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New Directions in Medication-Facilitated Behavioral Treatment for Substance Use Disorders

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Abstract A promising approach to addressing substance use disorders is to integrate pharmacotherapy with a behavioral treatment with which synergy is possible. In this review, we focus on recent research suggesting that this approach may be effective for cocaine and cannabis use disorders, both of which currently lack efficacious medications. We summarize potential targets of pharmacotherapy of particular relevance to combined medication-behavioral treatment and examine preliminary evidence of clinical efficacy. Common to these promising medications is a hypothesized mechanism of action predicated on reversing drug-related neural adaptations, such as high reactivity to stress or drug cues, that might undermine fruitful engagement with behavioral treatment. We also review emerging medications, such as certain glutamatergic and serotonergic agents, which may be feasibly integrated with existing treatments. We conclude with an outline of future directions for research.

Keywords Addiction · Behavioral treatment · Cocaine · Cannabis · Combined treatment · Medication · Use disorder

This article is part of the Topical Collection on *Substance Use and Related Disorders*

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Introduction

The identification of effective pharmacotherapy for substance use disorders (SUDs) has been beset by many challenges. Despite decades of research, there are no clearly effective, FDA-approved medications for cocaine use disorders [1]. Cannabis is regularly designated the most widely used illicit drug internationally [2] and yet cannabis use disorders also remain refractory to medication interventions [3]. Even when medications are found to be effective, as with disulfiram, naltrexone, or topiramate for alcohol use disorders, the effect size is modest or efficacy inconsistent [4, 5], which may explain to an extent why clinicians, including addiction specialists, underutilize them. To address these challenges, an alternative paradigm is to conceptualize medications for SUDs as facilitating specific behavioral interventions, rather than as standalone interventions. In this way, it is specific medication-behavioral intervention combinations that are tested and implemented.

In a now classic study, McLellan and colleagues showed the importance of combining methadone maintenance treatment with psychosocial treatment. In this three-group randomized trial among opioid dependent patients receiving methadone maintenance, patients receiving standard weekly counseling had substantially better drug use outcomes compared to those receiving minimal counseling, and there was a further benefit to patient who received counseling plus enhanced services [6]. Methadone maintenance is a powerful treatment for suppressing opioid use, but it requires good adherence, which could be promoted by a good psychosocial intervention, and it does not by itself address lifestyle changes or other problem areas of addicted patients. Subsequently, Carroll, Kosten, and Rounsaville, researchers experienced in both medications development and behavioral therapy development, reviewed the literature and conceptualized several

different models for combinations of medication and behavioral therapies [7]. Nonetheless, the field of medications development for substance use disorders has remained focused mainly on the medications themselves, rather than medication-behavioral therapy combinations.

Behavioral interventions are widely recognized as important to SUD treatment. Effective behavioral treatments include 12-step facilitation, contingency management (CM), and cognitive behavioral therapy (CBT) based approaches [8–10]. These treatments have been studied as platforms in a variety of medication trials. Some research has also aimed at understanding how behavioral interventions might increase compliance with SUD pharmacotherapy. Retention in treatment and adherence to medication-taking are universal problems in substance use disorder treatment. Adherence is a particular problem for medications that are not inherently reinforcing, such as disulfiram or the opioid antagonist naltrexone [11]. Here, we focus on combined medication-behavioral treatments that are primarily predicated on an hypothesis of synergy, with the behavioral treatment and pharmacotherapy components believed to enhance the effects of the other. This grows from research clarifying the neural deficits associated with SUDs; the ways in which these deficits might impact on the efficacy of behavioral interventions; and the utility of pharmacotherapy at targeting these deficits and therefore optimizing the response to behavioral treatments [12].

This approach has been most commonly adapted to CM, and to a lesser extent to CBT. Further, it has been applied to the treatment of cannabis and cocaine use disorders specifically given the lack of effective medications for them. As will be discussed, CBT and CM have lent themselves to pharmacological facilitation because the mechanisms by which they are hypothesized to be effective are believed to be modifiable by medications. In addition, the mechanisms of actions of certain medications are thought to be optimized if augmented by these behavioral interventions. We begin by evaluating the rationale behind and evidence for combining pharmacotherapy with CM for cocaine and cannabis use disorders, followed by a brief discussion of CBT-based approaches. Then, we discuss novel applications of this paradigm, as well as outline future directions.

