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Combination Pharmacotherapies for Stimulant Use Disorder: A Review of Clinical Findings and Recommendations for Future Research

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Abstract

Despite concerted efforts to identify a pharmacotherapy for managing stimulant use disorders, no widely effective medications have been approved. Innovative strategies are necessary to develop successful pharmacotherapies for stimulant use disorders. This manuscript reviews human laboratory studies and clinical trials to determine whether one such strategy, use of combination pharmacotherapies, holds promise. The extant literature shows that combination pharmacotherapy **produced results that were better than** placebo treatment, especially with medications shown to have efficacy as monotherapies. However, many studies did not compare individual constituents to the combination treatment, making it impossible to determine whether combination treatment is more effective than monotherapy. Future research should systematically compare combined treatments with individual agents using medications showing some efficacy when tested alone.

Keywords

Cocaine; Amphetamine; Pharmacotherapy; Human Laboratory Study; Clinical Trial

Stimulant use disorders are an unrelenting public health concern. Data from the National Survey on Drug Use and Health indicate that approximately 1.6 million Americans over 12 years of age report current (i.e., past month) cocaine use, making cocaine the most widely used stimulant in the United States [1]. That same survey indicated that approximately 440,000 Americans report current methamphetamine use and that 1.2 million Americans report current non-medical use of prescription stimulants, including d-amphetamine and mixed amphetamine salts. Of the individuals reporting illicit use, 1.1 million people met cocaine abuse or dependence criteria whereas 535,000 met general stimulant abuse or

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dependence criteria. Despite prevention and intervention efforts, prevalence of stimulant use and stimulant use disorders has remained relatively stable (e.g., the number of Americans who meet cocaine abuse or dependence criteria has hovered between 1 and 1.5 million for the past 10 years; [1]). The stable prevalence of problematic use (i.e., stimulant abuse or dependence) indicates that novel approaches ae necessary to help treatment seekers to stop using.

Chronic stimulant use by those with stimulant use disorders produces a number of direct health problems like cardiovascular toxicity, malnutrition or miscarriage in pregnant women [2,3,4,5,6,7]. Stimulant use disorders also increase risks for other health issues including smoking cigarettes, comorbid psychological disorders and acquiring and transmitting sexually transmitted infections [3,4,8,9,10]. Research that identifies promising therapies for stimulant use disorders will thus have significant public health implications beyond reducing the prevalence of illicit stimulant use and the social and legal issues associated with drug use in general [11]. A substantial amount of research has been conducted to develop pharmacotherapies to manage stimulant use disorders and their attendant health and societal concerns, without identifying a widely effective treatment.

A range of medications has been tested for treating stimulant use disorders, including antidepressants [12], anticonvulsants [13], antipsychotics [14] and monoamine agonists [15,16,17,18,19] for a general review of treatments for amphetamine use). The studies testing these medications have generally used them as single agents (i.e., monotherapies) and most have failed to demonstrate benefit relative to placebo for treating stimulant disorders. For example, antidepressants, as a class, do not reliably promote cocaine abstinence in clinical trials [12]. Greater efficacy may be observed for the tested medications at higher doses, but the emergence of side effects that could be dangerous or limit compliance prevent escalation to these doses. Other monotherapies, especially dopamine agonists, have **consistently displayed** efficacy for promoting stimulant abstinence [16,17,18]. Dopamine agonists are likely effective because they function as replacement medications, similar to methadone for opioid use disorder [20]. Unfortunately, the use of dopamine agonists for managing stimulant use disorders has met with resistance due to concerns regarding their abuse liability [21,22]. Given the lack of efficacy for many tested monotherapies and the resistance to adoption of others that have demonstrated some efficacy, innovative strategies are necessary for developing pharmacotherapies to treat stimulant use disorders.

Combining medications, either as add-ons to initial monotherapy or from the outset of treatment, is a strategy for many physical and psychiatric disorders, including human immunodeficiency virus [23], obesity [24], diabetes [25], hypertension [26], depression [27] and bipolar disorder [28]. Extending the use of combined pharmacotherapies to stimulant use disorder represents an innovation that may surmount some of the problems noted above. First, combining two medications at lower doses may reduce stimulant use while eliminating the risk of increased side effects with higher doses. The results of an elegant preclinical study demonstrate that the combination of low doses of two different drugs is an effective strategy to manage stimulant use disorders and avoid the untoward effects of the constituent compounds [29]. That study showed that combining low doses of the benzodiazepine

oxazepam and metyrapone, a corticosterone synthesis inhibitor, decreased cocaine self-administration. Importantly, the doses that were effective when combined, were ineffective at reducing cocaine taking when administered alone.

Second, combining two medications with **some** efficacy as monotherapies when tested preclinically or clinically may result in additive or synergistic reductions in stimulant use. Amphetamine isomers **reduce** cocaine use [30,31,32], but there is substantial room for improvement because not all patients achieve abstinence nor is a complete elimination of cocaine taking observed during active drug maintenance. Topiramate has also displayed some efficacy for treating cocaine use disorder [33,34]. Combining medications that promote cocaine abstinence to some extent when administered alone could better promote abstinence in more patients or completely eliminate cocaine taking altogether.

Third, as described below, cocaine and amphetamine produce their effects via interaction with a number of neurotransmitters, including dopamine, serotonin, norepinephrine and glutamate [35,36,37,38,39,40]. Using multiple pharmacotherapies with diverse pharmacological effects can more effectively target these systems to better manage cocaine or amphetamine use disorder than monotherapies that target a single neurotransmitter system.

Given the need for novel pharmacotherapeutic strategies for managing stimulant use disorder, and the strong rationale for testing combined treatments, the purpose of this manuscript is to review the extant clinical research on this topic. Because fairly little research has been conducted using this approach, we also provide recommendations for future human laboratory studies and clinical trials. Articles were initially identified through PubMed searches and review of references within identified articles. Only blinded, placebo-controlled, randomized studies were included for review. The outcomes for the clinical trials identified were diverse, including biologically verified cocaine abstinence (i.e., cocaine or benzoylecgonine negative urine samples), self-reported cocaine abstinence, trial retention, drug craving and withdrawal. Drug craving was typically assessed using standardized self-report measures asking questions about whether subjects wanted, craved or desired cocaine [41]. Drug withdrawal was also typically assessed using self-report measures examining changes in mood (e.g., irritation), as well as physical symptoms (e.g., headache) [42]. Results of a recent study indicate that biologically verified cocaine abstinence or percent of days abstinent may be better measures of clinical intervention success for cocaine dependence than trial retention, complete cocaine abstinence or reduced frequency of cocaine use [43].

A number of other studies were identified in which opioid-maintained patients received a pharmacotherapy for stimulant use disorder [31], however, these experiments are not reviewed because a placebo opioid maintenance condition could not be included. There are also several studies that have tested the efficacy of combined levodopa/carbidopa for reducing stimulant use [44], but these were also not reviewed as carbidopa is only included to enhance the ability of levo-dopa to cross the blood brain barrier. Both of these drugs only target a single neurotransmitter system, dopamine, which is not in keeping with one of the rationales for testing combined treatments described above.

