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REVIEW ARTICLE

Pharmacological interventions to modulate attentional bias in addiction

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Attentional bias in substance-dependent patients is the tendency to automatically direct attention to substance-related cues in the environment. Preclinical models suggest that attentional bias emerges as a consequence of dopaminergic activity evoked by substance-related cues. The aim of the current review is to describe pharmacological mechanisms underlying attentional bias in humans and to critically review empirical studies that aimed to modulate attentional bias in substance-dependent patients by using pharmacological agents. The findings of the reviewed studies suggest that attentional bias and related brain activation may be modulated by dopamine. All of the reviewed studies investigated acute effects of pharmacological agents, while measurements of chronic pharmacological treatments on attentional bias and clinically relevant measures such as relapse are yet lacking. Therefore, the current findings should be interpreted as a proof of principle concerning the role of dopamine in attentional bias. At the moment, there is too little evidence for clinical applications. While the literature search was not limited to dopamine, there is a lack of studies investigating the role of non-dopaminergic neurotransmitter systems in substance-related attentional bias. A focus on neurotransmitter systems such as acetylcholine and noradrenaline could provide new insights regarding the pharmacology of substance-related attentional bias.

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Clinical Implications

- The available evidence suggests that substance-related attentional bias in humans may be modulated by dopamine. However, clinical trials are needed to investigate the clinical implications of this knowledge.
- There is currently not sufficient evidence for pharmacological agents to be used in clinical practice to reduce attentional bias.
- A focus on neurotransmitter systems such as acetylcholine and noradrenaline could provide new insights regarding the pharmacology of substance-related attentional bias that may eventually be of clinical relevance.

Introduction

Substance abuse and addiction are associated with enhanced processing of substance-related cues.[1,2] Attentional bias is one of the mechanisms underlying enhanced processing of these cues and is defined as the tendency of substance-dependent individuals to automatically and involuntarily allocate and maintain their attention on drug-related stimuli when confronted with them.[3] Attentional bias has consistently been found in various types of addiction,[3–5] and has been determined by utilizing a wide range of experimental paradigms such as emotional Stroop and visual probe tasks. Attentional bias has been linked to subjective craving[6] and is likely involved in the continuation of addictive behaviors.[7] Therefore the investigation of modification of attentional bias is warranted and may eventually be of clinical relevance for substance-dependent patients. The purpose of the current review is to describe the pharmacological mechanisms underlying attentional bias and to critically review empirical studies that have aimed to reduce attentional bias in substance-dependent patients by using pharmacological agents.

In order to identify these studies, a PubMed/Embase literature search was conducted including the search term "attentional bias," which had to co-occur with a search term describing any substance-dependent population, as well as a search term related to any neurotransmitter system. A total of 7 studies[8–14] was identified that included a substance-dependent study group, employed a behavioral attentional bias task, and involved a pharmacological agent. Studies investigating acute effects of substances of abuse on attentional bias were not included. While these studies provide valuable insights in the continuation of addictive behaviors (eg, Nikolaou *et al*[15]), the aim of

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these studies is not to modulate attentional bias in a clinically relevant way, and therefore they do not fit the scope of this review. Table 1 displays relevant participant characteristics of all included studies. The main results of these studies are summarized in Table 2 and will be discussed and integrated in theoretical models below.

Theoretical Background and Dopaminergic Manipulations

There is a general consensus that the dopaminergic system, with projections from the ventral tegmental area (VTA) to the striatum, the anterior cingulate cortex (ACC), and other prefrontal brain regions, is responsible for reinforcement learning and experiencing reward.[16] Based on preclinical animal work, it has been suggested that this dopaminergic reinforcement learning system is also involved in the development of attentional bias via conditioned reinforcement learning.[17] After repeated drug intake, substance-related stimuli become conditioned stimuli and elicit phasic dopaminergic activity,[18–20] thereby signaling the expectation of a future reward (ie, the intake of the abused substance). Gradually, the dopaminergic system becomes sensitized for substance-related cues so that they become extremely salient; these cues become the focus of attention, and they elicit behaviors such as drug seeking and consumption.[21,22] Functional magnetic resonance imaging (fMRI) studies have indeed shown that attentional bias in substance-dependent patients is associated with activation in the ventral striatum, the ACC, and other limbic and prefrontal brain regions.[23–26] In contrast to the phasic dopaminergic responses to substance-related cues, the striatal dopamine system in substance-dependent patients is supposed to be generally blunted compared to healthy controls,[27] which is an effect that has even been observed for the acute intake of substances of abuse.[28] Based on these theoretical accounts, the most straightforward pharmacological manipulation to reduce attentional bias would be to prevent the phasic dopaminergic burst associated with conditioned substance-related cues. This blockade of the dopaminergic response would then lead to a reduction in substance-related attentional bias. Franken *et al*[14] were the first to test this dopaminergic attentional bias hypothesis in humans. In this study, heroin-dependent patients performed the heroin word Stroop task in a placebo-controlled, double-blind, randomized crossover study using a single dose of haloperidol (dopamine D2/D3 receptor antagonist) to modulate dopaminergic responses to heroin-related words. The findings of this study provided support for the dopaminergic theory of attentional bias in humans,

