REVIEW ARTICLE

Evidence-based Treatment Options in Cannabis Dependency

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SUMMARY

Background: Now that the consumption of natural and synthetic cannabinoids is becoming more widespread, the specific treatment of cannabis-related disturbances is an increasingly important matter. There are many therapeutic options, and it is not always clear which ones are evidence-based and appropriate for use in a given clinical situation.

Methods: This review is based on reports of pertinent randomized and controlled trials (RCTs) that were retrieved by a selective search in the PubMed and Cochrane databases.

Results: Cognitive behavior therapy (CBT) combined with other techniques has been found to have a moderate to large effect (Cohen's $d = 0.53$ – 0.9) on the amount of cannabis consumed as well as on the level of psychosocial functioning or the dependence syndrome. Systemic multidimensional family therapy (MDFT) has been found beneficial for younger adolescents who consume large amounts of cannabis and have psychiatric comorbidities. Short-term interventions with motivational talk therapy have been found effective for patients with or without an initial desire to achieve cannabis abstinence. All of these psychotherapeutic interventions are effective at evidence level Ia. The administration of gabapentin had a weak effect ($d = 0.26$) on the quantity consumed and on abstinence (evidence level Ib). Withdrawal symptoms can be alleviated with cannabinoid-receptor antagonists ($d = 0.223$ and 0.481) (evidence level Ib). On the other hand, there is evidence that serotonergic antidepressants can worsen withdrawal manifestations and increase the likelihood of relapse.

Conclusion: Psychotherapeutic techniques remain the foundation of treatment for cannabis dependence. No drug has yet been approved for the treatment of cannabis dependence because of the lack of scientific evidence. The rates of abstinence that are currently achieved, even with psychotherapy, are still only moderate. Further clinical studies are needed for the evaluation of combinations of various treatments that can meet the needs of individual patients.

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Cannabinoids are the group of the world's most commonly used illicit substances (e1). In Germany, no other illicit substance enjoys such a widespread acceptance as cannabis (e2) due to its reputation among users of a not so harmful substance with low dependence potential (e3). The risk of dependence on cannabis (6.2 %) is lower than that of alcohol (11.2%) or nicotine (36.0%) (e4). However, today 36% of all patients which contact the German addiction care system are cannabis users and 56% of the initial contacts made to addiction care facilities are related to problems with the use of cannabis (e5).

While for most of the other substances specific withdrawal syndromes have been defined, the existence of a cannabis withdrawal syndrome has been a controversial issue for years. With the description of a specific cannabis withdrawal syndrome in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (e6), the characteristics of cannabis as an addictive substance were operationalized for the first time (*Table 1*).

Despite the increasing demand for more effective treatment options (e5, e7), there is as yet no general accepted treatment approach (e8). Therefore, the aim of this study was to present the current evidence-based concepts for the treatment of cannabis dependence and their implementation in Germany.

Methods

A selective literature search was conducted in PubMed and the Cochrane Central Register of Clinical Trials. The current guideline for the treatment of cannabis dependence was published in 2004 (e9); thus, the search period extended from 1 January 2004 to 31 December 2015 to update the available evidence base. PubMed was searched using the MeSH terms “marijuana abuse/therapy” in combination with the search terms “dependence” or “use disorder”; altogether, 285 pertinent publications were identified. The search of the Cochrane database using the terms “cannabis dependence” or “cannabis withdrawal” yielded 67 hits. The literature references of the identified studies were also examined to discover further relevant studies. Initially, all articles with focus on the treatment of cannabis dependence or the cannabis withdrawal syndrome were used. All randomized controlled trials (RCTs) related to the treatment of cannabis withdrawal syndrome and cannabis dependence were included.