Contingency Management

Contingency management (CM) refers to behavioral interventions aimed at disrupting SUDs by providing rewards for abstinence, such as money or vouchers [13]. CM has been found effective for a variety of SUDs, including both cocaine and cannabis [14], and there are SUD-specific manuals that have been developed to allow for clinical dissemination [9, 15].

Alongside barriers to widespread implementation such as cost [16], CM faces challenges that stem from the unique vulnerabilities that afflict SUD individuals. Chronic problematic drug use may result in adaptations in reward circuitry that attenuate the salience of natural rewards while heightening drug seeking [17•]. Individuals with SUDs may therefore experience diminished motivation for and enjoyment from non-drug rewards such as money, while pursuing drug consumption pathologically. This interferes with CM insofar as patients may not be sufficiently motivated by the non-drug reward to pursue abstinence.

Another SUD-related neural deficit of relevance to CM is diminished prefrontal modulation of mesolimbic structures. This may manifest behaviorally as impulsivity, poor stress sensitivity or affect regulation, and increased reactivity to drug cues [18–20]. SUD individuals who experience these vulnerabilities may have difficulty with forgoing drug use in favor of deferred monetary advantages (e.g., delay discounting) [21] and with adhering to the CM framework of behavior modification due to heightened reactivity to environmental or affective triggers.

A related deficit that may impact on the efficacy of CM is neurocognitive impairment. Neurocognitive impairment may predate drug use and confer susceptibility to SUDs [22] and they may also result from chronic problematic drug use through neurotoxic mechanisms, as with alcohol [23]. These deficits may work to compromise the efficacy of CM in various ways, including impacting on the capacity for executive functioning. Alongside being involved in valuation and decision-making, executive functioning allows for adaptation to new situations, facilitating the requisite shifts in rule following and behavioral responses [24]. Thus, individuals with impairments in executive functioning demonstrate behavioral rigidity and maintain their customary patterns of decision-making in new circumstances, as in continuing to consume drugs even when placed in a system of robust contingencies and rewards that promotes abstinence.

Disruptions in various neural circuits are believed to contribute to these vulnerabilities in reward seeking, reactivity, impulsivity, and neurocognition. Dopamine and glutamate are the neurotransmitters most directly affected by drug use and have been implicated in many adaptations to problematic drug use, such as cue and stress sensitivity and impulsivity [25]. For example, drug-induced alterations in the long-term depression and potentiation of glutamate signaling have been implicated in the blunted salience of non-drug rewards and heightened drug seeking [26]. Down-stream effects on reduced mesolimbic dopamine neurotransmission are thought to further account for anhedonic responses to natural rewards and compulsive drug consumption [27]. These alterations have broader regional implications and may lead to the changes in prefrontal functioning observed with SUDs, which have been correlated with deficits in decision-making, affect modulation, and stress sensitivity [28]. Whether or not these deficits represent adaptations or pre-exist the problematic drug use, they constitute important targets of pharmacotherapy. Medications aimed at targeting

these deficits include glutamate modulators, such as d-cycloserine (DCS), topiramate, memantine, and N-acetylcysteine (NAC); dopaminergic agents, including amphetamine, modafinil, levadopa (L-dopa), and nepicastat and disulfiram, both of which impede the metabolism of dopamine; and a variety of anti-depressants [29–32].

The challenge of finding effective pharmacotherapy for cocaine use disorders exemplifies the hurdles of SUD treatment research more generally, especially as they pertain to translating promising medications from laboratory to clinical settings. While many of the agents above have shown promise preclinically, they have not demonstrated efficacy for cocaine use disorders in human research, either because they failed to demonstrate consistent effects, as with topiramate [30], or because they have yet to show any promising clinical effects altogether. That the mechanisms of these medications are recognized to address the neural deficits associated with cocaine use disorders has appropriately dissuaded researchers from dismissing them entirely, and has led instead to reconsideration of how they might be tested, and in what treatment model and clinical setting so as to best harness their behavioral benefits.

