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Pharmacotherapeutic strategies for treating cocaine use disorder—what do we have to offer?

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ABSTRACT

Background Cocaine use contines to be a significant public health problem world-wide. However, despite substantial research efforts, no pharmacotherapies are approved for the treatment of cocaine use disorder (CUD). **Argument** Studies have identified positive signals for a range of medications for treating CUD. These include long-acting amphetamine formulations, modafinil, topiramate, doxazosin and combined topiramate and mixed amphetamine salts extended-release (MAS-ER). However, valid conclusions about a medication's clinical efficacy require nuanced approaches that take into account behavioural phenotypes of the target population (frequency of use, co-abuse of cocaine and other substances, genetic subgroups, psychiatric comorbidity), variables related to the medication (dose, short-/long-acting formulations, titration speed, medication adherence) and other factors that may affect treatment outcomes. Meta-analyses frequently do not account for these co-varying factors, which contributes to a somewhat nihilistic view on pharmacotherapeutic options for CUD. In addition, the predominant focus on abstinence, which is difficult for most patients to achieve, may overshadow more nuanced therapeutic signals. **Conclusion** While there is an emphasis on finding new medications with novel mechanisms of action for treating CUD, currently available medications deserve further investigation based on the existing literature. Evaluating refined metrics of treatment success in well-defined subgroups of patients, and further exploring combination therapies and their synergy with behavioural/psychosocial interventions, are promising avenues to establishing effective therapies for CUD.

Keywords Cocaine, combination therapies, dopamine agonists, dopamine antagonists, novel mechanisms, pharmacotherapy, positive signals, therapeutic nihilism, treatment.

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BACKGROUND

In 2017, the United Nations Office on Drugs and Crime (UNODC) reported an all-time high in the estimated global illicit manufacturing of cocaine [1]. In 2018, an estimated 18.1 million people world-wide used cocaine for recreational purposes [2]. Approximately 30% of these cocaine users (12 years or older) resided in the United States, including 874 000 'new users' and 977 000 individuals diagnosed with cocaine use disorder (CUD) in the past year [3]. Nonetheless, only approximately 19% of people with CUD received treatment for this disorder [3]. In Europe, similar issues have evolved, with an estimated 3.9 million individuals between ages 15 and 64 reporting cocaine use and 73 000 individuals receiving treatment for CUD in 2017 [4].

Chronic cocaine use produces persistent changes in the vasculature that increase the likelihood of myocardial infarction, hypertension, atherosclerosis and stroke [5–9]. It also increases risks for various other health problems, including psychiatric disorders and sexually transmitted infections [10–12]. Psychiatric comorbidities and psychosocial factors, such as poverty, unemployment, homelessness, socio-economic status and legal issues, predict cocaine-related physical and mental health complications [13]. Almost all who seek treatment for CUD receive psychosocial interventions, but most will continue to use cocaine [14]. Pharmacotherapies may augment the effectiveness of psychosocial interventions, but no Food and Drug Administration (FDA)-approved medications for treating CUD are currently available.

Our views on the contribution of cocaine to drug overdoses have undergone a rapid shift. In 2017, a reported 52% of all fatal drug overdoses in the United States involved cocaine (n = 70237) [15]. While adulteration with synthetic opioids, such as fentanyl, may contribute to growing overdose rates [16], recent data indicate that one-quarter of cocaine overdose deaths were without any opioid involvement [15]. In Europe, stimulant overdoses account for a smaller proportion of drug-related deaths, but these rates vary widely by country [4].

PHARMACOTHERAPEUTIC STRATEGIES TO THE TREATMENT OF CUD—WHERE ARE WE?

Substantial efforts have been devoted to identifying medications that could augment the effectiveness of CUD treatments, with several medications having shown some promise. However, a looming sense of nihilism is pervasive—why?

In this paper, we (1) discuss and examine the pharmacological approaches that have thus far been tested for CUD treatment, (2) discuss a number of major issues with prior research constraining our opportunities to find an efficacious medication, (3) highlight potential avenues to pursue and offer critical considerations for future study and (4) encourage our colleagues to persist in their investigative efforts.

PHARMACOLOGY OF COCAINE

Cocaine stimulates the mesolimbic dopamine system—the brain's reward pathway [17]. Cocaine effects are produced through binding to, and inhibiting the function of, monoamine transporters for dopamine (DA), serotonin (5-HT) and norepinephrine (NE) [18]. These transporters inhibit neuronal communication by facilitating uptake of neurotransmitters from the extracellular space (i.e. the synapse) back into neighbouring neurones. DA accumulates, resulting in stronger and prolonged signalling with the pre- and post-synaptic neurone. This putatively produces the psychomotor stimulant effects [19] and contributes to the pleasurable effects of cocaine (e.g. euphoria). Despite the central role of DA, other neurotransmitter systems (NE, 5-HT) reflect viable targets for modulation with an impact on cocaine sensitization, craving and reinstatement [20].

CURRENT APPROACHES TO TREATING CUD

Pharmacological treatments for CUD to date form four distinct categories: agonists, antagonists/blockers, novel mechanisms and combination pharmacotherapies. Here, we discuss studies showing promising pharmacotherapeutic signals for CUD and examine potential reasons for why some findings have not been replicated. Table 1 depicts characteristics of the clinical trials that are discussed.