Combination Pharmacotherapies for Cocaine Use Disorder

A range of combined pharmacotherapies has been tested for managing different aspects of cocaine use disorder **(see Table 1)**. The combinations tested included constituent medications that have **generally** shown some efficacy on their own (e.g., d-amphetamine; [31], consistent with the idea that combining two effective medications may produce a synergistic improvement in the selected outcomes. Constituent drugs in the combinations have also had distinct pharmacological targets because cocaine interacts with diverse and numerous neurotransmitter systems. The primary abuse-related effects of cocaine have been attributed to the ability of cocaine to block reuptake of dopamine [39], so it is not surprising that many of these studies tested dopamine agonists (e.g., d-amphetamine, bromocriptine).

Cocaine also effectively blocks reuptake of norepinephrine, which **may** contribute to continued cocaine use [40,45]. Although the role of norepiphrine in cocaine taking remains to be determined and studies have failed to show an effect for some noradrenergic antagonists [46], **other noradrenergic agents** like propanolol and desipramine have been tested **in the studies reviewed here**. Although the abuse-related effects of cocaine have primarily been attributed to the ability of cocaine to block monoamine reuptake [35], cocaine also interacts with the glutamate system and can produce lasting impairments in glutamatergic functioning that contribute to relapse [37]. Modafinil, a drug that produces its effects via interaction with a number of neurotransmitter systems including glutamate [47,48] has been tested in one clinical trial, as described below.

In addition to testing medications that directly interact with neurotransmitter systems impacted by cocaine, other strategies have indirectly targeted these systems by administering medications that produce downstream effects in brain monoamine and glutamate systems. Most commonly, gamma-aminobutyric acid (GABA) and endogenous opioid modulating drugs (e.g., oxazepam and naltrexone, respectively) have been tested because brain monoamine tone is under the control of both GABA and opioid systems [49,50]. Finally, other strategies have targeted cocaine/dopamine metabolism (e.g., disulfiram), monoamine synthesis (e.g., ltryptophan, l-tyrosine), stress response (e.g., metyrapone) or the pressor effects of cocaine (e.g., isradipine). Taken together, the overall hypothesis of these studies has been to test combinations of medications with multiple neuropharmacological targets (e.g., testing d-amphetamine with topiramate, a drug with GABAergic and glutamatergic activity; [51] in order to more effectively treat cocaine use disorder. Unless specifically indicated below, the doses of the individual constituents that were tested are the same as those tested in the combined condition.

Human Laboratory Studies of Combination Treatments for Cocaine Use Disorder

We know of two human laboratory studies that assessed the impact of putative combined pharmacotherapies on the pharmacodynamic effects of cocaine in humans, both of which used double-blind, placebo-controlled, repeated measures designs [52,53]. In the more recent study, subjects diagnosed with a cocaine use disorder (N=8) were maintained on oral placebo or combined amantadine (a dopamine and glutamate releaser; 300 mg/day) and baclofen (a $GABA_B$ agonist; 90 mg/day) for 5 days before completing experimental sessions in which intravenous doses of cocaine (0, 20 and 40 mg) were administered [52].

Intravenous cocaine produced prototypic effects, increasing heart rate and blood pressure and subjective measures like High. During maintenance on the combination, subjective ratings of Desire to Use Cocaine were significantly attenuated relative to placebo maintenance.

In the earlier study, seven cocaine-using subjects first received **an acute pretreatment of** oral placebo, naltrexone (a mu opioid receptor antagonist; 50 mg), isradipine (a calcium channel blocker; 10 mg) or combined naltrexone and isradipine. Subjects then received intranasal cocaine (4 mg [placebo] or 100 mg/70 kg) [53]. Intranasal cocaine produced prototypic effects, increasing heart rate and blood pressure and subjective measures like High. Pretreatment with isradipine, alone or in combination with naltrexone, attenuated the pressor effects of cocaine, with greater reductions observed following administration of the combination. Pretreatment with naltrexone alone, but not in combination with isradipine, attenuated subject ratings of Good Effects produced by cocaine.

Clinical Trials of Combination Treatments for Cocaine Use Disorder

Seven blinded, placebo-controlled, randomized clinical trials have tested medication combinations for treating cocaine use disorder. Four of these studies selected cocaine abstinence, verified by negative urine benzoylecgonine screens, as the primary outcome variable [51,54,55,56], whereas three studies tested the efficacy of combinations to alleviate symptoms of cocaine withdrawal and/or reduce cocaine craving [42,57,58]. In the earliest study testing a combination to promote cocaine abstinence, treatment seeking cocaine dependent subjects (N=199) were enrolled in a 10-week study in which they were assigned to placebo, amantadine (300 mg/day), propranolol (a beta blocker; 100 mg/day) or combined amantadine and propranolol [54]. Using an intent-to-treat analysis revealed no differences in cocaine abstinence across treatment groups. A subsequent analysis revealed that propranolol alone increased both cocaine abstinence and treatment retention in highly adherent subjects, indicating that the combination treatment may have failed in the larger study population due to low adherence with the medication regimen.

The next study evaluated the effects of placebo, disulfiram (an aldehyde dehydrogenase and dopamine beta hydroxylase inhibitor; 250 mg/day), naltrexone (100 mg/day) and combined disulfiram and naltrexone on cocaine use in 208 co-morbid cocaine and alcohol dependent subjects **in an 11-week trial** [55]. Although both disulfiram and naltrexone are approved for treating alcohol dependence, the authors of this study note that disulfiram was selected for its potential utility to reduce cocaine use and naltrexone was selected to reduce alcohol use. As with the earlier study, primary analysis revealed no significant differences in cocaine use across treatments. In fact, cocaine use increased in all groups over time. Subsequent analysis revealed that disulfiram maintenance, alone or in combination with naltrexone, was more likely to result in abstinence from both cocaine and alcohol. The reasons for the lack of efficacy for the combined treatment are unknown, but, as noted in the manuscript, could be due to limited adherence to the medication regimen.

The study conducted by Mariani et al. [51] compared the effects of placebo with mixed amphetamine salts (a dopamine **and** norepinephrine releaser that also releases serotonin, but with a much lesser degree of selectivity than for dopamine and norepinephrine; 60 mg/day)

combined with topiramate (a GABA agonist and glutamate antagonist; 300 mg/day) in 81 cocaine dependent subjects over a 14-week trial. The group receiving active treatment was twice as likely to achieve three consecutive weeks of cocaine abstinence than the placebo group. Lastly, Schmitz and colleagues compared placebo to modafinil (a dopamine reuptake inhibitor, glutamate agonist and GABA inhibitor; 400 mg/day), d-amphetamine (a dopamine **and** norepinephrine releaser that also releases serotonin, but with a much lesser degree of selectivity than for dopamine and norepinephrine; 60 mg/day) and combined modafinil (200/mg/day) and d-amphetamine (30 mg/day) in 73 cocaine dependent subjects across a 16-week trial. The results of that study suggest that the combined treatment increased cocaine use while placebo and d-amphetamine alone decreased cocaine use across time. The reasons for the failure of the combined treatment to reduce cocaine use are unknown, but may be due to testing lower doses of d-amphetamine and modafinil in the combination relative to the doses for the individual constituent conditions. As with the other trials reviewed above that did not show efficacy for combined treatments, poor adherence to the medication regimen is also cited as a potential problem in this report.

