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# Treatments for stimulant use disorder – a rapid review for policy makers and practitioners

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# Contents

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## Abbreviations

| | |
|---|---|
| ACT | Acceptance and Commitment Therapy |
| ATS | Amphetamine Type-Stimulant |
| ATSUD | Amphetamine Type-Stimulant Use Disorders |
| CBT | Cognitive Behavioural Therapy |
| EOF | End-Of-Follow-up |
| EOT | End-Of-Treatment |
| RCT | Randomised Controlled Trial |
| SSRI | Selective Serotonin Reuptake Inhibitors |
| TAU | Treatment as Usual |

# Executive summary

## Stimulant use disorder and deaths – a global and national problem

The global prevalence of amphetamine (including methamphetamine) and cocaine use is estimated to be 0.7% and 0.4%. An estimated 11% and 16% of users are dependent (1). There are concerns that stimulant use disorder is increasing globally because of changes in the global markets of other drugs, including heroin.

Scotland's rate of drug-related deaths continues to be one of the highest in the world. An increasing number of deaths have been associated with the stimulant cocaine. Surveillance data also shows an increase in cocaine use among people who inject drugs.

Stimulant use, in particular cocaine, is an increasing concern in Scotland and there is a need for better understanding of the treatment options. This report gives an overview of evidence from systematic reviews of the safety and efficacy of psychosocial and pharmacological treatments for stimulant use disorder. We also note active areas of research with emerging evidence not included in systematic reviews.

## What is the evidence for treating stimulant use disorder?

Despite a large body of research evidence, there is a lack of consistent evidence of safety and effectiveness for most of the treatments that have been investigated. Contingency management (CM; which incentivises participation in the treatment) was the only treatment with consistent evidence of benefit. However, aside from improving treatment retention rates, this benefit was comparable to treatment as usual (TAU; supportive drug and alcohol counselling and group work). There is also evidence to support more complex interventions such as the matrix model which include CM along with other psychosocial interventions.

Acupuncture, dopamine agonists, antipsychotics, and most anticonvulsants and antidepressants do not provide effective treatment. Weak but promising results of effectiveness have been found for psychostimulants (dexamphetamine and methylphenidate) and other pharmacotherapies including mirtazapine, naltrexone, bupropion, and topiramate. Further studies involving these pharmacotherapies are needed but currently there is insufficient evidence to recommend any pharmacotherapies. Opioid agonist therapy (methadone and buprenorphine) may decrease stimulant use amongst people who have both opioid and stimulant use disorders.

More research is needed amongst sub-populations. A better understanding is needed of how treatments work for different types of stimulants (e.g. crack versus powder cocaine), people with polysubstance use or mental health co-morbidities, and women.

## Conclusion

In the absence of consistent evidence of safe and effective pharmacotherapies for stimulant use disorder, psychosocial interventions are the mainstay of treatment. CM is most supported by the evidence but only provides marginal benefits compared to currently provided TAU and is not widely available. People experience many barriers to accessing currently available treatments so these barriers should be addressed to improve treatment for people with stimulant use disorder.

# Background

## Prevalence and outcomes of stimulant use disorder

The main substances that are stimulants on which people become dependent are **cocaine, amphetamines,** and **methamphetamine**. The global prevalence of amphetamine-type stimulant (including amphetamine and methamphetamine) use is estimated to be 0.7%, and 11% of people actively using at any given point in time are estimated to be dependent. In contrast, an estimated 0.4% use cocaine with 16% being dependent (1). There are concerns that stimulant use disorder is increasing globally because of changes in the global markets of other drugs, including heroin (2).

Stimulant use disorder is associated with a range of short- and long-term adverse effects, including depressive symptoms, anxiety, psychosis, cardiovascular diseases, and HIV and hepatitis C infection (1). Compared to those who do not use stimulants, people with regular or problematic stimulant use are seven times more likely to die (1). Stimulant use concerns disproportionately impact intersectional priority populations including Indigenous People, adolescents, and LGBTQ+ populations (3-5).

Ultimately, treatments for substance use disorder aim to improve quality of life but can achieve this through different pathways. This includes managing symptoms related to withdrawal phenomena, helping people cut down or stop their substance use, preventing further harm from ongoing substance use and treating mental health co-morbidities. Most studies of treatments to date have focussed on substance use outcomes and treatment retention, rather than more globally on quality of life.