While we do not make any claim to completeness regarding the literature analyzed for this opinion piece, we reviewed all obtainable systematic reviews and meta-analyses on pharmacological treatments for CUD. A recent systematic review of reviews was used to identify those published until November 2019 [62]. A separate systematic search of peer-reviewed articles published between November 2019 and July 2020 was conducted via Pubmed, EMBASE and the Cochrane Database, using the same keyword search terms as those of the aforementioned systematic review of reviews. This search generated one additional systematic review evaluating cannabidiol in the treatment of CUD [63]. Studies of cannabidiol currently remain in the pre-clinical phase, except for one ongoing human trial (NCT02559167; results not yet posted). In addition, we refrained from including a detailed discussion of antidepressants, even though this is the most widely studied drug class for the treatment of CUD. However, findings from three separate systematic reviews, which included 37 (total N = 2891 [64]), 10 (n = 1226 [65]) and 19 (n = 1180 [66]) randomized controlled trials (RCTs), respectively, consistently showed that antidepressants had negligible effects on CUD [62], except for a potential monoamine augmentation of contingency management (CM) treatment [57,60].

An overarching problem with identifying efficacious CUD treatments is that a vast number of different medications have been tested but only a few studies have investigated each individual compound, and fewer still have adequately sized samples (Table 1). Such scarcity of data raises risks for overestimating the therapeutic potential of a medication or prematurely dismissing one with veridical utility. Further, pharmaceutical drug development typically follows a rigorous process of translating pre-clinical studies with animals to human laboratory experiments to human clinical trials. However, a strikingly small percentage of drugs tested in RCTs as treatments for CUD have previously undergone self-administration investigations in both non-human primates and humans [67]. This is somewhat disturbing, given that self-administration models provide the most direct point-to-point correspondence with addictive behaviour in the 'real world' [68–70] and offer potentially invaluable insights at low costs. The therapeutic potential of an intervention demonstrated under controlled laboratory models forms the necessary basis from which to pursue future costly clinical trials, specifically those of appropriate scale for detecting efficacious CUD treatments.

Table 1 Characteristics of clinical trials discussed.

Author, year	*Primary disorder*	*Other SUDs*	*Other psychiatric conditions*	*Primary medication used*	*Other medications*	*Maximum dose (mg)*	*Sample size r andomized (n)*	*Completers (n)*	*Follow-up period (weeks)*
Dopamine releasers (median sample size randomized: 101; completers: 34)									
Grabowski, 2004 [21]	Cocaine	Opioid	None	D-Amp	Methadone	60	120	34	26
Grabowski, 2001 [22]	Cocaine	No	None	D-Amp	None	60	128	–[a]	12
Shearer, 2003 [23]	Cocaine	Opioid	None	D-Amp	None	60	30	11	14
Mooney, 2009 [24]	Cocaine	No	None	Meth	None	30	82	25	8
Nuijten, 2016 [25]	Crack cocaine	No	None	D-Amp	Methadone/diacethylmorphine	60	73	65	12
Levin, 2015 [26]	Cocaine	No	ADHD	MAS-ER	None	60/80	123	93	13
Dopamine uptake inhibitors (median sample size randomized: 96; completers: 59)									
Anderson, 2009 [27]	Cocaine	No	None	Modafinil	None	400	210	125	12
Dackis, 2012 [28]	Cocaine	No	None	Modafinil	None	200/400	210	120	8
Kampman, 2015 [29]	Cocaine	No	None	Modafinil	None	300	94	71	8
Schmitz, 2012 [30]	Cocaine	No	None	Modafinil/D-AMP	None	400/60	73	15	16
Schmitz, 2014 [31]	Cocaine	No	None	Modafinil	Levodopa/ Carbidopa, Naltrexone	400	81	40	12
Levin, 2007 [32]	Cocaine	Opioid	ADHD	Methylphenidate	Methadone	80	98	47	12
Margolin, 1995 [33]	Opioid	Cocaine	None	Bupropion	Methadone	300	149	125	12
Shoptaw, 2008 [34]	Cocaine	No	None	Bupropion	None	300	70	12	16
Cocaine vaccine (median sample size randomized: 212; completers: 110)									
Martell, 2009 [35]	Cocaine	Opioid	None	TA-DC	Methadone	5 vaccinations	115	94	24
Kosten, 2014 [36]	Cocaine	No	None	TA-DC	None	5 vaccinations	310	126	24
GABA modulators (median sample size randomized: 103; completers: 58)									
Shoptaw, 2003 [37]	Cocaine	No	None	Baclofen	None	60	70	17	16
Brodie, 2009 [38]	Cocaine	No	None	Vigabatrin	None	3	103	52	9
Kampman, 2004 [39]	Cocaine	No	None	Topiramate	None	200	40	34	13
Johnson, 2013 [40]	Cocaine	Alcohol	None	Topiramate	None	300	142	72	12
Kampman, 2013 [41]	Cocaine	Alcohol	None	Topiramate	None	300	170	100	13
Umbricht, 2014 [42]	Cocaine	Opioid	None	Topiramate	Methadone	300	171	113	12
Nuijten, 2014 [43]	Crackccocaine	Opioid	None	Topiramate	None	200	74	58	12
Noradrenergic agents (median sample size randomized: 98.5; completers: 58)									
Shorter, 2013 [44]	Cocaine	No	None	Doxazosin	None	8	35	17	13
Zhang, 2019 [45]	Cocaine	No	None	Doxazosin	None	8	76	55	12
Carroll, 2004 [46]	Cocaine	No	None	Disulfiram	None	250	121	53	12
Schottenfeld, 2014 [47]	Cocaine	Opioid	None	Disulfiram	Buprenorphine	250	177	92	12