In the earliest study that examined medication combinations for reducing cocaine withdrawal, 36 cocaine users were randomized to receive placebo, bromocriptine (a dopamine and serotonin agonist; 2.5 mg/day) or bromocriptine combined with desipramine (a norepinephrine reuptake inhibitor; 200 mg/day) over a 99-day trial [57]. Bromocriptine dosing only occurred for the first 30 days of the study in both groups receiving active treatment. Active treatment with bromocriptine, alone or in combination, reduced cocaine withdrawal symptoms rated on the Brief Psychiatric Rating Scale relative to placebo. This improvement persisted after cessation of bromocriptine in both groups receiving active treatment, but combined treatment resulted in greater improvement, indicating a benefit for desipramine added to the bromocriptine regimen. The next study compared cocaine withdrawal and craving in 50 inpatient cocaine dependent subjects who were randomized to receive placebo or l-tryptophan (the precursor to serotonin; 1 g/day) combined with l-tyrosine (the precursor to dopamine; 1 g/day) over 4 weeks [42]. There was no effect of treatment, relative to placebo, in cocaine withdrawal or craving. The reasons for the failure of combining these neurotransmitter precursors for reducing cocaine withdrawal and craving are unknown, but, as suggested in the manuscript, may be due to the limited clinical efficacy of the individual constituents for reducing cocaine withdrawal and craving.

In the most recent study, 45 cocaine dependent subjects were randomized to placebo, metyrapone (a cortisol inhibitor; 500 mg/day) combined with oxazepam (a positive $GABA_A$ modulator; 20 mg/day) or metyrapone (1500 mg/day) combined with oxazepam for 6 weeks [58]. Cocaine craving was not reduced significantly in any treatment group across the full trial. However, subsequent analyses indicated that cocaine craving was decreased at several time points in the groups receiving active treatment relative to placebo. Cocaine abstinence was also significantly increased at the end of the study in the high-dose metyrapone group relative to placebo.

Summary

The studies reviewed above **show that** combining medications for treating cocaine use disorder produces better results relative to placebo, but greater effectiveness for combined treatments relative to monotherapies has yet to be demonstrated. For example, both human laboratory studies showed benefits of combined treatments over placebo for attenuating either the abuse-related subjective [52] or pressor [53] effects of cocaine. Only naltrexone alone reduced the abuse-related subjective effects of cocaine in the earlier study [53], however. Some of the clinical trials also showed greater efficacy for combined treatments relative to placebo on the selected primary outcome variables [51,57,58], but the utility of combined treatments was not supported by the outcomes of other clinical trials [42,54,55,56].

Due to the diverse range of tested medications and combinations, as well as the fact that no studies repeated exact combinations, discerning a pattern to the pharmacological systems targeted by successful combined pharmacotherapies is difficult. Two studies showed that combining a monoamine agonist with a GABA agonist successfully reduced cocaine use or attenuated the abuse-related subjective effects of cocaine [51,52]). Using monoamine agonists for treating cocaine use disorder is further supported by the consistent finding that amphetamine isomers reduce cocaine use in clinical trials [30,31,32,56]. Using GABA agonists for treating cocaine use disorder is also further supported by trials demonstrating modest efficacy of these compounds alone (i.e., topiramate; [33,34]) or in combination with other drugs (i.e., oxazepam with metyrapone reduced craving and cocaine use; [58]. Continued evaluation of monoamine and GABA agonists as mono- and combined therapies is clearly warranted.

One caveat to the studies reviewed above is that those which demonstrated efficacy for the combined treatments generally did not test all constituent medications alone [51,52,57,58] making it impossible to ascertain the unique effects produced by the individual compounds. Thus, whether the combination produced superior results to the constituents remains largely unknown. There has also not been any sequential work that has first screened medication combinations in the human laboratory then moved the most promising agents into clinical trials, which limits the ability to identify constituents or combinations that have shown promise across a range of measures and are worthy of further investigation. Addressing both of these gaps represents important future directions as described below.

Combination Pharmacotherapies for Amphetamine Use Disorder

There has been substantially less research examining the efficacy of combined medications for treating amphetamine use disorder compared to the research with cocaine **(see Table 2)**. Consistent with the cocaine literature, selected constituent drugs have **generally** demonstrated some efficacy for reducing amphetamine use (i.e., naltrexone promoted amphetamine abstinence as a monotherapy; [59,60]) and the combinations have had distinct pharmacological targets because amphetamine also interacts with diverse and numerous neurotransmitter systems. The primary abuse-related effects of amphetamine isomers have been attributed to the ability of amphetamines to release monoamines like dopamine and serotonin [35,38], but none of the extant studies have directly targeted monoamine systems.

Amphetamines also increase glutamate levels [36], so several studies have tested drugs that "normalize" glutamatergic function (i.e., n-acetylcysteine) or reduce brain glutamate levels (i.e., gabapentin). Again, as with cocaine, other studies have used the strategy of indirectly targeting brain monoamine systems by using GABAergic (i.e., alprazolam, flumazenil, gabapentin) or opioidergic (i.e., naltrexone) drugs. Taken together, the overall hypothesis of these studies has also been to test combinations of medications that activate multiple targets (e.g., testing alprazolam combined with naltrexone; [61]) in order to more effectively treat amphetamine use disorder.

Human Laboratory Study of Combination Treatments for Amphetamine Use Disorder

We know of one human laboratory study that assessed the effects of putative pharmacotherapies in combination with amphetamine in humans [61]. In this double-blind, placebo-controlled, randomized study, eight subjects with a stimulant use disorder first received **an acute pretreatment of** oral placebo, naltrexone (50 mg), alprazolam (a positive $GABA_A$ modulator; 0.5 mg) or combined naltrexone and alprazolam. Subjects then received oral d-amphetamine (0, 15 or 30 mg). Oral d-amphetamine produced prototypic effects, increasing blood pressure and subjective ratings like Good Effects. Pretreatment with naltrexone alone enhanced the diastolic pressor effects, whereas pretreatment with alprazolam or the combination reduced the systolic pressor effects, of d-amphetamine. Pretreatment with each of the individual drugs attenuated the subjective effects produced by d-amphetamine, especially those of the lower dose, but significant reductions were observed on a greater number of subjective ratings following pretreatment with the combination of naltrexone and alprazolam.

Clinical Trials of Combination Treatments for Amphetamine Use Disorder

Three blinded, placebo-controlled, randomized clinical trials have tested medication combinations for treating amphetamine use disorder. All of these studies examined the ability of these combinations to promote amphetamine abstinence, verified by negative urine amphetamine screens, but other variables like amphetamine craving were also measured [62,63,64]. In the earliest study, treatment seeking methamphetamine dependent subjects (N=31) were enrolled in an 8-week study in which they were assigned to placebo or naltrexone combined with n-acetylcysteine (a ligand at the glutamate/cysteine antiporter that increases reuptake of glutamate) [62]. The starting dose for naltrexone was 50 mg/day and the starting dose for n-acetylcysteine was 600 mg/day. Doses were increased throughout the trial to a final dose of 200 mg naltrexone/2400 mg n-acetylcysteine/day in the final 2 weeks. All subjects experienced improvement during the trial, but, due to a very small sample size, there were no statistically significant differences between the treatment groups on any outcome measure. Reductions in amphetamine use and amphetamine craving were greater in subjects receiving active treatment, however.

