 Sudden loss of consciousness or acute confusional state (coma or unresponsiveness)

A2 Pulse rate: < 50 / min or > 140 / min

A3 Blood pressure systolic < 90 or > 200 mm Hg / diastolic < 60 or > 120 mm Hg

A4 Acute loss of vision or sense of balance

A5 Acute loss of hearing

A6 Acute or progressive paralysis or other acute neurological symptoms

A7 Life-threatening infection or persistent intermittent fever (> 38.0 °C core temperature)

A8 Acute / subacute bleeding and/or drop in hemoglobin requiring intervention

A9 Severe electrolyte disturbance or blood gas imbalance or current imbalance of substances excreted in the urine

A10 Acute or progressive sensory, motor, functional, circulatory or respiratory or dermatological disorders as well as pain states that hinder or endanger the patient

A11 Strongly suspected or confirmed myocardial ischemia

A12 Disease that requires treatment with oncological chemotherapeutics or other potentially life-threatening substances

B Intensity of treatment

B1 Continuous or intermittent intravenous medication / infusion (not including tube feeding)

B2 Surgery, intervention or special diagnostic measure within 24 hours that require the particular medical equipment and facilities of a hospital

B3 Repeated control of vital signs, also via monitor, at least every 4 hours

B4 Treatment on intensive care unit Yes

B5 Intermittent, assisted or controlled ventilation several times a day or continuous

C Surgery / invasive measure (except for emergency measures)

C1 Surgery / procedure that can inarguably not be performed in an outpatient setting

C2 Services that should usually be rendered on an outpatient basis pursuant to the contract under Section 115b (1) German Social Code Book V (SGB V) (services labelled with an [*] asterisk from the current catalogue of outpatient operations and interventions replacing inpatient procedures according to Appendix 1 (and a criterion of the General Facts of the Case pursuant to Section 3 (3) contract under Section 115b (1) SGB V

D Comorbidities in association with surgeries or hospital-specific measures

D1 Significantly pathological pulmonary parameters

D2 Sleep apnea syndrome: History of moderate or severe sleep apnea syndrome

D3 Hematological disorders: Surgically relevant coagulation disorder; surgically relevant hematological disorder requiring treatment

D4 Manifest cardiac diseases: Angina pectoris (NYHA III / IV); manifest cardiac insufficiency (NYHA III / IV)

D5 History or family history of malignant hyperthermia

D6 Patients receiving treatment that requires special monitoring for the following diseases:

  - Endocrine diseases (e.g. diabetes)

  - Obstructive pulmonary diseases

  - Stroke and/or heart attack

- Treatment-relevant impairment of kidney / liver function

- Severe immunodeficiencies

- Hypertension with risk of hypertensive crisis

E Necessity for intensive care in association with surgeries or other hospital-specific measures

E1 Expected postoperative obligatory monitoring over 12 hours after end of anesthesia and intervention

E2 Amputations/replantations

E3 Vascular surgical interventions (arterial and/or central)

E4 Placement and removal of stabilizing implants, except for e.g. uncomplicated hand, wrist as well as foot and ankle surgeries

E5 Placement of drainage tubes with continuous monitoring of function

E6 Catheter-assisted pain therapy

F Social factors that obviate immediate medical care of patients in conjunction with surgeries or hospital-specific measures – reviewed and documented –

F1 No means of communication because the patient lives alone and cannot get to the phone

F2 No means of transportation or poor accessibility to emergency medical services

F3 Lack of ability to comply on the part of the patient

F4 Lacking means of care

Appendix 4: Further addresses and liaison centers[1]

Addresses

Federal Centre for Health Education (BZgA)

Maarweg 149–161

50825 Cologne

Phone: +49 (0)221 / 8992-0

Counseling telephone: +49 (0)221 / 8920-31

Fax: +49 (0)221 / 8992-300

Email: poststelle@bzga.de

www.drugcom.de

**German Centre for Addiction Issues
(Deutsche Hauptstelle für Suchtfragen e. V., DHS)**

Westenwall 4

59065 Hamm

Phone: +49(0)23819015-0

Fax: +49 (0)2381/9015-30

Email: info@dhs.de

www.dhs.de

Drug Commissioner of the Federal Government,
German Federal Ministry of Health
Friedrichstrasse 108