(*Continues*)

Table 1. (Continued)

Author, year	*Primary disorder*	*Other SUDs*	*Other psychiatric conditions*	*Primary medication used*	*Other medications*	*Maximum dose (mg)*	*Sample size r andomized (n)*	*Completers (n)*	*Follow-up period (weeks)*
Oliveto, 2011 [48]	Cocaine	Opioid	None	Disulfiram	Methadone	250	161	110	14
Kosten, 2013 [49]	Cocaine	Opioid	None	Disulfiram	Methadone	250	74	61	12
Antipsychotics (median sample size randomized: 35; dropout rate: 49.3%)[b]									
Beresford, 2017 [50]	Schizophrenia	Cocaine	None	Aripiprazole	Perphenazine	30	44	44	8
Novel mechanisms (median sample size randomized: 93; completers: 58)									
Carroll, 2018 [51]	Cocaine	Opioid	None	Galantamine	Methadone	8	120	92	12
DeVito, 2019 [52]	Cocaine	No	None	Galantamine	None	16	93	58	13
Dakwar, 2019 [53]	Cocaine	No	None	Ketamine	Midazolam	0.5/kg	55	32	5
Combination pharmacotherapy (median sample size randomized: 104; completers: 71.5)									
Kablinger, 2014 [54]	Cocaine	Alcohol	None	Metyrapone/oxazepam	None	1500/20	45	22	7
Pettinati, 2008 [55]	Cocaine	Alcohol	None	Disulfiram/naltrexone	None	250/100	208	95[c]	13
Mariani, 2012 [56]	Cocaine	No	None	MAS-ER/topiramate	None	60/150	81	64	12
Levin, 2012 [56]	Cocaine	No	None	MAS-ER/topiramate	None	60/100	127	79	14
Medications used to augment behavioural treatments (median sample size randomized: 133; completers: 66)									
Kosten, 2003 [57]	Cocaine	Opioid	None	Desipramine	Buprenorphine	150	160	78	12
Schmitz, 2008 [58]	Cocaine	No	None	Levodopa/carbidopa	None	400/100	161	66	12
Poling, 2006 [59]	Opioid	Cocaine	None	Bupropion	Methadone	300	106	62	25
Moeller, 2007 [60]	Cocaine	No	None	Citalopram	None	20	76	–[d]	12

D-Amp = dextro-amphetamine; MAS-ER = extended release mixed amphetamine salts; SUD = substance use disorder; TA-DC = anti-cocaine vaccine. [a]Number of completers not reported (study completion rates for placebo, 15–30 mg and 30–60 mg groups were 22.9, 40.4 and 8.7%, respectively [22]). [b]The median sample size randomized refers to the 14 studies included in a Cochrane review [61] plus the additional randomized controlled trial (RCT) testing aripiprazole [50]. The dropout rate was derived from studies included in the Cochrane review that reported dropout rate as an outcome. [c]Number of completers not reported (45.8% of patients who took 80% of their pills while in treatment [55]). [d]Number of completers not reported (overall, subjects remained in treatment for an average of 4.6 ± 4.4 weeks [60]).

Dopamine agonists

Agonist medications share pharmacodynamic mechanisms of action with the illicitly used drug, but typically have distinct pharmacokinetic qualities (e.g. enteral bioavailability, slower onset of action, longer duration of action) [21,71]. Agonist treatment utilizes a substitution approach to replace (or displace) the illicit drug for the purpose of stabilizing functioning. For example, methadone has been a highly effective agonist substitution method for managing opioid use disorder (OUD).

Although stimulants acutely increase available monoamines [DA/noradrenaline (NA)/5HT] [19,72,73], chronic users exhibit blunted monoaminergic functioning (low baseline DA, blunted DA release, low D2/D3 receptor availability). Stimulant-like agonists may help to reduce DA hypoactivity via tonic DA regulation [74] and attenuate the phasic DA responses promoting drug-seeking [75,76]. Moreover, agonist treatments alleviate the intensity of drug cravings and withdrawal symptoms that can contribute to relapse [77,78]. Other benefits of the agonist approach include familiarity with drug effects that may promote medication compliance [79–81].

One concern commonly put forth against agonist approaches is the potential for secondary abuse, given their subjective stimulant-like qualities. However, evidence thus far is relatively weak for abuse liability and cardiovascular risk of agonist medications, including amphetamine in cocaine users [82–85]. While carefully weighing therapeutic benefits against potential risks is undoubtedly important, a lack of (political) willingness to address the necessary regulatory and implementation procedures should not prevent the study of agonist medications or the clinical use of drugs that have proved efficacious. Another concern is the prolonged blunting of DA systems with stimulant maintenance. Evidence for the potential adverse effects associated with long-term stimulant medication use remain unclear, due to a lack of longitudinal studies [86]. However, preliminary evidence from non-human primates suggests that chronic exposure to long-acting stimulant medications does not produce aberrant DA functioning [87].