The two more recent trials evaluated the primary constituents in the proprietary Prometa® treatment in methamphetamine dependent subjects [63,64]. Ling and colleagues randomized 120 subjects to receive the placebo condition (the antihistamine hydroxyzine only; 50 mg/day for the first 10 days of the trial) or the active condition of gabapentin (a GABA agonist that also reduces brain glutamate levels; target dose of 1200 mg/day), flumazenil (a

benzodiazepine receptor antagonist; 5, 2 mg infusions) and hydroxyzine over a 40-day trial [63]. Improvements were seen on outcome variables including amphetamine use and craving after treatment across groups, but there were no between group differences. The study by Urschel and colleagues enrolled 135 subjects into a similar dosing protocol with the exception that the placebo group did not receive active hydroxyzine and the evaluation period was 30 days long [64]. Both groups improved on amphetamine use and craving throughout the study comparing baseline to day 30 measures, but active treatment produced significantly greater reductions on these outcomes relative to the placebo group.

Summary

Two of the four studies reviewed above showed that combination treatments resulted in significantly better outcomes relative to placebo [61,64], while the other two did not [62,63]. Only one study actually tested the combination and constituents alone, with the results indicating that the combination was more effective than the individual drugs in attenuating the effects of d-amphetamine [61]. Of note, two of the studies tested the same combined treatment, but produced conflicting results [63,64]. The reason for the differences between those two studies is unknown but may be due to trial duration or administration of hydroxyzine. Clearly, more research is necessary for testing and developing combination treatments for amphetamine use disorder. One common feature to the studies showing efficacy of the combination was the use of GABAergic agents, which would suggest that including a GABA modulator as one of the constituent compounds is a particularly promising avenue for future studies. Caution should be used in taking this path, however, because Ling and colleagues did not demonstrate a superior effect relative to placebo for the same regimen that reduced amphetamine use in the study by Urschel and colleagues. Naltrexone demonstrated efficacy in the human laboratory study, consistent with previous findings [59,60]). The clinical trial testing naltrexone with n-acetylcysteine [62] also demonstrated reduced amphetamine use in the active treatment group, but due to a very small sample size, the study was underpowered to detect statistical significance. These findings encourage the continued evaluation of naltrexone as a mono- or combination therapy for amphetamine use disorder, albeit with appropriately powered studies.

The methodological concerns identified for the cocaine studies are similar to those for the amphetamine studies. Three of the four studies reviewed did not compare the individual constituents to the combined treatment [62,63,64] and no sequential work has been conducted translating human laboratory work into clinical trials. Addressing these important concerns as a field will help to better identify effective combined treatments for managing stimulant use disorders.

Expert Commentary and Five-Year View

Stimulant use disorders remain a pervasive public-health concern. A widely effective pharmacotherapeutic adjunct has yet to be identified and approved for reducing or eliminating stimulant use. The clinical literature reviewed above suggests that combined treatments may be a viable option for managing stimulant use disorders. In this section we consider: 1) the outcomes of the extant research, 2) strengths and weaknesses of the extant research that can guide study design for future work in this area, 3) the safety and

tolerability of combined treatments for stimulant use disorder, 4) constituents and combinations that warrant further investigation and 5) a five-year view for development of combined treatments for stimulant use disorder.

Outcomes of Extant Research

The majority of clinical studies reviewed above demonstrated that combination treatments had **better** efficacy **than** placebo on selected outcomes [51,52,53,57,58,61,64], indicating that this strategy has some promise for managing stimulant use disorders. However, the superiority of combination treatments relative to monotherapies has yet to be determined, because only a small subset of those studies evaluated the effects of the individual constituents [53,61]. **This methodological problem leaves** the question of whether the combined treatments are more effective than their constituents alone essentially unanswered. Only **one** study showed greater efficacy (i.e., reduction of a greater number of positive subjective effects) for the combined treatment condition relative to the individual treatment conditions [61]. Several of the studies that did not demonstrate efficacy for the combined treatments showed that individual constituents significantly reduced drug taking [54,56], further supporting the need to compare the effects of the combined agents to those of individual compounds alone. In the next section, this design consideration, as well as a number of others, are outlined to guide future work.

Strengths and Weaknesses of Extant Research: Guidance for Future Work

Given the fairly recent interest in developing combined treatments for stimulant use disorders, it is important to identify the strengths and weaknesses of the extant research and provide guidance on the design of future work to better ensure a successful outcome. One of the primary strengths of the reviewed studies is the use of diverse and numerous outcome measures to evaluate the efficacy of the combined treatments for stimulant use disorder. Keeping with convention, the human laboratory studies measured a range of pharmacodynamic outcomes including subjective and cardiovascular effects [52,53,61]. Most of the clinical trials also evaluated numerous outcomes, including biologically verified stimulant use, self-reported stimulant use, combined alcohol and stimulant use, trial retention, craving and withdrawal [54,55,58,62]. The gold standard of efficacy for clinical trials of pharmacotherapies for stimulant dependence has been for putative treatments to promote sustained abstinence (e.g., three consecutive weeks of biologically verified abstinence from cocaine; [51]. Questions have recently arisen about whether complete drug abstinence “sets the bar too high” and has contributed to our inability to identify an effective pharmacological treatment [43,65,66]. These questions are especially germane to the development of combined treatments because a number of the studies reviewed above only showed efficacy for tested treatments with sub-analysis in adherent patients or at specific time points in the trial [54,58].

Complete abstinence is a common goal for comprehensive 12-step type programs, but a different outcome like **increased percentage of days abstinent** may be a better achievable and thus more clinically relevant endpoint for pharmacotherapies [43]. Adoption of different endpoints to define success of medications has been proposed in the treatment of other health problems [67,68], so such a change for substance use disorder research would not be

unprecedented. The onus is on researchers in the field of medications development for drug use disorders to define and empirically support an appropriate endpoint as we move forward in the approval process for putative combined pharmacotherapies.

Other strengths of the extant research that should continue to be included in future projects are the selection of placebo-controlled, randomized designs and testing of agents that have at least some efficacy for reducing or eliminating stimulant use as monotherapies either preclinically or clinically. These design features will allow for more conclusive determinations to be made about the efficacy of combined treatments and better ensure success because there is no evidence that combining completely ineffective agents would result in any benefit for stimulant using individuals [42]. Testing pharmacotherapies shown to be ineffective as individual constituents also presents ethical and safety concerns.

The primary methodological weakness of many of the studies reviewed above is that they did not test the individual constituents against the combined condition with a factorial design [42,51,52,57,58,62,63,64]. As an example, the study conducted by Mariani and colleagues showed the efficacy of mixed amphetamine salts combined with topiramate, but did not test the constituent drugs alone, making it impossible to determine whether one or both of these drugs contributed to the successful outcome. The doses of amphetamine (60 mg/day) and topiramate (150 mg/day) tested in combination are similar to those tested alone in previous studies and show similar efficacy to outcomes when the drugs were tested as single constituents [30,31,34].