10117 Berlin

Phone: +49 (0)30 18-441-1452

Fax: +49 (0)30-20640-4960

Email: drogenbeauftragte@bmg.bund.de

www.drogenbeauftragte.de

**Professional Association for Addiction e. V.
(Fachverband Sucht e.V.)**

Walramstr. 3

53175 Bonn

Phone: +49 (0)228-26 15 55

Fax: +49 (0)228-21 58 85

Email: Sucht@Sucht.de

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[1] This overview makes no claim to completeness and offers no guarantee relating to the correctness of the information provided (as of February 2016).

www.sucht.de

**Federal Association for Accepting Drug Work
(Bundesverband für akzeptierende Drogenarbeit)**

akzept e.V.

Christine Kluge Haberkorn
Südwestkorso 14

12161 Berlin

Phone: +49 (0)30-827 06 946

Email: akzeptbuero@yahoo.de
www.akzept.org

German Society for Addiction Medicine

c/o Centre of Interdisciplinary Addiction Research (ZIS)
of the University of Hamburg, University Medical Center Hamburg-Eppendorf

Department of Psychiatry and Psychotherapy
Simone Mollenhauer

Martinistr. 52

20246 Hamburg

Phone: +49 (0)40-7410-54221

Email: info@dgsuchtmedizin.de

www.dgsuchtmedizin.de

German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN)

DGPPN Head Office
Reinhardtstr. 27 B

10117 Berlin

Phone: +49 (0)30-240 477 220

Email: j.holzhausen@dgppn.de

www.dgppn.de

Deutsche AIDS-Hilfe e.V.

Wilhelmstr. 138

10963 Berlin

Phone: +49 (0)30-690087-0

Fax: +49 (0)30-690087-42

Email: dah@aidshilfe.de

www.aidshilfe.de

Support, counseling and therapeutic services

Outpatient and inpatient addiction help facilities

German Centre for Addiction Issues (Deutsche Hauptstelle für Suchtfragen e. V.)

Database with over 1400 outpatient addiction counseling centers and 800 inpatient facilities run by the addiction help services

www.dhs.de/einrichtungssuche.html

Inpatient therapy centers

Federal Association for Inpatient Addiction Support (Bundesverband für stationäre Suchtkrankenhilfe e.V., BUSS)

www.therapieplaetze.de

Examples of inpatient therapy for methamphetamine and stimulant problems:

- www.ahg.de/AHG/Standorte/Mecklenburg/Service/Veroeffentlichungen/Flyer/FLyer_Stimulantien_2013.pdf

- www.bezirkskliniken- oberfranken.de/pages/html/hochstadt/behandlungsbereiche/stimulantien.html

Regional support, counseling and therapeutic centers
via the German Centre for Addiction Issues (Deutsche Hauptstelle für Suchtfragen e.V., DHS)

www.dhs.de/dhs/lande centers.html

Addiction counseling centers

Federal Centre for Health Education (Bundeszentrale für gesundheitliche Aufklärung, BZgA)
www.bzga.de/?uid=5df2624da5b3f7a9a202fab9df892d8a&id=Seite48&sid=-1

Physician, board-certified in addiction medicine, or a clinic specialized in addiction therapy
Search for a physician in Germany via the Federal Association of Panel Doctors
www.kbv.de/html/arztsuche.php

Search for a physician in Germany via the German Medical Association
www.bundesaerztekammer.de/page.asp?his=2.5511

Telephone counseling, national

Hotline maintained by the Federal Centre for Health Education

Nationwide anonymous counseling, 24 hours, not toll-free: +49(0)1805-31 30 31

www.sucht-und-drogen-hotline.de

Crystal Hotline of the Bavarian State Ministry of Public Health and Care Services

Nationwide anonymous counseling, free of charge: +49(0)941-56 95 82 901

Mon to Fri from 10:00 to 16:00 CET, Sun 18:00 to 20:00 CET (answering machine for return calls)
www.drugstop.org/angebot/crystal-hotline

Information on nearby counseling facilities: +49 (0)221-89 20 31

Telephone counseling, regional

Unless stated otherwise, the services can be reached 24/7.