When paired with CM, dopaminergic agents have demonstrated greater or more consistent efficacy for cocaine use disorder, perhaps because they enjoy synergy with the behavioral platform. Amphetamine works to increase synaptic dopamine levels by promoting dopamine release as well as reducing pre-synaptic re-uptake [33]. These effects may work to counter the dopaminergic deficits, and specifically the alterations in mesolimbic reward circuitry, associated with cocaine dependence, thereby increasing synaptic dopamine levels and enhancing the efficacy of CM. Indeed, prior research, using raclopride PET to measure striatal dopamine release in response to a dose of a stimulant, has shown that reductions in stimulant-induced dopamine signaling correlate with poor treatment response for individuals engaged in CM [34], consistent with the hypothesis that increased dopaminergic activity works to enhance response to contingency-based behavioral treatment. In addition, amphetamine and other stimulants may improve neurocognitive performance [35], which may also work to improve treatment response.

In a three-arm placebo-controlled trial evaluating the efficacy of the amphetamine analogue methamphetamine in both immediate and sustained release formulations paired with CM, it was found that sustained release methamphetamine led to significant reductions in the number of cocaine negative urines compared to both the immediate-release preparation and placebo [36]. These preliminary results suggest that long-acting amphetamine compounds may serve to enhance the efficacy of CM. A preliminary trial comparing L-dopa and placebo paired with a variety of behavioral treatments found that L-dopa had a significant effect on cocaine use only when paired with a CM platform aimed at promoting abstinence [37, 38]. L-dopa is a precursor of dopamine, crosses the blood–brain barrier, and is converted by the enzyme aromatic L-amino acid decarboxylase to increase the concentration of synaptic dopamine [35]. Interestingly, L-dopa did not provide benefit if paired with a CM platform aimed at promoting adherence, suggesting that the efficacy of L-dopa is contingent on a specific abstinence-focused CM platform. [37] Another group has replicated these findings [38]. These results suggest that pairing CM with certain dopaminergic agents may be a promising treatment approach meriting further research.

Interestingly, similar synergy with CM contingent on abstinence has been suggested by trials of several antidepressant medications, including desipramine, bupropion, and citalopram [39–41]. Bupropion is a weak dopamine re-uptake inhibitor, but is thought mainly to work through norepinephrine. Desipramine is a norepinephrine re-uptake inhibitor, and citalopram a serotonin reuptake inhibitor. As noted above, antidepressant medications such as these have been extensively tested for cocaine dependence, with inconsistent results. As antidepressants, such medications reduce anhedonia, a core symptom of depression that represents a loss of reward salience. Though their potential utility for treatment of substance use disorders has been conceptualized in terms of reducing negative affective states associated with chronic drug or alcohol use [42, 43], they may also work to restore reward processing in addicted individuals. Thus these findings may also be viewed as consistent with the broad hypothesis of synergy between CM and medications capable of enhancing reward system functioning.

Modulation of glutamatergic neurotransmission has shown preclinical promise for the treatment of various SUDs. Glutamate is thought to be an important target given its involvement in neural plasticity, dopamine signaling, and prefrontal regulation of limbic structures [44]. Of particular interest to SUDs is the finding that mesolimbic dopamine neurons, including those of the nucleus accumbens, are controlled by the glutamatergic system, and glutamate modulators, such as N-methyl-D-aspartate (NMDA) receptor antagonists, may work to normalize the adaptations in reward-related neurotransmission arising from problematic drug use [44]. There is insufficient clinical evidence, however, that NMDA modulation works to improve cocaine or cannabis dependence at present. For example, memantine failed to show an effect for cocaine dependence in the context of voucher-based incentives for abstinence in a clinical trial [45]. Similarly, topiramate, an NMDA receptor modulator, has demonstrated inconsistent effects for cocaine use disorder, and specifically failed to promote abstinence when coupled with a contingency management platform. [30] A preliminary trial, however, suggests that topiramate and amphetamine may enjoy synergistic effects for cocaine problems [46].