Although we recognize that including these additional conditions adds to study complexity and cost, both human laboratory studies and clinical trials have been able to implement a completely factorial design [54,61]. Using complex, full factorial designs to evaluate treatments of different modalities is not uncommon in developing therapies for stimulant use disorder [69,70,71,72,73]. For example, in one clinical trial, 161 cocaine dependent subjects were randomized to receive levodopa/carbidopa or placebo combined with different “doses” of behavioral intervention: clinical management, clinical management with cognitive behavioral therapy or clinical management, cognitive behavioral therapy and voucher-based reinforcement therapy [72]. Active medication treatment combined with the three behavioral treatments was most effective in promoting cocaine abstinence. Using a fully factorial design with two medications should not be perceived as any more difficult or resource intensive than combining treatment of different modalities. Thus, in order to most effectively demonstrate the superiority of combined treatments, future research should include both the combination and individual constituents as conditions.

One way to most efficiently implement this design recommendation is to have a more systematic pipeline of development for combined treatments, which also addresses a weakness of the extant research in that very little translational work has been conducted moving from preclinical findings to human laboratory studies as an initial screen for a range doses of effective combinations, then moving the most promising agents into more costly clinical trials. Human laboratory studies, especially those that examine the reinforcing effects of stimulants, are ideally suited to determine initial efficacy and are a critical component of medications development efforts for at least four reasons. First, the initial

safety and tolerability of a potential medication in combination with the drug of abuse can be determined prior to studying it in a larger group enrolled in a clinical trial. Second, this research can be conducted efficiently, which allows it to serve as a screen for potential medications prior to testing in larger clinical trials. Self-administration procedures in the human laboratory have particularly good predictive validity for clinical trial outcomes, bolstering the screening role of human laboratory research. Although none of the human laboratory studies reviewed above included a self-administration component, the strong predictive validity for medication efficacy of these outcomes relative to subjective effects [74,75] suggests that future human laboratory screening for combination treatments must include measures of drug reinforcement. Third, appropriate controls can be used in human laboratory research, which helps refine medication development efforts. For example, targeted populations, drug doses or drug combinations can be studied in the human laboratory prior to investing in clinical trials targeting these groups, maximizing the chance for success. Such research can also provide insight into naturalistic determinants of drug use that may not be readily observable in larger clinical trials without extensive sub-analyses.

A final weakness noted by many of the clinical trials above [54,55,56] is limited adherence to medication regimen. Not taking medications as prescribed is a common problem across clinical conditions and increases health care costs [76], so it is not surprising that poor adherence is also observed in clinical trials for stimulant use disorder [32,54,55,56]. Poor adherence not only increases the likelihood and cost of health problems, it also reduces the ability of clinical trials to accurately identify effective treatments for managing stimulant use disorders. Future research should explore and develop methods to improve adherence to medication regimens in patients with stimulant use disorder [77].

Safety and Tolerability of Combined Treatments

The safety and tolerability of combined stimulant pharmacotherapies is of critical importance, because, as noted in the Introduction, using high enough doses of monotherapies to completely suppress drug use could result in side effects that are clinically significant or limit compliance. The human laboratory studies that provided information about side effects or adverse events indicate that the tested treatments were well tolerated and without incidence of clinically significant events [52,61]. The results of the clinical trials that provided information about side effects or adverse events clearly show that active treatment was associated with greater numbers or more severe ratings of adverse events [51,54,55,56,58,63,64], although one trial showed no difference between groups, which could again be due to small sample size [62]. Although a greater number of side effects or adverse events occurred during active treatment, several of the clinical trials report that the number of subjects reporting adverse events did not differ between placebo and active treatment [58,64]. Unfortunately, because many of these studies did not compare the individual constituents to the combined treatment, it is difficult to determine whether the combined treatments produced a different safety and tolerability profile than the single agents would have. Three studies did evaluate individual constituents and the combined treatments, with mixed results [54,55,56]. In the earliest study, the combined treatment (amantadine and propranolol) resulted in a greater incidence of medication-related, clinically significant adverse events [54]. In the next study, all active treatments increased incidence of

nausea relative to placebo, but only in the combined treatment group (naltrexone and disulfiram) was sexual arousal increased [55]. Lastly, the study by Schmitz and colleagues showed that the greatest incidence of side effects occurred in the d-amphetamine only condition and that adverse events occurred at fairly equal rates in all active treatment groups [56]. The conclusions that can be made about the safety and tolerability of combined pharmacotherapies for stimulant use disorder are limited, but the available data do not necessarily indicate that this strategy is associated with a worse side effect/adverse event profile than monotherapy.

Constituents, Combinations and Strategies Warranting Further Investigation

Evaluation of effective medication combinations for managing stimulant use disorder is a new area of research, and as such, a number of the tested combinations failed to produce promising outcomes. The design of many of the studies does not allow for a determination of whether the combinations tested were more or less effective than constituents alone, so recommendations for constituents and combinations warranting further investigation are made with some hesitation. In our opinion, the constituents that should continue to be tested are those that have consistently demonstrated **at least some** efficacy when used as monotherapies or in combination with other treatments. For cocaine use disorder, this would be monoamine releasers like d-amphetamine or mixed amphetamine salts [30,31,51,56] **combined with** GABA agonists like topiramate [33,34,51] or drugs that work in serotonin systems given that some theoreticians have suggested that a careful balance of dopamine and serotonin release is necessary for medications to most effectively reduce cocaine taking [78]. For amphetamine use disorder, naltrexone **warrants further study** [59,60,61,]. GABA agonists may also hold promise for managing amphetamine use disorder in combination with other medications [61,64].

Because combination treatments are increasingly common for other disorders, we would also advocate for looking to recent successes with combined pharmacotherapies for disorders that share behavioral and neurobiological underpinnings with stimulant use disorders like cigarette smoking [79], obesity [24] and attention deficit/hyperactivity disorder [8]. Lastly, in the studies reviewed above, medications were combined from the outset of treatment for the studies, so add-on pharmacotherapy based on initial response to monotherapy represents an additional important avenue of research that would model strategies taken with other disorders like hypertension and depression.

Five-Year View

Over the next 5 years, we envision that progress will have been made in identification of effective combined pharmacotherapies for stimulant use disorders, especially because some of the recommendations made here will have been adopted. We particularly look forward to development of a more systematic pipeline between human laboratory screening models and clinical trials, as well as the use of full factorial designs that evaluate the efficacy of placebo, individual constituents and combined treatments on a range of outcomes (e.g., negative drug urine screens, percent of days abstinent). This process will still be in its infancy, however, because a long timeline is necessary for full approval of pharmacotherapies for managing drug use disorders. Approval of buprenorphine for managing opioid dependence took nearly

20 years. We envision that the most promising candidate combinations will only be entering Phase III trials to demonstrate widespread efficacy within this 5-year time frame.