## The Scottish context

Scotland's rate of drug-related deaths is higher than any of the other UK nations and the United States (US) (6). Historically, many of these deaths have been associated with opioids and multiple other sedatives. An increasing number of deaths in Scotland have been associated with stimulants, in particular cocaine (7). In 2023, 439 (41%) of 1172 deaths involved cocaine compared to only 7% in 2010 and deaths involving amphetamines increased to 3% in 2023 from 0.6% in 2010 (7). This is also reflected in data relating to people who inject drugs. Recent (last six months) cocaine use increased to 60% in 2022-23 from 9% in 2010. Amphetamine use has however remained at a similar level (2% and 3%, respectively) in this population (8). Hence, cocaine use is becoming an increasing concern in Scotland and there is a need for better understanding of treatment options.

## Barriers to care and treatment

There are multiple barriers for people with substance use disorders to seek and access treatment (9) that are also relevant to people with stimulant use disorders. Systematic review evidence for barriers relating to methamphetamine treatment has highlighted that common barriers include the individual's belief that treatment is not needed, wanting to withdraw from methamphetamine without help, and feelings of embarrassment or stigma (10).

Qualitative research in Australia with women who were using methamphetamine regularly highlighted complex social issues such as trauma and intimate partner violence, along with stigma and fear of judgment, as key barriers to seeking and accessing treatment (11). It is therefore important to not only consider effective treatment but also barriers to accessing these treatments.

## The focus of this report

There is an urgent need to find effective approaches to treat stimulant use disorder and understand how treatments can be integrated into clinical care. We have undertaken a rapid review of research evidence on treatments for stimulant use disorder, which is summarised in this brief report. This report focuses on evidence from systematic reviews of RCTs, but as this is a rapidly evolving area we also highlight where emerging evidence supports or refutes previous systematic reviews. The definitions and concepts for this review are outlined in Figure 1.

**Figure 1. Overview of definitions and concepts**

# Summary of systematic review evidence

## Measuring outcomes of treatment for stimulant use disorder

Clinical trials to date have used different outcomes to measure treatment effectiveness. This includes self-reported drug use, use according to urine drug testing, measures of quality of life, treatment retention, and psychiatric comorbidities. This makes comparisons between trials challenging. An additional challenge is measuring longer term outcomes and the durability of treatment effects, as most trials have limited follow up time. The US Food and Drug Administration (FDA) recently published updated guidance on conducting trials of treatments for stimulant use disorder, including preferred outcome measures (12). There is a need to harmonise end-point measurement across clinical trials and this should be agreed on in collaboration with people with lived experience.

## Summary of evidence for different treatments

Most studies have investigated treatments for methamphetamine and/or amphetamines (collectively known as amphetamine type stimulants or amphetamine-type stimulants; ATS) and cocaine separately. Studies of both psychosocial treatments and pharmacotherapies for all stimulant use disorders have tended to find treatment effects vary according to pre-treatment stimulant use frequency and psychiatric comorbidity. Treatments tend to be less effective for severe substance use disorder (higher frequency, longer duration of use, intravenous use) and in those with psychiatric comorbidity (13,14). Evidence emerging from systematic reviews and meta-analyses is as follows:

- **Pharmacotherapies** – while many have been investigated, no pharmacotherapies have shown consistent effectiveness for stimulant use disorder (15). Some pharmaco-therapies (see below) have demonstrated weak signals of effectiveness and require further investigation (16, 17).
- **CM** – systematic reviews demonstrate evidence of benefit (18-20). While CM is cost effective in improving treatment retention, abstinence, and frequency of stimulant use, and has been endorsed by the National Institute for Health and Care Excellence (NICE) (21), clinical uptake has been limited (22). A recent Cochrane review identified that when compared to TAU (counselling and/or group support), CM was only more effective at reducing treatment drop out during the intervention (20).
- **Other psychosocial therapies** – specific psychosocial therapies such as CBT and motivational interviewing have demonstrated weak effects, high relapse rates, and are no more effective than care as usual (including counselling and group support) (20). The matrix model which combines modalities of psychosocial treatments has shown to be effective (23).

## Pharmacotherapies

A systematic review and metanalysis of randomised controlled trials (RCTs) of psycho-stimulant treatment (methylphenidate and dexamphetamine) for amphetamine-type stimulant use disorders (ATSUD) suggested psychostimulants reduced drug cravings but not use. However, there was a signal that higher doses of psychostimulants reduced ATS use, and longer treatment durations improved treatment retention that requires further investigation (16). Another review of all pharmacotherapies for ATSUD demonstrated mixed or weak positive signals (often in defined populations, e.g. men who have sex with men). Positive results have been noted for some but not all substance related outcomes and for subgroups (such as those with less severe use disorders) from treatments including mirtazapine, naltrexone, bupropion, and topiramate that require further investigation (15, 24, 25).

