PHARMACOLOGICAL TREATMENT OF METHAMPHETAMINE DEPENDENCE WITH CENTRAL STIMULANTS

SNN ČLS JEP recommendations for *off-label* use of central stimulants in methamphetamine addicts

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Introduction

The situation caused by the SARS-CoV-2 coronavirus pandemic had a significant impact on the drug landscape with indications that point to a decrease in the availability of addictive substances, a reduction in addiction services and other social and health services, and a worsening socio-economic situation of problem drug users. It was feared that these factors would lead to a wave of new complications: the emergence of new and more potent addictive substances, and the use of a combination of addictive substances with the consequent increased risk of overdose. The drug landscape is characterized by a high prevalence of problem injecting methamphetamine users. According to information collected by addiction services, a reduction in the availability and deterioration in the quality of the methamphetamine available has also been identified.

Although the development of the guidelines set out in this document was driven by the situation generated by the pandemic, pharmacological treatment with illicit stimulants, including substitution therapy, can be considered as a viable alternative to standard treatment in any circumstance. The use of drugs with central psychostimulant effects can also facilitate detoxification and withdrawal on an outpatient basis. Withdrawal, which usually lasts for several weeks and often includes symptoms such as severe fatigue and irritability, becomes milder and the withdrawal process more bearable for the person.

Characteristics

The use of central stimulant medication in the treatment of stimulant dependence is not a standard treatment. It is in fact off-label drug administration, due to the lack of strong enough evidence to recommend substitution therapy for stimulant dependence. The Czech Republic has experience with this type of treatment, compiled in clinical cases (Hampl, 2004), (Minařík et al., 2016). A number of larger studies have been conducted looking at the efficacy and safety of substitution therapy for the treatment of stimulant dependence (e.g., Castells et al., 2016; Gouzoulis-Mayfrank et al., 2017). Available sources agree that strong evidence on the efficacy of stimulant replacement therapy is lacking, and it is therefore not possible to clearly distinguish between the effect cause by the substance itself from that of psychosocial interventions. This conclusion is also evident in the German guidelines translated into Czech, which are based on a systematic review and experts' consensus (Gouzoulis-Mayfrank et al., 2017).

As with opioid substitution treatment, the principle in this indication is to provide a substitution substance at an optimized dose that effectively suppresses the client's withdrawal symptoms, while reducing cravings and allowing for a comprehensive improvement in the client's quality of life.

The central stimulant used in the Czech Republic for the replacement treatment of stimulant dependence is methylphenidate, which is available in two forms, extended-release (Concerta) and non-prolonged (Ritalin). Both drugs have been approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children. Its use with adults is not recommended because its effect is questionable. Nonetheless, they are used in adults with this indication as an alternative option for the non-indicated pharmacological treatment of ADHD in cases where atomoxetine does not work.

Although the Czech Republic has a relatively broad experience in the use of methylphenidate in psychostimulant dependence, no standardized procedure or collection of systematically ordered results on the effective connection between the various components of care has yet been established. There is however no doubt that, in addition to the pharmacological component, counseling and psychotherapy should be provided. In the early stages of treatment, it is necessary to maintain regular contact with the client, once a week is considered to be a minimum, and more frequent contact is preferable.

Goals of substitution therapy for stimulant dependence

- Maintain or improve the psychological and somatic condition of the client
- Reduce or stop patterns of substance use
- Reduction or cessation of consumption of illicit substances
- Reduction or cessation of substance use risk behaviour
- Reduction or cessation of the person's criminal behaviour
- Improve the client's social situation

Target population

Substitution therapy should be indicated as an alternative treatment for clients with addiction to psychostimulants (dg. F15.2, F19.2) when other abstinence-oriented interventions have failed and when the client's continued use of illicit substances or illegal abuse poses a significant risk to his or her health and those around him/or a significant risk to public health. In cases where drug dependence has not been determined, it is likely that the client will manage to stop using such substances himself without major complications.

Published clinical experience indicates that methamphetamine users who use lower doses over a long period of time are more successful in joining a substitution programme than those who use high doses intermittently.

It also appears that treatment with central stimulants mainly benefits clients with ADHD symptoms or who have developed ADHD in childhood or adulthood. It is therefore advisable to include an ADHD diagnostic panel when considering central stimulants (Kalina et al., 2014; Čablová et al., 2015).

Personal and technical requirements for substitution treatment

The professional guarantee of substitution treatment must be fall on the shoulders of a psychiatrist or a doctor certified in the field of addictive diseases, or a doctor who has completed a certified course at the Institute for Postgraduate Training in Health Care (hereinafter IPVZ) on substitution treatment, professionally endorsed by the SNN ČLS JEP.

Since substitution treatment for *off-label* psychostimulant dependence is a non-standard treatment procedure, it is advisable to initiate or warrant it by a doctor who meets the above requirements with a minimum of 6 years of experience in the treatment of addictive diseases, half of which should have been passed on to substitution treatment programmes.