Dopamine releasers

The most promising signals to date have been obtained with DA releasers, specifically with amphetamine maintenance [88,89]. Dextro-amphetamine (D-amp) yields similar efficacy in decreasing cocaine choice in monkeys as in humans [90]. Under controlled laboratory settings, D-amp maintenance reduced cocaine self-administration in cocaine-dependent participants with comorbid OUD (maintained on buprenorphine) [91] and those without the comorbid disorder [92].

Clinical trials have produced similar results showing that D-amp reduces cocaine use [22,23,82]. One study testing multi-stage dosing showed greatest treatment retention at 15–30 mg, and the lowest total percentage of cocaine-positive urine screens at 30–60 mg [22]. With immediate release (IR) methamphetamine (5 mg, 6×/day) and sustained-release (SR) methamphetamine (30 mg first dose, then 5× placebos), individuals who received the SR formulation had fewer cocaine-positive urine samples and greater reduction in cocaine craving [24]. These effects were attributed to overall higher medication adherence for the first dose of the day (95%), but lower for subsequent capsules. Moreover, cocaine-dependent patients in heroin-assisted treatment who were given 60 mg SR D-Amp exhibited fewer days of cocaine use compared to those treated with placebo [25]. These findings highlight the potential benefits of D-amp in CUD treatment, especially in the context of good medication adherence.

CUD frequently co-occurs with attention deficit hyperactivity disorder (ADHD), and cocaine use may be reflective of attempts to self-medicate [93]. A multi-site clinical trial evaluating the effects of extended-release mixed amphetamine salts (MAS-ER; 60 or 80 mg/day versus placebo) in patients with ADHD and comorbid CUD indicated that the higher dose, combined with cognitive behavioural therapy (CBT), reduced symptoms for both conditions [26].

Dopamine uptake inhibitors

A more recently tested medication with DA-transporter inhibitory properties is modafinil, a cognitive enhancer and wake-promoting agent that binds to the DA transporter, preventing DA re-uptake [94]. Modafinil is well tolerated [95,96] and does not alter acute cardiovascular effects in combination with cocaine or potentiate cocaine-induced euphoria [97]. Human experimental trials showed conflicting results regarding modafinil's effect on cocaine self-administration [98,99]; however, they differed by the magnitude of presented reinforcers (e.g. choose $1 or 0–20 mg cocaine versus $5 or 0–50 mg cocaine). Reinforcer magnitude has been shown to influence cocaine choice in the context of modafinil maintenance [100], where cocaine choice decreased only when both reward values and response effort demands were high.

In a meta-analysis of 11 RCTs comparing therapeutic outcomes of modafinil versus placebo, seven studies did not provide evidence for superiority of modafinil over placebo in sustaining cocaine abstinence [101]. However, *post-hoc* analyses from one study revealed that while modafinil maintenance had no effect on cocaine abstinence, those without a history of alcohol use disorder (AUD) exhibited increased percentage of days abstinent by week [27]. In support of these results, individuals with

CUD but not AUD who were treated with modafinil were significantly more likely to abstain from cocaine use during the last 3 weeks of the trial than those who received placebo [29].

While these results seem promising, findings of modafinil effects on CUD independent of AUD have not been replicated. While high dropout rates (33–60%) [30,31] and poor medication adherence may have limited conclusions about the effectiveness of modafinil, one study noted some important sex differences [28]. Men treated with the higher modafinil dose (400 mg/day) were more likely to remain abstinent relative to their placebo-treated counterparts, while women treated with placebo had the highest rates of abstinence in the female sample.

Results comparing human laboratory experiments and clinical trials provide a concordance of data supporting the efficacy of methylphenidate (60 mg/day) for treating CUD in individuals with ADHD [32,102]. However, subsequent RCTs investigating methylphenidate as an agonist replacement therapy in participants with CUD, both with and without comorbid ADHD, revealed mainly negative results. It is possible that insufficient dosage strengths may have contributed to the discrepant results [89].

In summary, even though systematic reviews of psychostimulants conclude that there is insufficient evidence to either support or discount their effectiveness for CUD [65,101,103–105], positive signals have been identified in studies testing dopamine agonist treatments, particularly for long-acting amphetamine formulations at sufficiently high doses and modafinil when medication adherence is ensured.

Antagonist/blocker approaches

In general, antagonists are thought to block the euphoric effects of cocaine and facilitate the decrease in cocaine use through extinction. Antagonist or blocker approaches are generally less effective in the treatment of substance use disorders (SUDs) compared to agonists because they require high levels of motivation at treatment initiation and maintenance; nonetheless, their efficacy can be high. A potential safety concern is compensatory drug use to 'over-ride' the blockade, especially when it is not a complete blockade. However, in practice these attempts are typically modest, because patients report that they may try the drug of abuse but will not waste their money if the effects are undesirable [106].

Antipsychotics

A Cochrane Review concluded that there is no evidence supporting the use of antipsychotic medications that block DA receptors to treat CUD [61]. However, the results came from only 14 trials with small sample sizes (median sample size of the 14 RCTs included: 33) and moderate to low-quality evidence. In addition, antipsychotics may require an acclimation period to take effect, as exemplified by an RCT testing aripiprazole. In participants with schizophrenia and comorbid CUD, the effect of aripiprazole on craving appeared at week 6 of treatment [50].