Table 1. *Patient characteristics in included studies*

Study	N	Mean age (SD)	Gender	Abstinence	Disorder status	Treatment status
Smokers						
Ersche *et al.* 2010	18 SDP	SDP: 34.3 (7.2)	SDP: 83% male	No abstinence required	DSM IV diagnosis dependence	Non-treatment seeking
	18 HC	HC: 32.7 (6.9)	HC: 83% male			
Franken *et al.* 2004	17 ODP	35.7 (6.4)	100% male	At least two weeks	Dependent patients	In treatment program
Goldstein *et al.* 2010	13 CDP	SDP: 46.2 (8.7)*	SDP: 92% male	4.9 (7.3) days before MPH	DSM IV diagnosis dependence	Current users
	14 HC	HC: 38.8 (6.2)*	HC: 100% male	6.3 (9.7) days before placebo		
Hitsman *et al.* 2008	14 S	25 (4)	56% male	No abstinence required	≥ 10 cigarettes a day, range 10–25	No intention to quit
Kamboj *et al.* 2012	32 S	PL: 32.3 (10.6)	PL: 69% male	Two hours abstinence followed by smoking a standardized cigarette before testing	≥ 15 cigarettes a day	Both quit intenders and non-intenders
		DCS: 30.0 (9.4)	DCS: 69% male			
Luijten *et al.* 2012	25 S	S: 22.6 (2.8)	S: 72% male	At least 3 hours	≥ 15 cigarettes a day. Smoking duration ≥ 2 years	No intention to quit
	24 HC	HC: 21.8 (1.8)	HC: 58% male			
Munafò *et al.* 2007	20 S	41 (13)	55% male	Overnight abstinence	≥ 10 cigarettes a day, range 10–25	n/m

*$p < .05$; SDP: stimulant-dependent patients, HC: healthy controls, ODP: opiate-dependent patients, CDP: cocaine-dependent patients, MPH: methylphenidate, S: smokers, PL: placebo, DCS: D-cycloserine, n/m: not mentioned.

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Table 2. *Overview of pharmacological studies investigating attentional bias in substance dependence*

Study	N	Pharmacological intervention	Study design	Measures	Main results for attentional bias
Ersche *et al*. 2010	9 SDP H-COM 9 SDP L-COM 18 HC	Amisulpride (400 mg): D2/D3 receptor antagonist & Pramipexole dihydrochloride (0.5 mg): D2/D3 receptor agonist	Single challenge double-blind randomized crossover design. 3 sessions, one for each medication type	Cocaine word Stroop task during fMRI	No overall effect of medication on attentional bias related brain activation and behavioral measures in SDP. L-COM showed a reduction in attentional bias related brain activation after PRA in left ventral PFC and right cerebellum. H-COM showed increased attentional bias related brain activation after PRA in PFC. Behavioral measures showed no attentional bias after PRA in L-COM, whereas the H-COM showed attentional bias after PRA. No effects of Amisulpride were found.
Franken *et al*. 2004	17 ODP	Haloperidol (2 mg): D2/D3 receptor antagonist (2 mg)	Single challenge double-blind randomized crossover design	Heroin word Stroop task	Attentional bias reduced after haloperidol
Goldstein *et al*. 2010	13 CDP 14 HC	Methylphenidate (20 mg): dopamine reuptake inhibitor	Single challenge single-blind counterbalanced crossover design	Adapted Cocaine word Stroop task during fMRI	Attentional bias related brain activation in the dACC was normalized after MPH (hypoactivation observed during placebo and not after MPH). No effect on behavioural measures.
Hitsman *et al*. 2008	14 S	Acute tyrosine/phenylalanine depletion*: reduced dopamine transmission	Single challenge double-blind counterbalanced placebo crossover design	Smoking word Stroop task	Attentional bias reduced after TYR/PHE depletion
Kamboj *et al*. 2012	16 S DCS 16 S PL	D-cycloserine (125 mg): partial glycine site NMDA agonist	Two times administration of DCS or placebo in a between- group double-blind randomized placebo design	Smoking related dot-probe task	No effect of DCS on attentional bias
Luijten *et al*. 2012	25 S 24 HC	Haloperidol (2 mg): D2/D3 receptor antagonist	Single challenge double-blind randomized crossover design	Attentional bias line counting task during fMRI	Attentional bias related brain activation in the dACC and DLPFC was reduced after haloperidol. No effect on behavioural measures.
Munafó *et al*. 2007	10 S TYR 10 S PL	Acute tyrosine depletion*: reduced dopamine transmission	Single challenge between-group double-blind randomized placebo crossover design	Smoking word Stroop task	Attentional bias reduced at trend level after TYR depletion in women and not in men.

*This mixture contained 15 g isoleucine, 22.5 g leucine, 17.5 g lysine, 5 g methionine, 17.5 g valine, 10 g threonine, and 2.5 g tryptophan. The placebo mixture additionally contained 12.5 g tyrosine and 12.5 g phenylalanine. Females received 20% less by weight of each amino acid than males.