Similarly for cocaine use disorder, moderate effect sizes have been found for increased abstinence with bupropion, topiramate, and psychostimulants (17, 26). However, missing data relating to missing study visits or participant drop out were common amongst these studies. Once these missing data were statistically accounted for, the measured beneficial effects of these treatments disappeared (28). Opioid agonist therapy (methadone and buprenorphine) appeared to be effective in decreasing cocaine use amongst people with opioid use disorder but again this effect disappeared once missing data were statistically accounted for (27).

There is insufficient evidence to support the use of any pharmacotherapy in the treatment of stimulant use disorder and further research is required.

## Psychosocial therapies

### Contingency Management (CM)

Within systematic reviews, CM was found to significantly increase treatment participation and abstinence from any stimulant use disorder (18-20,27). However, there is a lack of evidence around whether people remain abstinent once rewards come to an end. Regardless, this is recommended by NICE which provides guidance on how to implement this type of treatment (21).

**Figure 2. Definition of CM**

**What is CM?**

CM involves participants being rewarded for a specific and measurable desired behaviour, most often a negative urine drug test. The reward needs to be of value to the participant and examples include gift cards, vouchers or entry into prize draws. CM has often been used alongside other psychosocial (especially CBT and the matrix model) or pharmacological treatments.

Evidence of CM comes from the US and should be evaluated in the context of US health systems. Costs of CM need to be considered because some studies have reported per participant per day costs of around $120 (~£92), while others report costs as low as $1.46 (~£1.13). When compared to TAU; including individual or group counselling, case management, clinical management, or educational/informative interventions), the only advantage of CM is to reduce treatment drop out while rewards continue (20). An overview of treatment effect by outcome measure is provided in Table 1.

**Table 1. Overview of outcomes for CM and CBT compared to those receiving no treatment and TAU (20)**

| Outcome measure | No treatment | TAU |
|---|---|---|
| **Drop out**<br>*Those who did not complete the study protocol* | CM | CM |
| **Point abstinence EOT**<br>*Abstinence measured when the treatment ended* | | |
| **Point abstinence EOF**<br>*Abstinence measured when the follow-up period ended* | | |
| **Continuous abstinence EOT**<br>*Abstinence for at least half of the treatment period* | CM | |
| **Continuous abstinence EOF**<br>*For at least half of the follow-up period* | | |
| **Reduced frequency of use at EOT**<br>*Number of days use in a period prior to the end of treatment* | CM | |
| **Longest period of abstinence**<br>*Number of continuous abstinence during treatment or follow-up* | CM, CBT | |