Cocaine vaccine

An anti-cocaine vaccine (e.g. TA-CD) is one of several novel approaches utilizing an immunological mechanism of action for the treatment of SUDs. TA-CD, composed of a cocaine hapten conjugated to inactivated cholera toxin B, increases production of antibodies that target the cocaine molecule. The antibodies bind to cocaine in the blood and, because the antigen–antibody complexes are too large to cross the blood–brain barrier, prevent cocaine from entering the brain [107,108].

A human laboratory study found that peak plasma antibody levels, which were highly variable between subjects, predicted cocaine's effects in non-treatment-seeking cocaine-dependent participants [106]. Individuals producing the highest antibody titres had the greatest reductions in positive drug effect ratings and perceived cocaine quality. In addition, self-reported cocaine use showed a trend to decrease as a function of antibody titre.

Results from clinical trials for vaccines are inconsistent. A study of TA-CD administered to methadone-maintained individuals indicated that vaccinated participants who attained high immunoglobulin (Ig)G levels (≥ 43 μg/ml; 38% of vaccinated participants) had more cocaine-free urine samples than those with low IgG levels and those with placebo, during study weeks 9–16 [35]. In addition, the proportion of participants with a 50% reduction in cocaine use was significantly greater in the high IgG level group (53%) than the low IgG level group (23%). These results are promising, but they could not be fully replicated in individuals without comorbid OUD [36]. After week 8, more vaccinated than placebo participants attained abstinence for at least 2 weeks of the trial (24 versus 18%) and the high IgG group (67% vaccinated participants) had the most cocaine-negative urines during the last 2 weeks of treatment [odds ratio (OR) = 3.02]; however, neither result was statistically significant. Notably, almost 3× fewer high than low IgG participants dropped out of the study. The authors recommended for future studies: (1) a more structured setting to increase participant motivation for abstinence, (2) a shift in focus from abstinence initiation to relapse prevention and (3) greater integration of CBT to facilitate sustained abstinence [36].

GABA modulators

Several pre-clinical studies support the potential efficacy of GABAergic medications for the treatment of CUD. GABA is an important modulator of the mesolimbic reward system

[109–112], and medications that increase GABAergic activity such as vigabatrin and baclofen have been shown to reduce cocaine self-administration in animal models. Although clinical trials to date have not demonstrated efficacy for baclofen [37], positive outcomes have been found for vigabatrin in a study that ensured high medication adherence [38].

Topiramate, an anticonvulsant with multiple mechanisms of action (Na^+ and Ca^{++} channel blockade; carbonic anhydrase inhibition; GABA potentiation; glutamate antagonism) initially showed compelling evidence for efficacy in CUD treatment. Participants with CUD, both those abstinent [39] or using at baseline [40], showed increased abstinence rates with topiramate treatment relative to placebo. Because rapid dose titration of topiramate can result in uncomfortable central nervous system side effects, a slow titration is required to achieve target dose levels [39]. In individuals with comorbid CUD and AUD, topiramate produced longer periods of cocaine abstinence, even in the absence of differential weekly abstinence rates between those treated with topiramate versus placebo [41]. Among methadone-maintained patients, topiramate did not show superiority over placebo in sustaining cocaine abstinence, regardless of whether or not participants received incentives for drug abstinence [42]. In an open-label trial assessing topiramate as an adjunct to CBT, cocaine smokers reported no reduction in cocaine use, and only 14% of participants took topiramate for 11 of 12 weeks [43]. Negative findings may be attributed to poor medication adherence and discrepancies in dosages used across studies [40,41]. Nonetheless, *post-hoc* exploratory analyses showed reduced cocaine use in individuals with comorbid CUD and OUD treated with topiramate [43].

Noradrenergic agents

Doxazosin is a long-acting selective α-1 adrenergic antagonist that reduces central noradrenergic activity. Doxazosin has been found to limit the behavioural effects of stimulants, including amphetamine and cocaine [113–115], and attenuate cocaine-induced reinstatement of cocaine-seeking behaviour in rats [116,117]. A promising pilot study revealed that a rapid titration schedule of doxazosin (8 mg/day over 4 weeks) led to more cocaine-negative urines than slower titration (8 mg/day over 8 weeks) or placebo (35, 10 and 14% negative urines, respectively) [44].

In a recent trial, doxazosin-treated (8 mg/day) individuals exhibited a greater reduction in cocaine use relative to those treated with placebo [45]. Genetic subgroup analysis further indicated that the percentage of cocaine-positive urine toxicology screens for doxazosin-treated individuals was lower in the group with lower DA beta-hydroxylase (DβH) levels from T-allele carriers (CT or TT) than the group with higher DβH levels from the DβH CC genotype. This finding suggests that doxazosin may be more effective at blocking NE stimulation when the threshold for NE release is lower (CT/TT group) compared to when it is higher (CC group). A follow-up study by the same group explored pharmacogenetic response to doxazosin treatment based on an alpha-1 adrenoreceptor subtype D (ADRA1D) genetic variant [118]. Given that T-allele carriers with the ADRA1D SNP (T1848A) treated with doxazosin had a greater reduction in cocaine use, this polymorphism constitutes a potential pharmacogenetic marker in pharmacotherapy for CUD [118].