Another strategy for improving reward circuitry is to correct down-regulation of the cysteine–glutamate exchanger in the nucleus accumbens, a dependence-related adaptation that

has been linked to drug reinstatement [47]. N-acetylcysteine (NAC), a naturally occurring prodrug of the amino acid cysteine, is believed to correct this deficit by up-regulating the cysteine–glutamate exchanger, and may work to normalize reward circuitry so as to enhance the efficacy of CM [48]. In a preliminary controlled trial comparing 1,200 mg of NAC to placebo in conjunction with CM, it was found that the NAC group led to a significantly greater proportion of cannabis negative urine tests [49•]. Interestingly, a trial of NAC with doses up to 2,400 mg, in the absence of CM, demonstrated no effect on cocaine dependence, with comparable abstinence rates between the placebo and NAC groups [50]. These data suggest that NAC may be most effective if paired with a CM platform, and provide new directions for pharmacologically optimizing CM.

In summary, dopaminergic agents such as L-dopa and long-acting amphetamine analogues may work to enhance CM to more effectively promote abstinence in cocaine dependent individuals, while glutamate modulators such as NAC may also be effective when combined with CM, though this has only been observed in a single trial for cannabis dependence. More research is needed to better understand how to optimize CM with pharmacotherapy; to replicate the preliminary findings with NAC, L-dopa, and long-acting amphetamine analogues; and to test other glutamate modulators and dopaminergic agents in the context of CM.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a behavioral treatment found effective for a variety of psychiatric disorders, including SUDs [51]. The premise of CBT-based approaches is that entrenched ontological beliefs ("I am worthless") influence automatic cognitions and distortions that arise in certain situations ("Everybody hates me at this party"), which in turn precipitate a cascade of cognitive associations, affects, and ultimately behaviors (e.g., drinking to the point of inebriation) [51]. The aim of CBT is to correct these automatic cognitions by cultivating greater awareness of their emergence, promoting recognition of the manner in which they lead to problematic affects and behaviors, and providing guidance on challenging the cognitive distortions they contain. By exercising this kind of vigilance over their automatic thoughts, individuals may learn to acutely address pathological affect and behavior, while gradually recognizing and revising the entrenched beliefs from which they emerge.

CBT has been adapted to address SUDs, most popularly in the relapse prevention therapy (RPT) manual [52]. RPT tailors the CBT approach to addressing SUDs by emphasizing awareness of triggers, both environmental and subjective, that predispose to drug use. This involves conducting a "functional analysis" of the causal relationships perpetuating dependence-related behavior, as well as cultivating distress tolerance and nurturing healthier habits [52]. As with other forms of CBT, RPT is most effective if individuals do not demonstrate cognitive impairments that compromise their capacity to engage fruitfully with treatment; are sufficiently motivated to adhere to the program and practice RPT skills; and are able to adequately cultivate and maintain non-reactivity to cravings, stress, and other triggers [53]. Pharmacological targets to enhance the efficacy of RPT therefore include tenuous motivation for changing drug use, neurocognitive impairment, and heightened reactivity.

In a recent trial, Levin and colleagues tested the hypothesis that extended-release d-amphetamine improves treatment outcomes in cocaine-dependent individuals with attention-deficit hyperactivity disorder (ADHD) [54•]. All participants in this trial received RPT. ADHD is characterized by deficits in neurocognition (e.g., attention, executive functioning), as well as by impaired affect regulation and heightened arousal, that are recognized to be effectively treated by stimulant medications, such as amphetamine [55]. It was therefore thought that providing ADHD individuals with d-amphetamine would improve their response to RPT. Indeed, it was found that the amphetamine group exhibited higher rates of abstinence than did the placebo group [54•]. It remains to be tested, however, whether improvements in reactivity and neurocognitive functioning served to mediate the effect of d-amphetamine on abstinence rates in this population. It also remains to be tested whether this beneficial effect of slow-release amphetamine treatment depends on the patients also receiving RPT, or whether it is independent of the type of behavioral treatment offered.