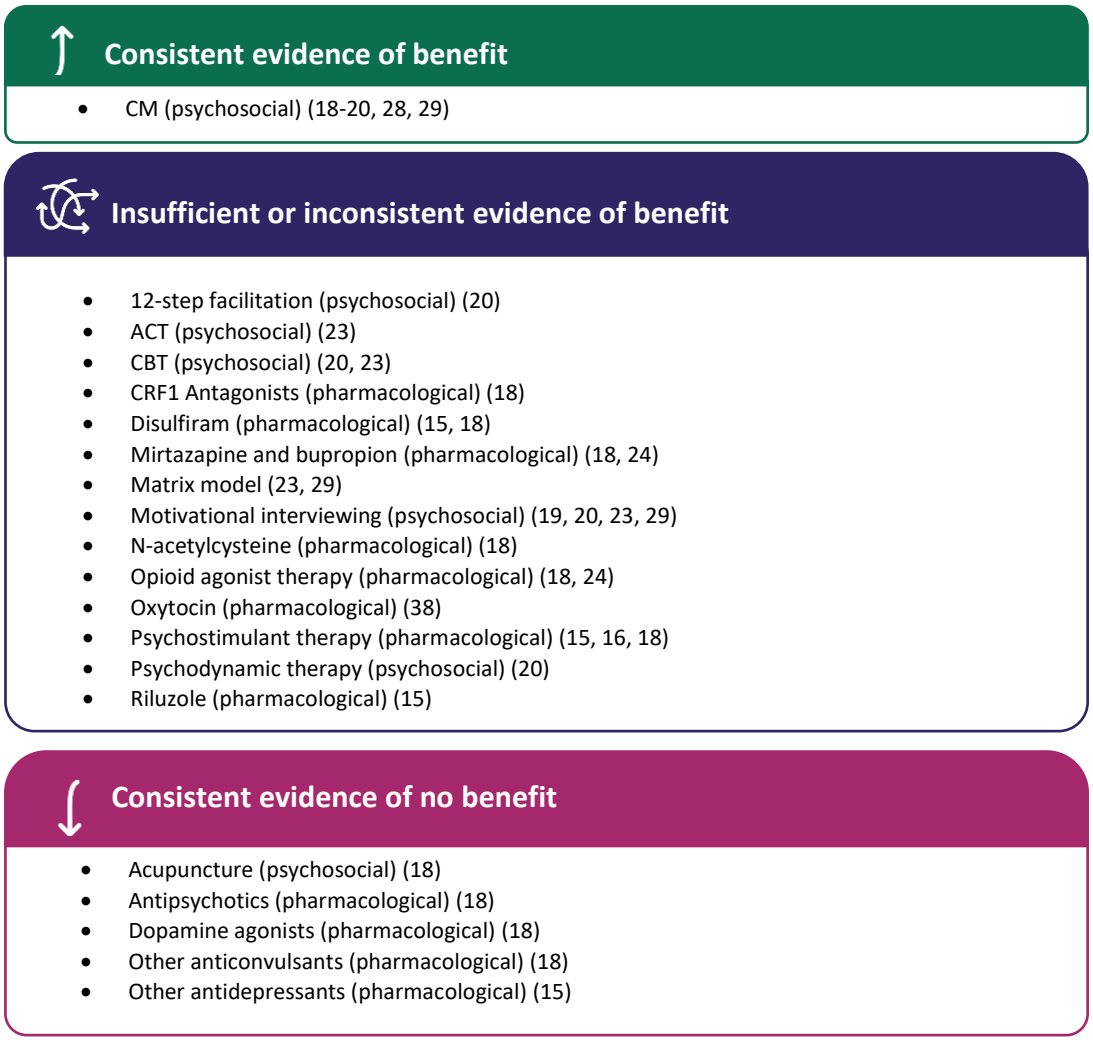
### *Other Psychosocial Therapies*

The matrix model has been proposed as a 16-week outpatient programme combining CM, CBT, family education groups, social support groups, and individual counselling. This approach increased the number and duration of abstinence periods. There is some evidence of effectiveness for this treatment model (23), but it is more costly compared to TAU with unclear cost-benefit and limited clinical uptake. Specific psychosocial therapies such as CBT, motivational interviewing, interpersonal therapy approach, psychodynamic therapy, supportive expressive therapy, and 12-step facilitation have demonstrated weak effects, high relapse rates, and according to a recent Cochrane review, no higher effectiveness than TAU (20).

## Summary of the direction of evidence based on systematic review evidence

Within systematic reviews on the efficacy and treatment of stimulant use disorder (see Table 1 in Appendix for summary), the authors noted that many studies were small and of low quality. There was also varying methodology across studies, including outcome measurement, which makes it difficult to compare across studies. This is important to consider for the evidence presented in this report. A summary of the direction of evidence is shown in Figure 3.

**Figure 3. Overview of evidence for benefit of stimulant use disorder treatment from systematic reviews primarily of RCTs**




*ACT - Acceptance and commitment therapy*

# Emerging treatments

There are also treatments where there is currently no systematic review evidence or has been included in systematic reviews but based on study designs other than RCTs. Some ongoing trials have shown positive effects that are worth mentioning, however this is not an exhaustive list.

There are a small number of completed and registered ongoing studies using psychedelic- (such as psilocybin) and ketamine-assisted psychotherapy (31-35). In addition, other non-pharmacological interventions that have been investigated include exercise therapy and repetitive transcranial magnetic stimulation (rTMS) (29). While there have been promising results from completed studies, this is an area of treatment where the evidence is still developing and is not included in systematic reviews.

### Residential rehabilitation

Other clinically available treatments, including long-stay residential rehabilitation, carry substantial constraints related to access, cost, and scalability (28). There is little evidence on residential rehabilitation and detoxification as treatment for stimulant use disorder. A systematic review only included four studies (non-RCTs) of the effect of residential rehabilitation that were tailored to people with stimulant use disorder (particularly methamphetamine). Included studies found that residential rehabilitation programmes effectively reduced methamphetamine use and cravings (29). While the evidence is promising, further evidence is required in this area.