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TABLE 1

DSM-5 Diagnostic Criteria for Cannabis Withdrawal Syndrome (e6)

A.	Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months)
B.	3 or more of the following signs and symptoms develop within approximately 1 week of Criterion A: – Irritability, anger or aggression – Nervousness or anxiety – Sleep difficulty (insomnia, disturbing dreams) – Decreased appetite or weight loss – Restlessness – Depressed mood – At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
C.	The signs or symptoms from criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
D.	The symptoms are not due to another medical condition and are not better explained by another mental disorder.

DSM-5, Diagnostic and Statistical Manual of Mental Disorders

Results

The most important endpoints were

- severity of the withdrawal symptoms
- amounts of cannabis consumed and abstinence rates
- severity of the dependence syndrome
- psychopathology
- cannabis-associated problems.

The severity of the withdrawal syndrome is likely associated with an increased probability of relapse; therefore, this condition is relevant to the general treatment prognosis (e10). A reduction of drug use may significantly improve the emotional state and psychosocial functioning of the user (e11). When analyzing the results, it should be taken into account that it is difficult to evaluate the impact of the various treatment options on the amount of substance used and the abstinence rates, because a retrospective quantification of the exact amounts of cannabis consumed is almost impossible. In addition, many studies did not obtain qualitative parameters, such as drug screening in urine (DSU). The use of synthetic cannabinoids creates an additional methodological challenge, since these substances cannot be detected with standard testing methods.

Proven methods of psychotherapy

Cognitive behavioral therapy (CBT) ranks among the best evaluated methods in the treatment of cannabis dependence (1–7). Typically, it is used in combination with other methods, such as motivational interviewing (MI) or motivational enhancement therapy (MET) [e12]. In a study with adult users (N = 450), the combination of CBT, MET and case management showed strong effects with regard to abstinence and reduction

of use in the intervention group as compared with the control group (Cohen's $d = 0.98$; $p < 0.001$, and $d = 1.14$; $p < 0.001$, respectively) (1).

In the German CANDIS study, CBT was combined with MET and psychosocial problem solving training (PST) (6). In a sample of 279 patients (7), the intervention group showed significantly more negative urine drug screenings and a significant reduction in the amount of substance consumed ($d = -0.9$; $p < 0.001$) after end of treatment. This effect was still observed after 3 months. In addition, psychosocial functioning significantly improved ($d = -0.7$; $p < 0.001$; Cannabis Problems Questionnaire). One study where subjects participated in 4 sessions of a telephone short intervention with elements from CBT and MET (4) showed a reduction in use compared with the control group after 4 months ($d = 0.6$; $p = 0.0003$). A combination of CBT and contingency management (CM) was also evaluated in several studies, but contradictory results were obtained (2, 3, 5) (Table 2).

Multidimensional family therapy (MDFT) (8) was investigated in the European INCANT study (9–13). In a sample population of 450 users, aged 13–18 years, MDFT was compared with standard psychotherapy (10). While both interventions were effective, MDFT proved superior with regard to treatment adherence ($p < 0.002$) and effects on cannabis dependence symptoms ($d = 1.27$; $p = 0.015$). In a high-user sub-group, additionally a more marked reduction in the amounts of cannabis consumed ($d = 0.6$; $p = 0.002$) was found 12 months after intervention. The efficacy of MDFT had already been proven in earlier comparative studies (e13, e14). MDFT combines one-to-one sessions with adolescents and parents with family group sessions and also includes the non-family social environment (8, 9).

In addition, numerous studies provided evidence of the efficacy of MI-based short interventions in cannabis-using patients. Here, 1–4 sessions over a period of several weeks already resulted in significant, although moderate, effects, even if the patients initially did not ask for treatment (1, 14–22).