The benefits of d-amphetamine might optimize behavioral treatment response more broadly, as discussed in the previous section on CM. A step-wise controlled trial is currently being conducted to evaluate whether cocaine dependent individuals who fail to benefit from an initial course of RPT might show a better response if initiated on d-amphetamine while continuing behavioral treatment, even if they do not have ADHD, with the expectation that it will improve certain vulnerabilities that might have compromised RPT response previously (NCT01986075). These vulnerabilities may include neurocognitive deficits [56], as well as the dopaminergic adaptations discussed earlier. As in this ongoing trial with d-amphetamine, more research is needed for clarifying how CBT-based approaches might be effectively optimized by pharmacotherapy, and to continue identifying medications that might serve to address the deficits, including tenuous motivation and high reactivity, which compromise behavioral treatment efficacy.

New Directions

Pharmacotherapy aimed at correcting the adaptations related to SUDs by promoting neuroplasticity represents a novel

treatment approach, with important implications for integrated medication-behavioral treatments. A promising, but unconventional, candidate for promoting plasticity and improving SUD-related deficits is the NMDA antagonist and widely used dissociative anesthetic ketamine. Recent findings with ketamine signal new directions for how medication and behavioral treatment for SUDs might be feasibly integrated.

Though the psychiatric effects of NMDA modulation were first predicted more than two decades ago [57], ketamine is the first NMDA antagonist to demonstrate efficacy in humans. A single sub-anesthetic infusion has been shown to rapidly improve depression and anxiety, with the effect continuing to grow in magnitude after all metabolites have cleared [58]. It has been proposed widely that ketamine may lead to these unprecedented therapeutic effects because alongside acute modulatory effects on glutamate neurotransmission, it exerts unique down-stream effects on neural plasticity and connectivity. Emerging data suggest that ketamine promotes increased prefrontal synaptic remodeling and neural plasticity through mechanisms involving brain-derived neurotrophic factor (BDNF) and other factors [59–62]. These persistent effects are believed to address problematic prefrontal neuroadaptations and to account for the relatively sustained anti-depressant benefits observed after a single dose.

These unique effects on plasticity may address SUDS, as they do depression, by counteracting the drug-related synaptic deficits discussed above, and restoring healthy prefrontal functioning through neural remodeling [61–63]. Recent research indicates that ketamine improves dopamine signaling in rodents experiencing withdrawal from amphetamines [64], and preclinical data suggest that the promotion of neural plasticity in the prefrontal cortex via mechanisms related to BDNF reduces cocaine self-administration [65]. Other down-stream effects of ketamine include modulation of neural networks [60, 66]. Ketamine may regulate ACC activity [67], which some evidence suggests might serve to reduce impulsivity [68] and the risk of relapse [69]. It has also been observed that ketamine modulates (24 h post-infusion) default-mode connectivity and excitability [66], which have been shown to be altered in SUDs and may be associated with craving [70, 71].

Consistent with these preclinical findings, ketamine has demonstrated promising effects for a variety of SUDs. Laboratory investigations with cocaine dependent individuals indicate that a single sub-anesthetic infusion of ketamine significantly reduces two vulnerabilities associated with neural adaptations: cue-induced craving and low motivation for non-drug rewards [72]. Ketamine has also been shown to reduce cocaine self-administration in a human laboratory model designed to detect shifts in the relative value of cocaine now vs. money later [73]. In a series of preliminary trials investigating intramuscular ketamine integrated with an existential framework intended to promote healthier values, behaviors, and beliefs, Krupitsky and colleagues found that ketamine improved outcomes for individuals with alcohol and opioid use disorders, with substantially higher rates of abstinence in the ketamine group, as compared to the control [74, 75]. While these results may have little bearing on whether ketamine holds promise for cocaine or cannabis use disorder, they provide examples of how ketamine might be integrated into addiction-oriented behavioral treatments so as to leverage its benefits into sustained behavioral changes, such as abstinence. Indeed, ketamine is currently being tested in a randomized 5-week trial for cocaine dependence; the primary outcome is end-of-study abstinence in individuals engaged in mindfulness-based relapse prevention, a modified form of RPT that facilitates mindful (e.g., non-reactive, accepting, and deliberate) awareness and the attendant shifts in perspective and values (clinicaltrials.gov NCT01535937).