## Limitations that need addressing in future research

Looking over the evidence included in this report, there are several limitations that need addressing in future research:

- People who are stimulant dependent represent a heterogenous group of individuals who use different types of stimulants, have varying patterns of use and use disorder severity, use other drug concomitantly, and belong to population sub-groups that may respond differently to treatments. Much of the evidence has been generated using population samples that may not be generalisable to all stimulant users. For example, studies have excluded people with co-morbidities, such as stimulant induced psychosis, or people using more than one substance.
- Different types of stimulants have been most often studied separately and it cannot be assumed that treatments are equally effective across all stimulants.
- Studies have used a range of outcome measures to demonstrate effectiveness, limiting comparisons across trials. The US Food and Drug Administration (FDA) has recently published updated guidance on how to conduct trials of treatments for stimulant use disorder, including preferred outcome measures (12).
- Retaining participants in trials has proven difficult, as is retention in treatment (30).
- Women are underrepresented in the evidence and treatment. This may reflect concerns that revealing their substance use might result in their children being taken into care, or financial barriers to accessing treatment (11).
- There are multiple barriers to accessing treatment as usual for stimulant use disorder. Future research should include approaches to address these barriers.

## Conclusion

In the absence of consistent evidence of safe and effective pharmacotherapies for stimulant use disorder, psychosocial interventions are the mainstay of treatment. CM is the treatment most supported by the evidence but is of comparable effectiveness to currently provided TAU. People experience many barriers to accessing treatment so these barriers must be addressed to improve treatment access for people with stimulant use disorder.

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# Appendix – Summary of systematic reviews

## Table A1. Summary of systematic reviews for treatment of stimulant use disorder

| Reference | | Siefried et al. (15) | Sharafi et al. (16) | Castells et al. (17) | Ronsley et al. (18) | Tran et al. (19) | Minozzi et al. (20) | Stuart et al. (23) | Bakoumi et al. (24) | Chan et al. (26) | Bentzley et al. (27) | AshaRani et a. (29) | Lee-Cheong et al. (38) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of review** | Review of systematic reviews | | | | ✓ | ✓ | | | | ✓ | | | |
| | Systematic review | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Review characteristics** | Evidence up to | Jun 2019 | Aug 2022 | Feb 2016 | Nov 2019 | Nov 2020 | Sep 2023 | Nov 2018 | Oct 2022 | Nov 2017 | Dec 2017 | Feb 2020 | Jul 2020 |
| | Number of studies/reviews | 43 RCTs | 10 RCTs | 26 RCTs | 29 reviews | 11 reviews | 64 RCTs | 10 RCTs | 8 RCTs | 7 reviews and 48 RCTs | 157 RCTs | 44 studies | 6 studies |
| | Number of participants | 4,065 | 561 | 2,366 | | | 8,241 | 2,375 | 1,239 | | 15,842 | 7,730 | 303 |
| **Substance** | Cocaine | | | ✓ | ✓ | | ✓ | | | ✓ | ✓ | | ✓ |
| | Amphetamines | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | | | | ✓ |
| | Methamphetamines | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ | | | | ✓ |
| | Other amphetamine* | | ✓ | | | | | | ✓ | | | ✓ | |
| **Treatment** | Pharmaceutical | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | | ✓ |
| | Psychosocial | | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | |
| **Outcome measures** | Stimulant use | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | |
| | Abstinence | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| | Retention in treatment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | |
| | Adverse events | | ✓ | ✓ | | ✓ | | | | ✓ | | ✓ | |
| | Other | ✓[a] | ✓[b] | ✓[c] | | ✓[d] | | ✓[e] | ✓[f] | ✓[g] | | ✓[h] | ✓[i] |

*Review included amphetamine type-stimulants (ATS); RCTs - randomised controlled trials; [a]Cravings; craving, withdrawal, depression; [b]Cravings, withdrawal symptoms, depressive symptoms; [c]Cravings, survival, clinical severity, depression ADHD symptom severity for studies with cocaine users with ADHD; [d]Change in drug-related behaviours increasing risk of harm (e.g. needle sharing, risky sexual behaviours); [e]Psychiatric symptoms, other drug use, BBV risk taking behaviour, physical health, quality of life; [f]Cravings, withdrawal symptom severity, anxiety symptoms, depression symptoms, cognition, treatment safety; [g]Lapse and relapse; [h]psychiatric symptoms, cognitive function, severity of risky behaviours; [i]Withdrawal, stress, cravings.