In addition, cost effective, low-threshold online interventions are available, such as online CBT as part of the “Reduce your use” program (23). In a sample population of 225 users, this method showed a minor effect on reduction of use, which was still present after 3 months ($d = 0.33$; $p = 0.02$). A further example is the “Quit-the-Shit program” (24), offering a weekly chat with a therapist. A sample of 206 users showed effects on the reduction of use in comparison to the control group ($d = 0.75$ – 0.98) and on self-efficacy ($d = 0.6$) (each $p < 0.001$). In the “Can-reduce” program, online CBT in combination with a chat achieved significant higher abstinence rates (Odds Ratio [OR] 0.21; $p = 0.05$) and a more marked reduction in use ($d = 0.34$; $p = 0.02$) compared with online CBT alone (25).

Especially challenging is the treatment of cannabis dependence in the presence of comorbid psychiatric disorders. There is a high rate of cannabis users among patients with psychosis or near-psychosis symptoms in

TABLE 2

Psychotherapeutic and psychosocial approaches to the treatment of cannabis dependence

Intervention (I); control (C); study	FU	n; age (yrs/mean)	Abstinence	Reduction of use	PFN/dependence
Cognitive behavioral therapy					
I1: CBT+MET+CaseM; C: DTC; (1)	12	450; 18–62	I1: $d^{*1} = 0.98$; $p < 0.001$	I1: $d = 1.14$; $p < 0.001$	$d = 0.53$; $p < 0.001$ (MPS)
I: CBT+MET+PPS; C: DTC; (6)	6	122; 16–44	$d^{*2} = 1.2$; $p < 0.01$	$d^{*2} = 0.89$; $p < 0.001$	I: $d^{*2} = 0.23$; $p < 0.001$ (ASI f.)
I: CBT+MET+PPS; C: DTC; (7)	3	272; 16–63	I: 46.3 %; C: 17.7 % $d = n. a.$; $p < 0.001$	$d = -0.9$; $p < 0.001$	$d = -0.7$ (CPQ)/ -0.6 (SDS) -0.9 (ICD-10); $p < 0.001$
I: CBT+MET(by phone) C: DTC; (4)	3	160; > 16 (36)	$d = 0.6$; $p = 0.001$ (PDA)	$d = 0.6$; $p < 0.001$	$d = 0.8$; $p = 0.001$ (CPQ)
I1: CBT+MET; I2: CM I3: CBT+MET+CM; C: CaseM; (2)	12	240; > 18 (32.7)	I1: n. s.; I2: $d = 1.16$; $p < 0.05$; I3: n. s.	n. s.	n. s.
I: CBT+MET+CMabs+FamilyM C: CBT+MET+CMpart+PP; (3)	12	69; 14–18	$d = 0.51$; $p = 0.04$	n. s.	n. s.
I1: CBT+MET+CMhome; I2: CBT+MET+CMabs.; C: CaseM; (5)	12	215; >18 (32.7)	n. s.	n. s.	n. s.
Family-based therapy					
I: MDTF; C: TAU; (10)	12	450; 13–18	n. a.	n. s.; Subgr. ^{*4} : $d = 0.6$; $p = 0.002$	n. a.
I: MDTF; C: TAU; (9)	12	120; 13–18	n. a.	$d = 0.31$; $p < 0.001$	n. a.
I: MDTF; C: CBT; (11)	12	109; 13–18	n. a.	n. s.	n. s.
I: MDTF; C: CBT; (e13)	12	224; 12–17	n. a.	n. s.	$d = 0.59$; $p < 0.05$ (PEI)
Motivational interviewing					
I2: MET; C: DTC; (1)	12	450; 18–62	I2: $d^{*1} = 0.34$; $p < 0.001$	I2: $d = 0.59$; $p < 0.001$	$d = 0.41$; $p < 0.001$ (MPS)
I: MI; C: DTC; (14)	6	40; 14–19	n. a.	$d = 0.71$; $p = 0.03$	$d = 0.70$; $p = 0.04$ (DSM-IV)
I1: MI; I2: Info; C: DFC; (15)	12	188; 18–57	n. a.	$d = 0.47$ (I1 vs I2: $d = 0.42$); $p < 0.05$	$d = 0.58$; $p = 0.04$ (DSM-IV)
I: MI; C: Info; (e33)	12	326; 16–19	n. s.	n. s.	n. s.
I: MI(Tel.) C: Info; (16)	6	524/1 744 ^{*5} ; >18 (25)	OR = 1.6; $d^{*3} = 0.25$; $p < 0.05$; NNT = 7	n. a.	n. a.
I1: MET; I2: Info; C: DFC; (17)	12	310; 14–19	n. s.	$\text{Eta}^2 = 0.04$; $d^{*3} = 0.4$; $p < 0.01$	I1: $d^{*3} = 0.53$; I2: $d^{*3} = 0.63$; $p < 0.05$
I: MI; C: AO; (18)	6	332; 18–24	n. a.	OR = 0.53; $d^{*3} = -0.35$; $p = 0.01$	n. a.
I: MI + MM; C: DTC; (20)	3	34; 18–29	n. s.	$z = -2.23$; $d^{*3} = -0.82$; $p = 0.026$	n. a.
I: MI; C: Info; (19)	12	134; 18–28	n. s.	n. s.	n. a.
I: MI; C: AO; (21)	6	212; 18–25	n. a.	RR = 0.9; $p < 0.05$	n. s.
I: MI; C: Info; (22)	3	119; 14–21	n. a.	n. s.	n. s.
I1: MI+RP (kurz); I2: MI+RP (lang); C: DTC; (e34)	4	62; 18–58	n. s.	I1: -29.29 %; I2: -31.95 %; C: -7.5 %; $d = n. a.$; $p = 0.0003$	n. s.
Online interventions					
I: MI C: AO; (e35)	6	341; 17–19	n. a.	n. s.	n. s.
I: Chat; C: DTC; (24)	3	206/1 292 ^{*6} ; (24.7)	n. a.	$d = 0.98$ (per-protocol) and $d = 0.2$ (ITT); $p < 0.001$	$d = 0.6$ (per-protocol) and $d = 0.15$ (ITT); $p < 0.001$ (SE)
I: CBT+MET; C: Info; (23)	3	225; (31)	n.s.	$d = 0.33$; $p = 0.02$	$d = 0.33$; $p = 0.01$ (SDS)
I1: CBT+MET+Chat I2: CBT+MET C:DTC; (25)	3	436; (29.8)	I1 vs C: n. s.; I1 vs. I2: OR = 0.21; $p = 0.05$	I1: $d = 0.2$; $p = 0.03$; I2: n.s.	n. s.