Berlin: +49 (0)30-19237

www.drogennotdienst.org

Essen: +49 (0)201-40 38 40

www.essen.de/location/locationdetailseite_156233.de.jsp

Frankfurt/M.: +49 (0)69-623451

Monday to Friday from 8:00 to 23:00 CET, Saturday and Sunday from 12:00 to 24:00 CET www.basis-ev.eu/beratung/telefonische-beratung

Hamburg: +49 (0)40 -41 92 38-10

Daily from 8:00 to 24:00 CET
www.jugendhilfe.de/drobinn.de/gz-8.html

Cologne: +49 (0)221-19700

Daily from 10:00 to 24:00 CET

www.sucht-und-drogen-hotline.de/wirueberuns/suchtnotruf_koeln.html

Leipzig: +49 (0)341-21122 10

Tuesday and Thursday from 13:00 to 17:00 CET

www.drugscouts.de

Munich: +49 (0)89-2828 22

www.suchthotline.info

Nuremberg: +49 (0)911-19237

Daily from 8:00 to 22:00 CET

Regensburg +49(0)941-56 95 82 901

Monday to Friday from 10:00 to 16:00 CET, Sunday from 18:00 to 20:00 CET (answering machine for return calls)

Online counseling

Chat and email counseling by the Federal Centre for Health Education (BZgA)
Chat counseling: Monday to Friday from 15:00 to 17:00 CET (except for bank holidays)
www.drugcom.de/beratung-finden

Online counseling run by Mindzone

www.mindzone.info/beratung/onlineberatung

Online counseling run by mudra – Alternative Youth and Drug Aid (Alternative Jugend- und Drogenhilfe e.V.)

mudra.beranet.info

Online counseling run by "Youth helps Youth" (Jugend hilft Jugend) in Hamburg

www.de.jugend-hilft-jugend.de/Online-Angebot/chat

Counseling services listed by federal states

Baden-Wuerttemberg

Counseling centers and facilities run by the addiction help services

www.suchtfragen.de/Suchthilfe.9.0.html

Bavaria

Coordination office of the addiction help services in Bavaria

www.kbs-bayern.de

Berlin

Berlin Center for Addiction Issues

www.sucht-drogen-rat-hilfe.de/content

Brandenburg

Brandenburg State Office for Addiction Issues

www.blsev.de

Bremen

Addiction Counseling Guide of the Health Authority Bremen (pdf, 126.7 KB)

www.gesundheitsamt.bremen.de/sixcms/media.php/13/2_Steu_Beratungsf%FChrer%20Sucht.pdf

Hamburg

Counseling, self-help and therapy services

www.kursbuch-sucht.de/suchthilfe/amphetamine-und-speed/0/hamburg

Pregnancy – Child – Addiction (Schwangerschaft – Kind – Sucht)

www.lina-net.de/suchthilfe

Counseling centers and self-help

www.rauschbarometer.de

Hessen

Hessian State Office for Addiction Issues

www.hls-online.org

Mecklenburg-Western Pomerania

Mecklenburg-Western Pomerania Coordination Office for Addiction Prevention (LAKOST) www.lakost-mv.de

Lower Saxony

Lower Saxony State Office for Addiction Issues

www.nls-online.de/home16/index.php/adressen

North Rhine-Westfalia
NRW State Offices for Addiction

www.landesstellesucht-nrw.de

Rhineland-Palatinate

Rhineland-Palatinate State Office for Addiction Issues
www.liga-rlp.de/

Saarland

Saarland State Office for Addiction Issues
www.landesstelle-sucht-saarland.de

Saxony

Internet portal of the addiction help services in Saxony
www.suchthilfe-sachsen.de

Saxony-Anhalt

Saxony-Anhalt State Office for Addiction Issues

www.ls-suchtfragen-lsa.de/start

Anonymous crystal meth office hours for all in the city of Halle
www.checkpoint-c.de