These preliminary findings indicate that ketamine represents a novel and promising approach to addressing some of the deficits related to dependence-related neural adaptations, and that a single infusion may serve to provide long-term benefit for SUDs in the context of behavioral treatments with which synergy is possible, including possibly CM and CBT. Research is needed to continue clarifying the efficacy of this approach, as well as to evaluate the effectiveness of related compounds operating through similar pro-plasticity and modulatory mechanisms, such as d-cycloserine, , and an emerging class of glutamatergic modulators modeled on ketamine, including the glyxins (specific NMDA receptor subunit modulators also referred to as GLYX compounds) [76–79].

It is interesting to consider the aim of behavioral therapies that were combined with ketamine in these preliminary investigations [72–75]. The existential therapy in Krupitsky's work aimed at changing values and beliefs, and in more recent trials with ketamine, a mindfulness-based framework is employed. Both of these can be viewed as aimed at changing a patient's perspective on him/herself. This contrasts with CM and CBT approaches, which focus on responding to alternative rewards, and fostering cognitive control, respectively. There has also been a re-emergence of interest in the therapeutic potential of serotonergic hallucinogens, such as psilocybin [80, 81], where it is hypothesized that the pharmacotherapy assists patients in achieving fundamental changes in their views of themselves in the world. This raises the possibility that it is not the specific pharmacodynamic mechanism, glutamatergic, or serotonergic, but rather the experience of altered consciousness occasioned by the pharmacotherapy which allows patients to emerge with different values and motivations that may translate into changes in behavior. Indeed, a recent analysis suggests that mystical-type experiences, but not dissociative effects, mediated the effects of ketamine on motivation to quit [82]. This is consistent with the hypothesis, first articulated by William James, that certain non-ordinary, spiritual experiences are associated with dramatic changes in perspective and values, and that these experiences may lead to enduring personal benefits [83].

Conclusions

Though effective medication options for SUDs, and particularly cannabis and cocaine use disorders, remain elusive, recent research demonstrates the utility of integrative approaches that pair pharmacotherapy exerting promising effects on dependence-related deficits with potentially synergistic behavioral treatments. Alongside neurocognitive impairments, deficits that might jeopardize attempts at behavioral modification include drug-related glutamatergic and dopaminergic adaptations, which may manifest as blunted reward sensitivity, heightened behavioral reactivity, and craving. Emerging data suggest that addressing these deficits through dopamine agonists, including L-dopa and amphetamine, serves to optimize response to CM and RPT in cocaine-dependent individuals, and that NAC may work to improve response to CM in cannabis dependence by normalizing glutamate homeostasis at the nucleus accumbens. New findings with ketamine suggest that its pro-plasticity and modulatory mechanisms may extend beyond anti-depressant and anti-anxiety efficacy to address SUDs, perhaps by promoting prefrontal inhibition of limbic structures and improving dopamine signaling through down-stream effects. Further, there may be psychological mechanisms pertaining to the psychoactive effects of medications like ketamine, and that might be leveraged into sustained behavioral changes when embedded in a therapeutic framework aimed at facilitating perspectival shifts. These data provide hope for better addressing these often intractable disorders and outline new directions for pharmacotherapy research and combined medication-behavioral treatments.

A significant methodological limitation that might be addressed by future research is that most of the studies reviewed above examined a medication versus medication control conditions, in the setting of one particular behavioral therapy. This provides only suggestive evidence that the specific behavioral therapy is important to the beneficial effect of the medication, through some putatative synergy. Only a few studies have implemented two-way factorial designs, where patients are randomly assigned to medication and placebo control, and also randomized to one of two behavioral treatments. This type of design provides direct evidence around whether a specific behavioral treatment is important to the effect of the medication, by examining the interaction of medication condition by behavioral therapy condition. Medication treatments always take place in some type of therapeutic context, if only that of a supportive clinician-patient relationship. Research on developing medications for substance use disorders might be advanced by thinking more deeply around which type of behavioral intervention might synergize best with the medication, and testing for such synergy with two-way designs.

Compliance with Ethical Standards

Conflict of Interest Elias Dakwar and Edward V. Nunes declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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