*1 from (e9); *2 provided by Davis et al. (e36); *3 self-calculated; *4 subgroup with high use; *5 Altogether 1744 patients were randomized; only those with follow-up data available (n=524) were included; *6 Altogether 1292 patients were randomized; the results refer either to all randomized patients (ITT) or only to those 206 patients with follow-up data available (per-protocol); AO, assessment only (no intervention); ASI f., Addiction Severity Index, subcategory family; C, control; CaseM, case management; CBT, cognitive behavioral therapy; CM, contingency management; CMabs, contingency management rewarding abstinence; CMhome, contingency management rewarding homework; CMpart, contingency management rewarding participation; CPQ, Cannabis Problems Questionnaire; d, Cohen's d (0.2–0.4 small effect size, 0.4–0.8 medium effect size, > 0.8 large effect size); due to methodological differences, the comparability of the effect sizes in the various studies is limited; DFC, delayed feedback control; DSM-IV, Diagnostic criteria for dependence in the Diagnostic and Statistical Manual of Mental Disorders 4th edition; DTC, delayed treatment control; Family M, family management; FU, follow-up period; I, intervention; Info, provision of information; ITT, intention-to-treat analysis; yrs/mean, age as age span (yrs., years) and mean (mean; in brackets); MDTF, Multidimensional Family Therapy; MET, Motivational Enhancement Therapy; MI, Motivational Interviewing; MM, mindfulness meditation; MPS, Marijuana Problem Scale; NNT, number needed to treat; n, sample size; n. a., not stated; n. s., non-significant; OR, odds ratio; p, significance level; PDA, proportion of days abstinent; PFN, psychosocial functioning; PEI, Personal Experience Inventory; PPS, psychosocial problem solving; PP, parent psychoeducation; RP, relapse prevention; RR, rate ratio; SDS, Severity Of Dependence Scale; SE, self-efficacy; TAU, treatment-as-usual; vs., versus; z, z-value