A complex picture of mixed findings is apparent with disulfiram, a copper chelator that acts upon multiple enzymes including DβH, which results in an inhibition of norepinephrine synthesis [119]. For example, disulfiram treatment (versus placebo) in combination with CBT was associated with reduced cocaine use [46]. These effects were most pronounced for participants without AUD at baseline and those who fully abstained from drinking during treatment. Further, buprenorphine-treated participants reported reduced cocaine use following disulfiram treatment [47], with no difference in number of collected cocaine-negative urine samples or consecutive weeks abstinent between disulfiram- and placebo-treated individuals. Another study with methadone-maintained participants compared three disulfiram doses and placebo in combination with CBT. Cocaine-positive urine samples increased over time with the lower two dosages (62.5 or 125 mg/day) but decreased in the 250 mg group [48]. However, there was no difference between the 250 mg disulfiram group and the placebo group.

A pharmacogenomic study found that disulfiram reduced cocaine-positive urines in methadone-stabilized participants by 18% during the course of the 10-week study, and this effect varied as a function of genotype groups [49]. Participants with the normal DβH level genotype showed a reduction by 28% on disulfiram, whereas no effects were found in those with low DβH level genotype. Moreover, men treated with disulfiram sustained a greater number of days abstinent and percentage of drug-free urine samples than those with placebo, whereas women had a moderate outcome regardless of treatment arm [120].

An early systematic review found insufficient evidence to either support or discount the effectiveness of disulfiram for CUD [121], and a recent meta-analysis of seven RCTs found worse retention rates for disulfiram than placebo (relative risk 0.90) [65]. The mechanisms by which disulfiram exerts its effects on cocaine-related behaviours remain unclear. This, and side effects reported in some studies (e.g. hepatotoxicity) [122], may limit its potential use.

Novel mechanisms—tested in humans

Galantamine is a cholinesterase inhibitor that improves concentration and attention. A recent RCT tested galantamine against placebo in the context of standard methadone treatment and computerized CBT as treatments for CUD [51]. Results indicated a reduction in cocaine use frequency over time, with galantamine superior to placebo and CBT superior to methadone alone. There was no evidence of an additive or synergistic effect of combined galantamine and CBT on cocaine use. In a separate RCT that excluded those with comorbid SUDs, neither galantamine dose (8 or 16 mg/day) improved cocaine-use outcomes [52].

Ketamine is a potent N-methyl-D-aspartate receptor (NMDAR) antagonist that is effective in the treatment of severe depression [123]. Ketamine is hypothesized to extend beyond NMDAR modulation to downstream effects on other neurotransmitter systems and pre-frontal synaptogenesis. Subanaesthetic ketamine infusions (0.41 mg/kg) increased motivation to quit cocaine use and reduced cue-induced cocaine craving relative to those who received active control (2 mg lorazepam), and higher dose infusions (0.71 mg/kg) produced even further reductions in cravings [124]. A separate study using the same higher ketamine dose yielded decreased cocaine self-administration 28 hours post-infusion compared to the control condition (0.025 mg/kg midazolam) [125]. Furthermore, ketamine increased self-reported distress tolerance 48 hours post-infusion relative to controls. By creating a reprieve from reactivity to distress, ketamine treatment may help individuals with CUD to access and experience the full benefit of behavioural interventions.

The first clinical trial with ketamine involving individuals with CUD undergoing mindfulness-based relapse prevention showed that a single subanaesthetic ketamine infusion (0.5 mg/kg) was capable of increasing cocaine abstinence relative to an active control (midazolam) [53]. Thirteen ketamine-treated participants remained abstinent during the final 2 weeks of the trial, while only three controls managed to do the same. The study further reported that those in the ketamine group were less likely to drop out of treatment or relapse to cocaine use, and they reported less craving for cocaine.

Combination approaches

Combination pharmacotherapy

Combining pharmacotherapeutic approaches for the treatment of CUD is a viable strategy for a number of reasons: use of lower doses of individual constituents may minimize side effects, additive or synergistic effects may be achieved with combinations and the diverse neurotransmitter systems impacted by stimulant drugs can be targeted [126]. Nonetheless, given that there are no medications with a broad signal for CUD, combining two medications with weak (or no) signals may increase the occurrence of adverse events and thus unfavourably impact the risk : benefit ratio. Another issue of assessing combination pharmacotherapy in clinical trials is that very few individual constituents have been tested against combination approaches. Thus, the superiority of combination over monotherapy remains to be determined.

Thus far, combination approaches that have shown some promise in increasing cocaine abstinence in clinical trials include metyrapone/oxazepam, disulfiram/naltrexone and topiramate/MAS-ER treatment. While there were no treatment group differences in overall analyses for metyrapone/oxazepam [54] and disulfiram/naltrexone treatment [55], subgroup analyses indicated that disulfiram maintenance, both alone and in combination with naltrexone, increased abstinence from cocaine and alcohol, and longer abstinence periods were observed in the high-dose metyrapone/oxazepam group (1500 mg metyrapone/20 mg oxazepam) compared to placebo. The significance of the latter result is attenuated, however, by an overall low retention rate of randomized subjects (22 of 45).

In other studies, combination MAS-ER/topiramate doubled the rate of participants achieving three consecutive weeks of cocaine abstinence (33.3%) relative to placebo (16.7%) [56]. Exploratory *post-hoc* analyses revealed that MAS-ER/topiramate was more effective for participants who had a greater frequency of cocaine use at baseline. A larger follow-up investigation of MAS-ER/topiramate in heavy, frequent cocaine users showed even greater differences between treatment versus control groups for cocaine abstinence both during the trial (21.9 versus 6%) and ≥ 3 consecutive weeks at the end of the trial (14 versus 0%) [127].