The necessary laboratory tests shall be carried out in appropriate specialised laboratories (biochemical, toxicological, microbiological, etc.) that meet the adequate professional standards. In cases when specialized examinations are needed, relevant specialists should be consulted.

Prescription and notification of *off-label* administration of a medicinal product

In order to provide optimal health care when providing health services to individual clients, the doctor may use a medicine authorised for a particular treatment and use it to treat other conditions, which is called "off-label" use (Section 8(3) and (4) of Act No 378/2007 Coll. on Medicinal Products and on amendments to certain related laws (the Medicines Act), as amended.

In case of prescribing an unregistered medicine, the doctor is obliged to indicate this fact in the prescription and to electronically notify the SUKL within a 7-day period after issuing the prescription by filling in the correct form on the SÚKL website:

http://www.sukl.cz/modules/unregistered/?rewrite=modules/unregistered.

Medical treatment process

In addition to establishing a clinical diagnosis, it is necessary to ensure that none of the general contraindications mentioned in the Summary of Product Characteristics are present. It is also essential to confirm the absence of any toxic psychotic as this constitutes an absolute contraindication to the therapeutic administration of psychostimulants.

People with multiple addictions who use several substances at the same time may be at risk of complications. Initiating substitution treatment with them therefore requires caution and an experienced team. Clients diagnosed with ADHD are otherwise suitable for treatment with psychostimulants.

Initial phase - inclusion of the client in substitution therapy

Before considering substitution therapy, it is advisable to pay attention to:

- Medical history focused on:
  - General health
  - History of addiction
  - Pattern of methamphetamine use including doses used and typical rate of use
  - Pre-treatment of addiction

- Determination of diagnosed addiction
- Exclusion of comorbidities, especially psychotic illnesses and more severe symptoms of depression, manic disorder or severe anxiety.
- It is advisable to carry out a toxicological examination.
- Perform an analysis of possible somatic diseases.
- Carry out a laboratory examination: viral hepatitis, HIV, blood count, liver tests, ionogram.
- ECG, blood pressure, pulse.
- Height, weight, BMI.
- Indicative diagnosis of ADHD: The WURS-25 screening scale is included in the appendix to this guide as one of the tools for diagnosing ADHD.

Treatment Plan:

- The usual daily dose is 20-60 mg of methylphenidate.
- Dose assessment is individualized in collaboration with the client.
- The client receives the first pack with instructions to start with 1 tab. 10 mg in the morning, and add 1 tab. 10 mg at noon depending on the effect. Later the dose is increased to 2-1-0 (daily dose of 30 mg) until reaching a maximum dose of 3-2-1 (daily dose of 60 mg).
- According to the manufacturer the safe dose is up to 60 mg per day. This is a sufficient dose for the treatment of methamphetamine users.
- The initial treatment usually lasts 1 month. During this time it is advisable to be in regular contact with the client, at least once a week, preferably more often.
- It is typical to increase the dose to the maximum, in the next phase some clients reduce the dose gradually.
- It is important to include in the treatment from the beginning complementary interventions, such as psychotherapy, social counselling, psychiatric care.

Maintenance phase of substitution therapy

Although the duration of the maintenance phase of substitution therapy is individual, it is advisable that the maintenance phase has a minimum duration of one year. In some clients it is possible to discontinue substitution therapy after achieving certain psychological, physical and social stability, but in other cases maintenance treatment may become permanent.

The parameters that allow the monitoring of the effectiveness of substitution treatment are abstinence (objective toxicology in urine), client reports on the level and frequency of cravings, the degree of stabilization or social integration and quality of life. The optimal outcome is a client fully integrated into society who does not use addictive substances, including tobacco and alcohol, and who does not suffer from episodes of compulsive cravings. An adequate dose of substitution

medication together with appropriate therapeutic support and follow-up, all contribute to a positive outcome.

Guidelines for Maintenance Therapy

- The dose determined by the doctor is maintained unless there are side effects requiring a reduction or the client requests a reduction. It often occurs that the client requests a gradual reduction of the dose due to the dysphoria that the subject experienced during the period of strong stimulation.

- Maintain and possibly reconfigure complementary interventions based on the client needs and clinical status.

- Check the client's clinical status and toxicology tests to ensure that abstinence continues.

- Sometimes people in the substitution programme fail to abstain completely and relapse into illicit methamphetamine consumption. It has been repeatedly observed that if the client's general condition has improved, relapses and contacts with the drug world usually cease gradually. Because relapse with methamphetamines is not as threatening as with opioids (there is no risk of respiratory deficiency), it does not pose a significant barrier to continuing the treatment.

Examination recommendations for maintenance treatment

- During each visit the tension and pulse should be measured to ensure that they are within the norm. Later it will be enough to measure them quarterly.

- Measure height, weight, and BMI once a month until dose stabilization, then once every 3 months. After a year, it will be enough to measure them every 6 months.

- It is recommended to repeat the ECG after dose stabilization and at least once a year thereafter.