TABLE 3

Medications for the treatment of cannabis dependence

Cannabinoid 1 (CB1) receptor agonists				
Substance (study)	Patient characteristics	Treatment setting/ duration of interventions	Withdrawal symptoms	Amount consumed/ abstinence
Nabiximols (26)	N = 51, age: 18–65 cannabis dependence	Inpatient, 9 days Nabiximols vs. placebo Follow-up: 28 weeks	d = 0.481; p < 0.01	Non-significant
Dronabinol (27)	N = 156, age: 18–60 cannabis dependence	Dronabinol vs. placebo Duration: 84 days	d = 0.223; p = 0.02	Non-significant
GABAergic substances und anxiolytics				
Valproic acid (28)	N = 25, age: 18 and older cannabis dependence	Outpatient, cross-over-design: Valproic acid vs. placebo Duration: 6 weeks	Non-significant	Non-significant
Gabapentin (29)	N = 50; age: 18–55 cannabis dependence	Outpatient, Gabapentin (1200 mg/day) vs. placebo	Greater improvements in MWC; d = n. a.; p < 0.001	d* = 0.26; p = 0.026
Buspirone (30)	N = 50; age: 18–65 cannabis dependence	Outpatient, Buspirone (N = 23) (up to 60 mg) vs. placebo (N = 27) Duration: 12 weeks	No information	Non-significant
Buspirone (31)	N = 175; age: 18–65 cannabis dependence	Outpatient, Buspirone (N = 45) vs. placebo (N = 47), duration 12 weeks	Non-significant	Time to first positive DSU slightly longer in women with buspirone (p = 0.007)

* Information provided by authors; N, number of subjects; age range in years; duration of study in days/weeks. effect size reported as Cohen's d; significance level (p-value). Nabiximols: Cannabis extract, contains tetrahydrocannabinol (THC) and cannabidiol (CBD); dronabinol: semi-synthetic tetrahydrocannabinol (THC) analogue; MWC, Marijuana Withdrawal Checklist; DSU, Drug Screening in Urine

specialized early psychosis detection centers (e15). The concomitant medical and psychotherapeutic treatment of addiction and comorbid disorders requires an individualized and disorder-specific differentiated treatment concept incorporating a cross-sector approach (e16, e17).

Pharmacotherapy of cannabis dependence

Whether the concept of replacement therapy can also be applied to cannabis use was studied for cannabinoid receptor-1 (CB1) agonists. Agonists are used because their action on the receptor is similar to that of the addictive substance, allowing them to reduce withdrawal symptoms while ideally not triggering a “high” or craving. In an inpatient treatment setting, a significant effect of nabiximols (N = 52; d = 0.442; p = 0.01) and dronabinol (N = 152; d = 0.282; p = 0.02) on withdrawal symptoms was demonstrated; however, at the follow-ups after 28 weeks and 84 days, respectively, both substances had no impact on abstinence or the amount of substance consumed (26, 27) (Table 3).

Another—presently experimental—approach, known from the treatment of opioid dependence, is the administration of receptor antagonists, such as rimonabant (e18); however, clinical studies investigating this approach are not yet available.

Furthermore, GABAergic medication (e.g. valproic acid and gabapentin) were evaluated for this indication.