Medications used to augment behavioural treatments

CM is a powerful behavioural technique that uses reinforcers to elicit behaviour change [128]. There is sufficient evidence from reviews to support the effectiveness of CM for CUD [129–133]. The evidence is limited, however, for the efficacy of CBT in the treatment of CUD. CBT offers the benefit of reduced dropout rates, but shows little impact on the maintenance of cocaine abstinence [132].

Several agonists have been tested in conjunction with CM. One RCT compared desipramine (150 mg/day) and placebo in buprenorphine-maintained cocaine users, in addition to either CM or a non-contingent voucher control. Results indicated both independent and additive effects from combined CM/desipramine [57]. Moreover, those

who underwent both active treatments returned more drug-free urines (50% of total urines) than all other treatment groups (25–29%). CM and desipramine alone, however, revealed a rapidly increasing drug–urine count across time. Sustained-release levodopa/carbidopa (400/100 mg b.i.d.) versus placebo was also assessed alongside either: (1) clinical management alone (ClinMan), (2) ClinMan and CBT or (3) ClinMan + CBT + CM. Levodopa was found to be superior in increasing cocaine-negative urines and consecutive cocaine abstinence relative to placebo, but only in the context of CM involvement [58]. In methadone-maintained individuals, bupropion, an atypical antidepressant with stimulant properties, combined with CM decreased cocaine-positive urine samples during weeks 3–13 with rates remaining stable in the weeks following [59]. CM alone decreased cocaine use gradually from weeks 14 to 25, while bupropion alone, voucher control and placebo yielded no improvements. Lastly, citalopram (20 mg/day) alongside both CBT and CM produced fewer cocaine-positive urine samples relative to placebo in combination with a similar behavioural regimen [60].

MANY POSITIVE SIGNALS—WHAT HAVE WE BEEN MISSING?

The evidence above suggests that specific pharmacological approaches, either alone or in combination with other interventions, may vary as a function of specific subject-related factors (e.g. biopsychosocial traits and status), the pharmacodynamics of the candidate compound or combination medicine and the interactions of these variables. Thus, future investigation of candidate medications may call for careful consideration of target (sub)populations as well as procedural designs that not only optimize dose response but also medication tolerability and adherence.

Procedural and subject-related factors

Table 2 provides an overview of procedural and subject-related factors that have been shown to impact medication effectiveness. Of note, in the CUD treatment literature, there is a heavy focus upon samples of cocaine users who receive medications for OUD. While the apparent aim is clinically relevant in addressing the high

Table 2 Procedural and subject-related factors that may impact treatment effectiveness.

Subject-related factors	
Cocaine use severity	Heavier cocaine users may benefit from MAS-ER/topiramate combination [56,127]
Comorbid substance use disorders	Comorbid alcohol use disorder may interfere with the benefits of modafinil [27,29] and disulfiram [46] treatment, while topiramate [41] or combination treatment with disulfiram/naltrexone [55] seem well-suited for the treatment of CUD patients who are alcohol-dependent. Topiramate [43] and galantamine [51] seem to be viable options for the treatment of patients with comorbid CUD and OUD
Co-occurring attention deficit hyperactivity disorder (ADHD)	In patients with co-occurring CUD and ADHD, methylphenidate [32,102] or MAS-ER at robust doses [26] may be the pharmacotherapies of choice to treat symptoms arising from the overlapping neurophysiological deficits
Sex	Men seem to benefit more from disulfiram [120] and modafinil [28] treatment than women
Genetic subgroups	Those with normal DβH level genotype may benefit most from disulfiram [49], and those with lower DβH level from doxazosin [45]. In addition, efficacy of doxazosin treatment is highly correlated with the ADRA1D T-allele [118]
Procedural factors	
Medication dose	The importance of sufficient medication dose has been highlighted in several trials; e.g. for dextro-amphetamine [22], disulfiram [48], metyrapone [54], topiramate [43] and methylphenidate [32,102]
Titration schedule	Studies indicate the benefits of slow titration of topiramate to avoid uncomfortable side effects [39] but superiority of fast titration of doxazosin [44]
Medication adherence	Medication adherence impacts medication effectiveness, which is evident in trials that failed to replicate positive findings for modafinil [28], topiramate [43] or vigabatrin [134]
Incentive structure	Satisfactory medication adherence (60–70%) [39–41] may be achieved by incentive-based interventions
Release formulation	ER formulations (taken once a day) show greater adherence compared to IR (dosing multiple times per day) [24], in addition to having lower potential for misuse compared to IR formulations [135–137]

CUD = cocaine use disorder; OUD = opioid use disorder; DβH = dopamine beta-hydroxylase; ER = extended release; IR = immediate release; MAS = mixed amphetamine salts.

percentage of opioid-dependent individuals who use cocaine, findings are not likely to replicate across other subgroups of cocaine users. This is seen in prior divergent findings with the cocaine vaccine TA-CD [35,36] and galantamine [51,52]. Furthermore, attention to medication adherence is highly inconsistent throughout clinical trials or inadequate (e.g. counting pills [55]). One possible solution to this problem is the employment of biomarkers to track medication exposure. Studies also suffered from poor participant retention rates (see Table 1). The precise reasons for dropout are often unknown or unreported, but this information may prove invaluable to determining better tolerated treatment trial parameters.