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References

1. Substance Abuse and Mental Health Services Administration. Results from the 2012 national survey on drug use and health: National findings. Office of Applied Studies; Rockville: 2013.
2. Chen K, Scheier LM, Kandel DB. Effects of chronic cocaine use on physical health: A prospective study in a general population sample. Drug Alcohol Depend. 1996; 43:23–37. [PubMed: 8957140]
3. Hando J, Howard J, Zibert E. Risky drug practices and treatment needs of youth detained in New South Wales Juvenile Justice Centres. Drug Alcohol Rev. 1997a; 16:137–145. [PubMed: 16203420]
4. Hando J, Topp L, Hall W. Amphetamine-related harms and treatment preferences of regular amphetamine users in Sydney, Australia. Drug Alcohol Depend. 1997b; 46:105–113. [PubMed: 9246558]
5. Richards JR, Bretz SW, Johnson EB, et al. Methamphetamine abuse and emergency department utilization. West J Med. 1999; 170:198–202. [PubMed: 10344172]
6. Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. Circulation. 2010; 122:2558–2569. [PubMed: 21156654]
7. Vearrier D, Greenberg MI, Miller SN, et al. Methamphetamine: history, pathophysiology, adverse health effects, current trends, and hazards associated with the clandestine manufacture of methamphetamine. Dis Mon. 2012; 58:38–89. [PubMed: 22251899]
8. Rounsaville BJ, Anton SF, Carroll K, et al. Psychiatric diagnoses of treatment-seeking cocaine abusers. Arch Gen Psychiatry. 1991; 48:43–51. [PubMed: 1984761]
9. Substance Abuse and Mental Health Services Administration. Results from the 2009 national survey on drug use and health: National findings. Office of Applied Studies; Rockville: 2010.
10. Van Tieu H, Koblin BA. HIV, alcohol, and noninjection drug use. Curr Opin HIV AIDS. 2009; 4:314–318. [PubMed: 19532070]
11. Greberman SB, Wada K. Social and legal factors related to drug abuse in the United States and Japan. Public Health Rep. 1994; 109:731–737. [PubMed: 7800780]
12. Pani PP, Trogu E, Vecchi S, Amato L. Antidepressants for cocaine dependence and problematic cocaine use. Cochrane Database Syst Rev. 2011; 12
13. Minozzi S, Amato L, Davoli M, et al. Anticonvulsants for cocaine dependence. Cochrane Database Syst Rev. 2008; 2
14. Amato L, Minozzi S, Pani PP, Davoli M. Antipsychotic medications for cocaine dependence. Cochrane Database Syst Rev. 2007; 3
15. Amato L, Minozzi S, Pani PP, et al. Dopamine agonists for the treatment of cocaine dependence. Cochrane Database Syst Rev. 2011; 7(12)
16. Castells X, Casas M, Pérez-Mañá C, Roncero C, Vidal X, Capellà D. Efficacy of psychostimulant drugs for cocaine dependence. Cochrane Database Syst Rev. 2010; 2
17. Rush CR, Stoops WW. Agonist replacement therapy for cocaine dependence: A translational review. Future Med Chem. 2012; 4:245–265. [PubMed: 22300101]
18. Stoops WW, Rush CR. Agonist replacement for stimulant dependence: a review of clinical research. Curr Pharm Des. 2013; 19(40):7026–35. [PubMed: 23574440]
19. Brackins T, Brahm NC, Kissack JC. Treatments for methamphetamine abuse: a literature review for the clinician. J Pharm Pract. 2011; 24(6)

20. Ling W, Rawson RA, Compton MA. Substitution pharmacotherapies for opioid addiction: From methadone to LAAM and buprenorphine. J Psychoactive Drugs. 1994; 26:119–128. [PubMed: 7931856]
21. Rush CR, Essman WD, Simpson CA, et al. Reinforcing and subject-rated effects of methylphenidate and damphetamine in non-drug-abusing humans. J Clin Psychopharmacol. 2001; 21:273–286. [PubMed: 11386490]
22. Stoops WW, Glaser PE, Fillmore MT, et al. Reinforcing, subject-rated, performance and physiological effects of methylphenidate and d-amphetamine in stimulant abusing humans. J Psychopharmacol. 2004; 18:534–543. [PubMed: 15582920]
23. Burgess MJ, Kasten MJ. Human immunodeficiency virus: what primary care clinicians need to know. Mayo Clin Proc. 2013; 88(12):1468–74. [PubMed: 24290121]
24. Halpern B, Faria AM, Halpern A. Fixed-dose combination of phentermine-topiramate for the treatment of obesity. Expert Rev Clin Pharmacol. 2013; 6(3):235–41. [PubMed: 23656337]
25. Meneghini LF. Intensifying insulin therapy: what options are available to patients with type 2 diabetes? Am J Med. 2013; 126(9 Suppl 1):28–37.
26. Neldam S, Dahlöf B, Oigman W, Schumacher H. Early combination therapy with telmisartan plus amlodipine for rapid achievement of blood pressure goals. Int J Clin Pract. 2013; 67(9):843–52. [PubMed: 23952464]
27. Rogóż Z. Combined treatment with atypical antipsychotics and antidepressants in treatment-resistant depression: preclinical and clinical efficacy. Pharmacol Rep. 2013; 65(6):1535–1544. [PubMed: 24553002]
28. Sachs GS, Peters AT, Sylvia L, Grunze H. Polypharmacy and bipolar disorder: What's personality got to do with it? Int J Neuropsychopharmacol. 2013; 26:1–9. [PubMed: 24067291]
29. Goeders NE, Guerin GF. Effects of the combination of metyrapone and oxazepam on cocaine and food self-administration in rats. Pharmacol Biochem Behav. 2008; 91(1):181–9. [PubMed: 18692521]
30. Grabowski J, Rhoades H, Schmitz J, et al. Dextroamphetamine for cocaine-dependence treatment: A double-blind randomized clinical trial. J Clin Psychopharmacol. 2001; 21:522–526. [PubMed: 11593078]
31. Grabowski J, Rhoades H, Stotts A, et al. Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: Two double-blind randomized clinical trials. Neuropsychopharmacol. 2004; 29:969–981.
32. Mooney ME, Herin DV, Schmitz JM, et al. Effects of oral methamphetamine on cocaine use: A randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend. 2009; 101:34–41. [PubMed: 19058926]
33. Johnson BA, Ait-Daoud N, Wang XQ, et al. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. JAMA Psychiatry. 2013; 70(12):1338–46. [PubMed: 24132249]
34. Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. Drug Alcohol Depend. 2013; 133(1):94–9. [PubMed: 23810644]
35. Fleckenstein AE, Gibb JW, Hanson GR. Differential effects of stimulants on monoaminergic transporters: Pharmacological consequences and implications for neurotoxicity. Eur J Pharmacol. 2000; 406:1–13. [PubMed: 11011026]
36. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol. 2008; 75(1):218–65. [PubMed: 17706608]
37. Kalivas PW. Glutamate systems in cocaine addiction. Curr Opin Pharmacol. 2004; 4(1):23–9. [PubMed: 15018835]
38. Rothman RB, Baumann MH. Therapeutic potential of monoamine transporter substrates. Curr Top Med Chem. 2006; 6(17):1845–59. [PubMed: 17017961]
39. Ritz MC, Lamb RJ, Goldberg SR, et al. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science. 1987; 237:1219–1223. [PubMed: 2820058]
40. Weinshenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacology. 2007; 32(7):1433–51. [PubMed: 17164822]