A group of 25 adult patients in an outpatient treatment setting showed no significant differences between valproic acid treatment and placebo, neither with regard to withdrawal syndrome nor abstinence (28). Following reports on the efficacy of gabapentin in treating certain alcohol withdrawal symptoms (e19), a favorable effect of gabapentin has now also been demonstrated in patients with cannabis dependence (29). A study with 50 patients treated with gabapentin in an outpatient setting showed a reduction in withdrawal symptoms (p < 0.001). Furthermore, in patients receiving gabapentin or placebo over a period of 12 weeks a favorable effect of gabapentin on the amount of substance consumed (verified by urine testing; d = 0.26; p = 0.026) and on cannabis-related mental (p = 0.028) and physical (p = 0.046) symptoms was found. Cognitive functions improved as well (p = 0.029).

As anxiety is also a symptom of cannabis withdrawal, the non-GABAergic anxiolytic agent buspirone was studied for this indication, but no significant results were found (p = 0.55 [30] or p = 0.86 [31]) (Table 3).

Similarly, antidepressants were tested as medications to treat cannabis dependence. In these studies, nefazodone (32) and fluoxetine (33) were not superior to placebo. In fact, an increase in depressive symptoms was observed among patients with cannabis withdrawal syndrome receiving bupropion (e20). A 12-week study

with 103 adult users reported an increase in withdrawal symptoms under venlafaxine treatment (risk difference [RD] 0.20; $p = 0.014$) (34) and a higher abstinence rate in the placebo group ($p < 0.01$) (35). A trend towards lower abstinence rates in the intervention group was found in a study evaluating the serotonergic antidepressant escitalopram ($p = 0.077$) (36). Lithium showed in a sample population of 38 adult cannabis users in an outpatient setting no effects on withdrawal syndrome and the amount of substance consumed (37, 38) (eTable).

The effect of N-acetylcysteine, a nutritional supplement and mucolytic agent, is probably due to an increased expression of cysteine glutamate exchangers in the nucleus accumbens. Their levels are typically reduced by drug use (e21). A study (39) involving 116 adolescents in the 13–21 years age group found increased cannabis abstinence rates under treatment with N-acetylcysteine, measured as negative drug screening in urine (OR 2.4; $p = 0.029$); however, at 4-weeks follow-up, these changes were no longer significant ($p = 0.131$) (39).

Discussion

Treatment recommendations have to take the significant heterogeneity of patients with cannabis dependence into account; therefore, differentiated and appropriately graded advice and treatment concepts are needed (40). Subject to individual requirements and needs, patients can undergo treatment in a youth care, addiction care, outpatient psychotherapy, or inpatient psychiatric setting.

The combination of CBT, MET and PPS (CANDIS manual [e22]) is currently regarded as the best-evaluated approach for adults with cannabis dependence (evidence level: Ia) (6, 7). However, this combination treatment requires an initial motivation for change and wish for abstinence; therefore, younger adolescents, not yet able to make resolutions of this kind, may not be fully reached with this type of treatment. In addition, on formal grounds this approach is not always directly compatible with addiction rehabilitation. Therefore, combinations of CBT and other methods are usually offered by statutory health insurance-funded outpatient psychotherapists.

The efficacy of MDFT is well backed by evidence (evidence level Ia). Yet, there are data indicating that older adolescents and young adults benefit more from CBT/MET (6, 7), while younger adolescents with heavy use or comorbid psychiatric disorders appear to show a better response to MDFT (10–12). Here, it has to be taken into account that an initial wish for abstinence is no requirement for participation in MDFT. This method is more complex and requires more effort than CBT/MET, resulting in increased costs and difficulties with implementation (40). Nevertheless, more wide-spread use is conceivable, provided that adequate finance models are developed and youth care and addiction care are better integrated into child and adolescent mental healthcare.