Schleswig-Holstein

Schleswig-Holstein State Office for Addiction Issues
www.lssh.de

Thuringia

Thuringia State Office for Addiction Issues
www.tls-suchtfragen.de

Self-help

Breaking Meth

Virtual self-help portal for individuals with methamphetamine / crystal meth experience (Centre for Interdisciplinary Addiction Research of the University of Hamburg)

www.breaking-meth.de

JES

Self-help network for junkies, former users and persons on replacement therapy

www.jes-bundesverband.de

Mountain Activity Club e. V.
Peer-supported self-help group
www.mountain-activity-club.de

NA

Narcotics Anonymous Germany

www.narcotics-anonymous.de

Counseling for family members and friends

Bundesverband der Eltern und Angehörige für akzeptierende Drogenarbeit e.V.

Non-profit German national association of parents and family members for
"An acceptance orientated drug policy"
www.akzeptierende-eltern.de

BVEK

Bundesverband der Elternkreise suchtgefährdeter und suchtkranker Söhne und Töchter e. V.
Non-profit German national association of parents of sons and daughters with addictive disorders
Braunsbergstr. 23

48155 Münster

Phone: +49 (0)251-14207-33

Mobile: +49 (0)151 -43 11 23 33

Fax: +49 (0)251 -13 30 27 57

Email: info@bvek.org
www.bvek.org

ELSA

Counseling of parents with children and adolescents at risk of addiction or addicted
www.elternberatung-sucht.de/ueber-uns

NACOA

Interessenvertretung für Kinder aus Suchtfamilien e. V.
Non-profit political lobby group for children from addiction-afflicted families
Gierkezeile 39

10585 Berlin

Phone: +49 (0)30 -35 12 24 30

Email: info@nacoa.de
www.nacoa.de

Harm reduction

KISS

Behavioral Self-Control Training for the Targeted Reduction of the Use of Legal and Illegal Drugs
www.kiss-heidelberg.de/

SKOLL

Self-control training for a responsible use of narcotic drugs and other addictive phenomena (service of Caritas)

www.skoll.de

Harm reduction in party settings

Provision of information, strategies and actions for the health promotion and risk reduction in socially unremarkable drug users:

Alice Project (Frankfurt/Main)

www.alice-project.de

Chillout (Potsdam)

www.chillout-pdm.de

Drug Scouts (Leipzig)

www.BERCHTOLD.biz

DroGenKult (Berlin)

www.drogenkult.net

Drogerie Projekt (Erfurt)

www.drogerie-projekt.de

Eclipse e. V. (Berlin)

www.eclipse-online.de

Fixpunkt Party-Team (Berlin)

www.fixpunkt-berlin.de

Mindzone (Munich)

www.mindzone.info

mudra enterprise (Nuremberg)

www.mudra-online.de

partypack.de (Cologne)

www.partypack.de

Partyprojekt Odyssee (Kiel)

www.odyssee-kiel.de/partyprojekt

Remedy Berlyn (Berlin)

www.remedyberlyn.de

Information material

Information material on various drug-related topics is made available free of charge by the:

The German Centre for Addiction Issues

www.dhs.de

Federal Centre for Health Education

www.bzga.de

"Crystal Meth" brochure issued by the Federal State Prevention Council Saxony

www.publikationen.sachsen.de/bdb/artikel/17190

"Crystal Meth" information booklet of Mindzone

www.mindzone.info/infomaterial/bestellungen

Appendix 5: Referenced practice guidelines

- Association of the Scientific Medical Societies in Germany (AWMF), German Society for Psychiatry, Psychotherapy and Neuropsychiatry (DGPPN), German Society for Addiction Research and Addiction Therapy (DG-Sucht), et al. S3 Practice Guideline "Screening, diagnostics and treatment of harmful and addictive tobacco use". AWMF Guidelines Register No. 076/-006. 2010. (as of 9 February 2015): 2014 [cited: 2015 Jun 17]. Accessible at: http://www.awmf.org/uploads/tx_szleitlinien/076-006l_S3_Tabak_2015-02.pdf

  - Association of the Scientific Medical Societies in Germany (AWMF), Heinen F, Landgraf M. S3 Practice Guideline: Diagnostics of fetal alcohol syndrome (FAS). AWMF Guidelines Register No. 022/-025. 2010. (as of 10 December 2012): 2012 [cited: 2016 May 24]