41. Tiffany ST, Singleton E, Haertzen CA, et al. The development of a cocaine craving questionnaire. Drug Alcohol Depend. 1993; 34:19–28. [PubMed: 8174499]
42. Chadwick MJ, Gregory DL, Wendling G. A double-blind amino acids, L-tryptophan and L-tyrosine, and placebo study with cocaine-dependent subjects in an inpatient chemical dependency treatment center. Am J Drug Alcohol Abuse. 1990; 16(3-4):275–86. [PubMed: 2288326]
43. Carroll KM, Kiluk BD, Nich C, et al. Toward empirical identification of a clinically meaningful indicator of treatment outcome: Features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes. Drug Alcohol Depend. 2014 EPub Ahead of Print.
44. Mooney ME, Schmitz JM, Moeller FG, Grabowski J. Safety, tolerability and efficacy of levodopa-carbidopa treatment for cocaine dependence: two double-blind, randomized, clinical trials. Drug Alcohol Depend. 2007; 88(2-3):214–23. [PubMed: 17134849]
45. Woolverton WL. Evaluation of the role of norepinephrine in the reinforcing effects of psychomotor stimulants in rhesus monkeys. Pharmacol Biochem Behav. 1987; 26:835–839. [PubMed: 3496618]
46. Shorter D, Nielsen DA, Huang W, et al. Pharmacogenetic randomized trial for cocaine abuse: Disulfirm and Alpha1A-adrenoceptor gene variation. Eur Neuropsychopharmacol. 2013; 23:1401–1407. [PubMed: 23849431]
47. Madras BK, Xie Z, Lin Z, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. J Pharmacol Exp Ther. 2006; 319:561–569. [PubMed: 16885432]
48. Olive MF, Cleva RM, Kalivas PW, Malcolm RJ. Glutamatergic medications for the treatment of drug and behavioral addictions. Pharmacol Biochem Behav. 2012; 100(4):801–10. [PubMed: 21536062]
49. Shorter D, Kosten TR. Novel pharmacotherapeutic treatments for cocaine addiction. BMC Med. 2011; 9:119. [PubMed: 22047090]
50. Yoo JH, Kitchen I, Bailey A. The endogenous opioid system in cocaine addiction: what lessons have opioid peptide and receptor knockout mice taught us? Br J Pharmacol. 2012; 166(7):1993–2014. [PubMed: 22428846]
51. Mariani JJ, Pavlicova M, Bisaga A, Nunes EV, Brooks DJ, Levin FR. Extended-release mixed amphetamine salts and topiramate for cocaine dependence: a randomized controlled trial. Biol Psychiatry. 2012; 72(11):950–6. [PubMed: 22795453]
52. Rotheram-Fuller E, De La Garza R, Mahoney JJ, Shoptaw S, Newton TF. Subjective and cardiovascular effects of cocaine during treatment with amantadine and baclofen in combination. Psychiatry Res. 2007; 152(2-3):205–10. [PubMed: 17449110]
53. Sofuoglu M, Singha A, Kosten TR, McCance-Katz FE, Petrakis I, Oliveto A. Effects of naltrexone and isradipine, alone or in combination, on cocaine responses in humans. Pharmacol Biochem Behav. 2003; 75(4):801–8. [PubMed: 12957222]
54. Kampman KM, Dackis C, Lynch KG, et al. A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. Drug Alcohol Depend. 2006; 85(2):129–37. [PubMed: 16697124]
55. Pettinati HM, Kampman KM, Lynch KG, et al. A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. Addict Behav. 2008; 33(5):651–67. [PubMed: 18079068]
56. Schmitz JM, Rathnayaka N, Green CE, Moeller FG, Dougherty AE, Grabowski J. Combination of modafinil and d-amphetamine for the treatment of cocaine dependence: A preliminary investigation. Front Psychiatry. 2012; 3:77. [PubMed: 22969732]
57. Giannini AJ, Billett W. Bromocriptine-desipramine protocol in treatment of cocaine addiction. J Clin Pharmacol. 1987; 27(8):549–54. [PubMed: 3308977]
58. Kablinger AS, Lindner MA, Casso S, et al. Effects of the combination of metyrapone and oxazepam on cocaine craving and cocaine taking: a double-blind, randomized, placebo-controlled pilot study. J Psychopharmacol. 2012; 26(7):973–81. [PubMed: 22236504]
59. Jayaram-Lindström N, Wennberg P, Beck O, Franck J. An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. Nord J Psychiatry. 2005; 59(3):167–71. [PubMed: 16195116]

60. Jayaram-Lindström N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. Am J Psychiatry. 2008; 165(11):1442–8. [PubMed: 18765480]
61. Marks KR, Lile JA, Stoops WW, Rush CR. Separate and combined impact of acute naltrexone and alprazolam on subjective and physiological effects of oral d-amphetamine in stimulant users. Psychopharmacology (Berl). Jan 25.2014 [Epub ahead of print].
62. Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. Eur Neuropsychopharmacol. 2010; 20(11):823–8. [PubMed: 20655182]
63. Ling W, Shoptaw S, Hillhouse M, et al. Double-blind placebo-controlled evaluation of the PROMETA™ protocol for methamphetamine dependence. Addiction. 2012; 107(2):361–9. [PubMed: 22082089]
64. Urschel HC, Hanselka LL, Baron M. A controlled trial of flumazenil and gabapentin for initial treatment of methylamphetamine dependence. J Psychopharmacol. 2011; 25(2):254–62. [PubMed: 19939864]
65. McCann DJ, Li SH. A novel, nonbinary evaluation of success and failure reveals bupropion efficacy versus methamphetamine dependence: reanalysis of a multisite trial. CNS Neurosci Ther. 2012; 18(5):414–8. [PubMed: 22070720]
66. Winchell C, Rappaport BA, Roca R, et al. Reanalysis of methamphetamine dependence treatment trial. CNS Neurosci Ther. 2012; 18:367–368. [PubMed: 22533722]
67. Beitz J. Trial endpoints for drug approval in oncology: Chemoprevention. Urology. 2001; 57:213–215. [PubMed: 11295630]
68. Abadie E, Ethgen D, Avouac B, et al. Group for the Respect of Excellence and Ethics in Science. Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. Osteoarthr Cartil. 2004; 12:263–268. [PubMed: 15023377]
69. Carroll KM, Rounsaville BJ, Nich C, Gordon LT, Wirtz PW, Gawin F. One-year follow-up of psychotherapy and pharmacotherapy for cocaine dependence. Delayed emergence of psychotherapy effects. Arch Gen Psychiatry. 1994; 51(12):989–997. [PubMed: 7979888]
70. Carroll KM, Nich C, Ball SA, McCance E, Rounsaville BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction. 1998; 93(5):713–727. [PubMed: 9692270]
71. Poling J, Oliveto A, Petry N, et al. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. Arch Gen Psychiatry. 2006; 63(2): 219–228. [PubMed: 16461866]
72. Schmitz JM, Mooney ME, Moeller FG, et al. Levodopa pharmacotherapy for cocaine dependence: Choosing the optimal behavioral therapy platform. Drug Alcohol Depend. 2008; 94(1-3):142–150. [PubMed: 18164144]
73. Schmitz JM, Lindsay JA, Stotts AL, Green CE, Moeller FG. Contingency management and levodopa-carbidopa for cocaine treatment: A comparison of three behavioral targets. Exp Clin Psychopharmacol. 2010; 18(3):238–244. [PubMed: 20545388]
74. Comer SD, Ashworth JB, Foltin RW, et al. The role of human drug self administration procedures in the development of medications. Drug Alcohol Depend. 2008; 96:1–15. [PubMed: 18436394]
75. Haney M, Spealman R. Controversies in translational research: drug self-administration. Psychopharmacology(Berl). 2008; 199:403–419. [PubMed: 18283437]
76. Igua AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy. 2014; 7:35–44. [PubMed: 24591853]
77. Galloway GP, Coyle JR, Guillèn JE, Flower K, Mendelson JE. A simple, novel method for assessing medication adherence: Capsule photographs taken with cellular telephones. J Addict Med. 2011; 5:170–174. [PubMed: 21844832]
78. Rothman RB, Blough BE, Baumann MH. Dopamine/serotonin releasers as medications for stimulant addictions. Prog Brain Res. 2008; 172:385–406. [PubMed: 18772043]
79. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: A randomized trial. JAMA. 2014; 311(2): 155–163. [PubMed: 24399554]