Additionally, treatment approaches that are based on motivational interviewing (MI) can be recommended (evidence level Ia). These are effective in combination with CBT and as part of MDFT. On the other hand, MI, as a short intervention, is also effective in the treatment of cannabis dependence, even if not combined with other methods. This method is comparatively easy to learn, economical and effective. MI also plays a special role in early-intervention and consultation programs (40). In addition, some other early-intervention and counselling programs are worth mentioning, in particular FreD (e23), CAN Stop (e24) and Realize-it (e25) which have been initiated in Germany in recent years. These programs were established in numerous German addiction counselling facilities. They are also easy to learn, cost-effective and highly accepted (40). Online programs were evaluated in several studies and to some extent implemented in standard care, due to their low threshold and their cost effectiveness.

No recommendation can presently be made for pharmacological treatment, even though there is evidence in support of the efficacy of gabapentin (29) and CB1 agonists (26, 27) (each evidence level Ib). Here, further studies are needed to evaluate the benefits of the clinical use of these medications. Antidepressants cannot be recommended for the treatment of cannabis dependence. In fact, there is evidence that especially venlafaxine, but also bupropion and possibly escitalopram, have adverse effects on the withdrawal syndrome and may increase relapse probability.

It is striking that, despite treatment, abstinence rates generally are rather moderate and relapse rates rather high (e26, e27). Consequently, there is a high need for the development of evidence-based standards for the treatment of cannabis dependence (e28). A further issue is that no other substance is so controversially discussed with regard to its health risks as cannabis (e29–e32). Besides the establishment of treatment standards, primary and secondary prevention play an important role.

KEY MESSAGES

- Clinically and scientifically, the existence of a cannabis withdrawal syndrome is widely accepted today.
- Multi-dimensional Family Therapy (MDFT) is effective in younger adolescent patients with heavy use, while in adults cognitive behavioral therapy in combination with other methods is supported by the highest level of evidence.
- Elements of motivational interviewing are effective alone or in combination with other methods, even in patients initially having no wish for abstinence.
- Pharmacological evidence suggests that cannabinoid receptor 1 agonists and gabapentin are effective, while some antidepressants have an adverse impact on withdrawal symptoms and may increase the probability of relapse.
- Presently, no medication has been approved for the treatment of cannabis dependence.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Supplementary material for:

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eTABLE

Antidepressants and lithium for the treatment of cannabis dependence

Substance (study)	Patient characteristics	Treatment setting/duration of intervention	Withdrawal symptoms	Amount consumed/abstinence
Bupropion SR and nefazodone (32)	N = 106, age: 19–63 cannabis users with treatment wish	Nefazodone (600 mg)/ Bupropion-SR (300 mg) vs. placebo Duration: 13 weeks	Non-significant	Non-significant
Fluoxetine (33)	N = 70; age: 14–25 + depression	Outpatient, Fluoxetin(20 mg /day) vs. placebo; duration: 12 weeks	Not reported	Non-significant
Venlafaxine XR (34, 35)	N = 103; age: 18–60 + depression/dysthymia	Outpatient, Venlafaxin (up to 375 mg) Duration: 12 weeks	Withdrawal symptoms increased under venlafaxine Week 8: RD = 0.20, p = 0.014	Placebo achieves higher abstinence rates than venlafaxine d = 0.559; p<0.01
Escitalopram (36)	N = 52; age: 20–45	Escitalopram (10 mg) vs. placebo 9 weeks, Follow-up after 14 weeks	Non-significant	Trend towards less abstinence in escitalopram group (p = 0.077)
Lithium (37)	N = 38; age 40 (mean)	Inpatient, lithium (500 mg) 2 x daily vs. placebo, Duration 8 days, FU 90 days	Non-significant	Non-significant
Lithium (38)	N = 38	Inpatient: lithium or placebo	No significant effect on sleep or other withdrawal symptoms	Not reported

Abs., abstinence; age in years; duration in days or weeks (wks.); DSU, Drug Screening in urine; effect size reported as Cohen's d; effect size also reported as risk difference (RD); FU, Follow-up in days; N, number of subjects; p-value, significance level