- Laboratory tests: viral hepatitis, HIV, blood count, liver tests, ionogram every 3 months. When the person is stabilized, it will be enough to do it every 6 months and then once a year.

- Toxicological tests should initially be performed frequently. Once the client is stable, it is enough to perform them once a year.

Final phase: completion of substitution therapy

Termination of substitution therapy should be done in consultation with the client and following their consent. Other people involved in providing care to the client, such as the psychotherapist or social worker, may also be consulted before terminating the substitution therapy in order to reach an agreement whereby the client continues to receive their care. It is advisable to give the client as much support as possible. In case of relapse and deterioration of the person, it is also advisable to agree on a possible return of the client to the programme. The danger of relapse after completing a long-term substitution programme is considerable and discontinuation of substitution therapy is not always successful.

Treatment can also be discontinued prematurely, even against the wishes of the client, after serious and repeated violations of the treatment regimen. In this case it is also advisable to agree in advance with the person the end of treatment in order to prevent relapse and negotiate the follow-up of care, or agree on the conditions of a possible return to the programme.

Therapeutic contract for the provision of substitution therapy

In the field of addictive diseases, it is customary to close a therapeutic contract with a client that defines the scope of the treatment and reflects the treatment plan as envisaged by the client together with his/her doctor and other care providers (these are cases of prolonged substitution treatment). On the part of the doctor who provides the pharmacological treatment it is convenient that the contract includes:

- Instructions on the course of substitution treatment and all its risks.
- The client's commitment to comply with the substitution treatment regimen of which he or she has been previously informed
- The risks of interaction of the substitute substance with other substances.
- Information about the risks of performing certain activities such as driving, operating machinery, weapons, etc.
- Commitment by the client to keep other doctors who provide or will provide any treatment informed that he is undergoing substitution therapy.
- The client undertakes to inform the doctor providing the substitute substance of any treatment given to him by another doctor.
- Agreement by the client that, in the event that a substitute substance is provided for use at home, the client shall store it in such a way as to avoid the risk of theft or accidental use by another person.
- Commitment by the client that the substitution substance prescribed or supplied will be used exclusively by him/her.

Continuous client assessment

The monitoring of the client will be carried out continuously throughout the substitution treatment.

This monitoring process includes regular and ad-hoc toxicological tests to check for the presence of the substitute substances and its metabolites, and to verify the possible presence of other addictive substances in the body, including alcohol, as well as to monitor the social situation and quality of life of the person. For this follow-up, it is advisable to use tools such as standard questionnaires, monitoring of the objectives set in the therapeutic contract or joint sessions with the client, the doctor, the psychotherapist, the social worker or the people close to the client. The results should be evaluated and, if necessary, the treatment plan and therapeutic contract adjusted accordingly.

Annex

Wender Utah Rating Scale for Attention Deficit Hyperactivity Disorder (ADHD) analysis – a 25-item scale (WURS-25) for the diagnosis of ADHD in adulthood (Ward et al., 1993).

As a child, I had the following symptoms	Nothing or almost nothing	Seldom	Sometimes	Often	Very often
1. Concentration problems, easy distraction	0	1	2	3	4
2. Anxiety, worry	0	1	2	3	4
3. Nervousness, restlessness	0	1	2	3	4
4. Lack of attention and daydreaming	0	1	2	3	4
5. Anger, irritability – low boiling point	0	1	2	3	4
6. Explosive and choleric temperament	0	1	2	3	4
7. Difficulty persevering in something, not finishing things started	0	1	2	3	4
8. Obstinacy, strong will	0	1	2	3	4
9. Anguish, sadness, depression and unhappiness	0	1	2	3	4
10. Difficulty obeying parents, rebellious	0	1	2	3	4
11. Low opinion of oneself	0	1	2	3	4
12. Irritability	0	1	2	3	4
13. Ascending and descending mood	0	1	2	3	4
14. Feelings of anger	0	1	2	3	4
15. Thoughtlessness, impulsivity	0	1	2	3	4
16. Tendency to immaturity	0	1	2	3	4
17. Feelings of guilt, regret	0	1	2	3	4
18. Loss of self-control	0	1	2	3	4
19. Tendency to behave or be irrational	0	1	2	3	4

As a child, I had the following symptoms	Nothing or almost nothing	Seldom	Sometimes	Often	Very often
20. Unpopularity in a group of children, Difficulty keeping friends, failure with other children	0	1	2	3	4
21. Difficulty seeing things from the perspective of others	0	1	2	3	4
22. Difficulties with authority, with the school, with visits to institutions	0	1	2	3	4
23. A bad student in general, slow reader	0	1	2	3	4
24. Problems with mathematics and numbers	0	1	2	3	4
25. No desire to realize oneself	0	1	2	3	4

Score: The numbers in the table indicate the number of points. The minimum total score is 0. The maximum total number of points is 100. A score of 46 or higher is indicative of ADHD. Values of around 40 points also appear in the literature as indicating ADHD (e.g., Kouros et al., 2018).

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