80. Childress AC. Guanfacine extended release as adjunctive therapy to psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. Adv Ther. 2012; 29(5):385–400. [PubMed: 22610723]

Key Issues

-Effective pharmacotherapies for stimulant use disorders remain to be identified.

-Use of innovative strategies, like combination treatment, is necessary to develop successful medications to manage cocaine or amphetamine use disorder.

-Combination treatment is a viable strategy for a number of reasons, including use of lower doses of individual constituents to minimize side effects, the possibility of achieving additive or synergistic effects with combinations and targeting the diverse neurotransmitter systems impacted by stimulant drugs.

-Superior efficacy of combined treatments relative to placebo has been demonstrated for a wide range of outcomes, including objective and self-reported drug abstinence.

-A number of methodological concerns, including not systematically testing putative combinations from the human laboratory to the clinic and not evaluating individual constituents, make more definitive conclusions about the promise of this strategy impossible.

-Future research should more systematically evaluate drug combinations and include individual constituents that have at least some efficacy when tested alone to overcome these methodological limitations.

Table 1

Outcomes of Clinical Studies of Combination Treatments for Cocaine Use Disorder.

Citation	Study Type	Treatment Conditions[+]	Outcomes	Rationale[*]
Sofuoglu et al., 2003	Human Laboratory	Placebo, Naltrexone (50 mg), Isradipine (10 mg), Naltrexone and Isradipine	Isradipine, alone or with naltrexone, reduced the pressor effects of cocaine. Greater reductions in blood pressure were observed with the combination. Naltrexone alone reduced subjective ratings of Good Effects produced by cocaine.	2, 3
Rotheram-Fuller et al., 2007	Human Laboratory	Placebo, Amantadine (300 mg/day) and Baclofen (90 mg/day)	Combined amantadine and baclofen reduced subjective ratings of Desire to Use Cocaine.	2, 3
Giannini and Billett, 1987	Clinical Trial	Placebo, Bromocriptine (2.5 mg/day), Bromocriptine and Desipramine (200 mg/day)	Bromocriptine, alone or with desipramine, reduced cocaine withdrawal symptoms. Greater reductions were observed for the combination relative to bromocriptine alone.	2, 3
Chadwick et al., 1990	Clinical Trial	Placebo, I-Tryptophan (1 g/day) and I-Tyrosine (1 g/day)	No treatment group differences.	3
Kampman et al., 2006	Clinical Trial	Placebo, Amantadine (300 mg/day), Propanolol (100 mg/day), Amantadine and Propanolol	No treatment group differences in overall analysis. Sub-analysis indicated that highly adherent subjects in the propranolol alone condition were more likely to be cocaine abstinent and stay in treatment.	2, 3
Pettinati et al., 2008	Clinical Trial	Placebo, Disulfiram (250 mg/day), Naltrexone (100 mg/day), Disulfiram and Naltrexone.	No treatment group differences in overall analysis. Sub-analysis indicated that disulfiram maintenance, alone or with naltrexone, increased abstinence from cocaine and alcohol.	2, 3
Kablinger et al., 2012	Clinical Trial	Placebo, Metyrapone (500 mg/day) and Oxazepam (20 mg/day), Metyrapone (1500 mg/day) and Oxazepam	No treatment group differences in overall analysis. Sub-analysis indicated that both active treatments reduced cocaine craving. Cocaine abstinence was also increased in the high-dose metyrapone group.	1, 2, 3
Mariani et al., 2012	Clinical Trial	Placebo, Mixed Amphetamine Salts (60 mg/day) and Topiramate (300 mg/day)	Combined amphetamine salts and topiramate doubled the likelihood that subjects would achieve three consecutive weeks of cocaine abstinence.	2, 3
Schmitz et al., 2012	Clinical Trial	Placebo, d-Amphetamine (60 mg/day), Modafinil (400 mg/day), d-Amphetamine (30 mg/day) and Modafinil (200 mg/day)	Combined d-amphetamine and modafinil increased cocaine use. Placebo and d-amphetamine alone decreased cocaine use.	1, 2, 3

[+] Unless otherwise indicated, doses of the combined medications were the same as those tested for individual constituents.

[*] Rationales were selected from the three provided in the introduction including 1) combining medications using lower doses to minimize side effects, 2) combining medications that demonstrate some efficacy as individual constituents either preclinically or clinically and 3) combining medications that target different neurotransmitter systems.

Table 2

Outcomes of Clinical Studies of Combination Treatments for Amphetamine Use Disorder.

Citation	Study Type	Treatment Conditions[+]	Outcomes	Rationale[*]
Marks et al., 2014	Human Laboratory	Placebo, Naltrexone (50 mg), Alprazolam (0.5 mg), Naltrexone and Alprazolam.	Combined naltrexone and alprazolam significantly reduced a greater number of subjective effects produced by d-amphetamine than placebo, naltrexone or alprazolam alone.	2, 3
Grant et al., 2010	Clinical Trial	Placebo, Naltrexone (200 mg/day final dose) and n-Acetylcysteine (2400 mg/day final dose)	No treatment group differences.	2, 3
Urschel et al., 2011	Clinical Trial	Placebo, Hydroxizine (50 mg/day), Gabapentin (1200 mg/day target dose) and Flumazenil (5, 2 mg/ infusions)	Active treatment reduced amphetamine use and craving.	2, 3
Ling et al., 2012	Clinical Trial	Placebo (Hydroxizine, 50 mg/day), Hydroxizine, Gabapentin (1200 mg/day target dose) and Flumazenil (5, 2 mg/infusions)	No treatment group differences.	2, 3

[+] Unless otherwise indicated, doses of the combined medications were the same as those tested for individual constituents.

[*] Rationales were selected from the three provided in the introduction including 1) combining medications using lower doses to minimize side effects, 2) combining medications that demonstrate some efficacy as individual constituents either preclinically or clinically and 3) combining medications that target different neurotransmitter systems.