- Association of the Scientific Medical Societies in Germany (AWMF), #Deutsche STI-Gesellschaft (DSTIG), Robert Koch Institute (RKI), et al. S1 Guideline "STI/STD Counselling". AWMF Guidelines Register No. 059/-006. 2010. (as of 15 July 2015): 2015 [cited: 2016 May 24]. Accessible at: http://www.awmf.org/uploads/tx_szleitlinien/059-006l_S1_STI_STD-Beratung_2015-07.pdf

- Deutsche AIDS-Gesellschaft (DAIG), Österreichische AIDS-Gesellschaft (ÖAIG), Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), et al. S2k Guideline. German-Austrian recommendations for HIV treatment during pregnancy and for newborns exposed to HIV. AWMF Register No. 055-002. (as of 31 May 2014): 2014 [cited: (2016 Mar 24) Accessible at: http://www.awmf.org/uploads/tx_szleitlinien/055-002l_S2k_HIV- Therapie_Schwangerschaft_Neugeborenen_2014-05.pdf

  - German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). Schizophrenia Treatment Guideline. Darmstadt: Steinkopff; 2006 (S3 Practice Guidelines in Psychiatry and Psychotherapie; 1).

- German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). S2 guidelines for personality disorders. Darmstadt: Steinkopff; 2009

- German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). S3 Practice Guideline: guideline "Psychosocial therapies in severe mental disorders". 2013 [cited: 2016 May 1]. Accessible at: http://www.awmf.org/uploads/tx_szleitlinien/038-020l_S3_Psychosoziale_Therapien_10-2012.pdf

- German Society for Psychiatry, Psychotherapy and Neuropsychiatry (DGPPN), German Medical Association (BÄK), National Association of Statutory Health Insurance Physicians (KBV), et al. S3 Practice Guideline//National Clinical Practice Guideline Unipolar Depression - long version, 2nd Ed. Version 3. 2015 [cited: 2016 Apr 13]. Accessible at: http://www.leitlinien.de/mdb/downloads/nvl/depression/depression-2aufl-vers3-lang.pdf DOI: 10.6101/AZQ/000277|

- German Society of Psychosomatic Medicine and Medical Psychotherapy (DGPM). S3 Practice Guideline: Anxiety disorders. 2014 [cited: 2016 May 2]. Accessible at: http://www.awmf.org/uploads/tx_szleitlinien/051-028l_S3_Angstst%C3%B6rungen_2014- 05_2.pdf

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- Drug & Alcohol Services South Australia (DASSA), McIver C, McGregor C, et al. Guidelines for the medical management of patients with methamphetamine-induced psychosis. Morphett Vale: DAS-SA Southern Service; 2006 Accessible at: http://www.sahealth.sa.gov.au/wps/wcm/connect/cbad29804178755b94d1ff67a94f09f9/Guidelines+methamphetamine-induced+psychosis-DASSA-Oct2013.pdf?MOD=AJPERES&CACHEID=cbad29804178755b94d1ff67a94f09f9

- German Society for Addiction Research and Addiction Therapy (DG-Sucht). S3 Practice Guideline on "Alcohol-related disorders": Screening, Diagnose and Behandlung#. 2014 [cited: 2016 May 1]. Accessible at: http://www.awmf.org/uploads/tx_szleitlinien/076-001l_S3-Leitlinie_Alkohol_2016- 02.pdf

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- Flatten G, Gast U, Hofmann A, et al. S3 Guideline #Posttraumatische Belastungsstörung. Trauma & Gewalt 2011;5(3):202-10

- Gesellschaft für Neonatologie und pädiatrische Intensivmedizin, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Deutsche Gesellschaft für Kinderheilkunde und Jugendmedizin (DGKJ), et al. S2k Guideline. Frühgeborene an der Grenze der Lebensfähigkeit. AWMF Register No. 024-019. (Status as of 30 April 2014): 2014 [cited: 2016 Apr 5]. Accessible at: http://www.awmf.org/leitlinien/detail/ll/024-019.html

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