The pharmacological mechanisms of medications impact treatment outcome differentially across stimulant drugs. Despite many similarities [19,138], promising signals for cocaine do not generalize to other psychostimulants [139]. Studies suggest that DA re-uptake inhibitors (e.g. methylphenidate [140,141]) are more effective for reducing use of DA releasers (e.g. amphetamines), and DA releasers (e.g. amphetamine isomers [22,24,142,143]) are more effective for reducing use of cocaine, a DA re-uptake inhibitor. Thus, pharmacotherapy formulation requires tailoring to the primary drug used as well as to the individualized needs of the patient. To achieve the latter, a combination approach may be beneficial, such as targeting drug withdrawal and cravings and allowing patients to benefit more from behavioural/psychosocial interventions [20].

The issues that may arise from discounting subject-related and procedural factors, when assessing a medication's clinical utility, are perhaps best depicted in the discrepancy of outcomes between two meta-analyses. A Cochrane Review of 26 RCTs testing nine different psychostimulants as potential CUD interventions (bupropion, D-Amp, lisdexamfetamine, methylphenidate, modafinil, mazindol, methamphetamine, MAS and selegiline) yielded weak evidence to support their viability in facilitating cocaine abstinence [risk ratio (RR) = 1.36), with no overall reduction in cocaine use [103]. However, the number of studies per candidate medication is too limited to provide adequate representation. The pitfall of pooling studies of disparate designs, end-points and subpopulations together, and treating them as though they were homogeneous, is failing to see what the proverbial apple offers that an orange does not. Indeed, a more recent meta-analytical review, specifying only the inclusion of psychostimulants with sufficient dopaminergic potency [modafinil, methylphenidate or prescription amphetamines (MAS, lisdexamphetamine and D-amp)], concluded that the evidence was robust in supporting CUD treatment with psychostimulants. Results were indicative of increased rates of abstinence (RR= 1.45), and prescription amphetamines were efficacious in promoting abstinence (RR = 2.41) [144]. Although the researchers acknowledged that a broad range of factors, including medication dose, ADHD status and concurrent OUD underpins some degree of heterogeneity across trials [144], such sharp contrasts in findings potentially lead to highly divergent paths in both research and clinical development.

Medication expectations: definition and measurement of meaningful end-points

Sustained abstinence, most commonly determined with qualitative urine screens, is the gold standard for determining treatment success in clinical trials evaluating pharmacotherapies for CUD. However, employing urine toxicology results as evidence of treatment success is by no means clear-cut, as a multitude of decisional challenges impact the interpretation of outcome measures (for an overview, see [145]).

A critical issue for interpreting a medication's effectiveness is the expectation we hold about medication effects themselves. This begs the question: are we having difficulty finding an efficacious medication because of an insistence on abstinence as the only acceptable end-point?

As highlighted by most of the studies referenced here, complete abstinence is difficult to achieve for most individuals with CUD. It is intuitive that other end-points, similar to 'percent subjects with no heavy drinking days' as an efficacy end-point for medications used to treat AUD [146,147], may also indicate meaningful change [145,148]. Given the many physical and psychosocial issues that accompany CUD [148], treatment benefits are perhaps better measured through subjective indicators, such as quality of life and daily functioning, or perhaps those on a more macro scale, such as the individual burdens imposed on our health-care resources [145]. Regardless, the constraints of time and resources often preclude the direct observation of such changes. Therefore, reductions in stimulant use that are predictive of clinically relevant improvements in one's relative functioning and wellbeing may be conceived as useful alternative indicators of treatment success. Nevertheless, the jury is still out on the constituents of meaningful change, and there remains to be established a 'safe' level of stimulant use or a standard stimulant drug dose [145].

CONCLUSION—WHERE DO WE GO FROM HERE?

There is an emphasis on finding new medications with novel mechanisms of action for treating CUD (e.g. [63]). In addition, the available results for ketamine are highly promising, notwithstanding the necessity of further investigations involving larger samples and longitudinal designs to establish the long-term behavioural effects and

limitations to this intervention. Nonetheless, currently available medications deserve further investigation based on the existing literature; these include long-acting amphetamine formulations, modafinil, topiramate, doxazosin and combined topiramate/MAS-ER treatment.

There is certainly no need for therapeutic nihilism. However, the CUD treatment landscape is pockmarked by the outcomes of under-powered studies with high dropout rates and poor medication adherence. This, and some rather undifferentiated reviews of the literature, may dampen the enthusiasm of seasoned researchers and novitiates alike to pursue further inquiries into medications for CUD. Indeed, this would seem consistent with the recent paucity of primary research examining pharmaceutical interventions for CUD [149]. To find renewed vigour in the search for efficacious treatment models, researchers need persistence matched with adequate financial support and commitment by professional societies and funding agencies. Sorting the manifold issues around rigour in research, pharmacology, medication formulation and characteristics of the patient population is an important first step towards successfully navigating this seemingly serpentine road. Evaluating new and refined metrics of treatment success in well-defined behavioural, genetic and psychiatric patient groups, and further exploring combination therapies as well as their synergy with behavioural/psychosocial interventions, are promising avenues to establishing effective therapies for CUD—perhaps those prescribed by the characteristics of a patient, but tailored individually to their needs.

Declaration of interests

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Author Contributions

Laura Brandt: Conceptualization; visualization. **Sandra D. Comer:** Conceptualization; supervision. **Frances R. Levin:** Conceptualization; supervision.

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