SDP: stimulant dependent patients, H-COM: high compulsive, L-COM: low compulsive, HC: healthy controls, PRA: pramipexole dihydrochloride, ODP: opiate dependent patients, CDP: cocaine-dependent patients, MPH: methylphenidate, S: smokers, TYR/PHE: tyrosine/phenylalanine, DCS: D-cycloserine, PL: placebo, TYR: tyrosine, DLPFC: dorsolateral prefrontal cortex, dACC: dorsal anterior cingulate cortex: PFC: prefrontal cortex.

as attentional bias for heroin words was eliminated after haloperidol was administered. These results were partly replicated for smoking-related stimuli using a smoking word Stroop task in two subsequent studies in smokers.[11,12] In both these studies, an amino acid mixture that lacks tyrosine (TYR) and its precursor phenylalanine (PHE) was used to modulate dopamine responses to smoking-related stimuli. As the synthesis of dopamine in the brain is dependent on the availability of these amino acids from plasma, the acute administration of a TYR/PHE-free amino acid mixture has been shown to reduce dopaminergic activity in the brain.[29] The findings of the first study employing this method[11] showed a gender-specific reduction in smoking-related attentional bias after the TYR/PHE-free amino acid mixture was administered. Stroop interference scores (ie, reaction times for smoking-related versus neutral words) were reduced relative to the placebo condition in women but not in men. The second study using the same study design,[12] however, showed a reduction in smoking-related attentional bias among both smoking men and women (no gender-specific analyses were performed). These findings suggest that attentional bias may indeed be reduced in smokers, perhaps more strongly in women, when dopaminergic transmission is prevented during the exposure to smoking related cues.

Studies measuring brain activation concurrently with behavioral measures of attentional bias could test the dopaminergic hypothesis of attentional bias in more detail, as brain regions involved in salience detection and attentional bias can be directly evaluated. A pictorial line counting attentional bias task was used in a recent placebo-controlled, double-blind, randomized crossover pharmacological fMRI study in smokers.[8] The dopamine challenge consisted of a single administration of the dopamine D2/D3 receptor antagonist haloperidol. While haloperidol did not alter behavioral measures of attentional bias for smoking-related stimuli, brain activation in the dorsal ACC and dorsolateral prefrontal cortex (DLPFC), which are associated with attentional bias, was reduced in smokers by haloperidol. That is, no differences in brain activation between smokers and non-smokers were found after haloperidol intake. As the dorsal ACC is involved in the salience detection network, as well as in top-down control of attention in cooperation with the DLPFC, these findings suggest that a reduction in dopamine may affect the salience detection of smoking-related stimuli in smokers, as well as top-down control over these cues to continue ongoing behavior.

A placebo-controlled, double-blind, randomized crossover pharmacological fMRI study in stimulant-dependent patients measured brain activation associated with the performance of a stimulant word Stroop task under several dopaminergic conditions.[9] This study involved both a single challenge of a D2/D3 dopamine antagonist (amisulpride) as well as a D2/D3 dopamine agonist (pramipexole dihydrochloride). While no effects were found of both medications on attentional bias–related brain activation or behavioral measures for the total stimulant-dependent patients group, compulsivity levels within the patient group appeared to modulate due to medication effects. On a behavioral level, attentional bias was reduced in low-compulsive stimulant-dependent patients after the dopamine agonist, whereas the high-compulsive stimulant-dependent patients still showed an attentional bias. In line with behavioral findings, the dopamine agonist pramipexole enhanced attentional bias–related brain activation in the left ventral prefrontal cortex and the cerebellum in high-compulsive stimulant-dependent patients, whereas it reduced activation in these regions in low-compulsive stimulant users. These findings suggest that individual differences in compulsivity levels may modulate the effects of a dopamine agonist for behavioral attentional bias measures as well as attentional bias–related brain activation. Compulsive behavior has previously been associated with striatal dopamine transmission.[30] More specifically, it has been suggested that optimal dopamine levels for cognitive functioning follow an inverted U-shaped curved depending on personality traits such as compulsivity.[31] In contrast to the study in smokers, attentional bias–related brain activation was not reduced following the administration of the dopamine antagonist amisulpride in either low- or high-compulsive stimulant-dependent patients.

Goldstein *et al*[10] performed a placebo-controlled, single-blind, counterbalanced pharmacological fMRI study using a crossover design in cocaine-dependent patients using methylphenidate (a dopamine transporter blocker) as the pharmacological agent. Instead of investigating whether a dopamine antagonist can ameliorate attentional bias and related brain activation, this study implemented a different approach, as methylphenidate is known to increase synaptic dopamine levels. Findings of this study revealed that cocaine-dependent patients displayed reduced brain activation in the dorsal ACC for cocaine-related words relative to controls after placebo, whereas this hypoactivation was normalized after methylphenidate administration. No medication effects were found for behavioral measures. These findings may suggest that methylphenidate could be beneficial for brain activation associated with attentional bias. While these findings seem to contradict the dopaminergic theory of attentional bias, they can be explained by the known cognitive enhancing properties of methylphenidate.[32] Current addiction models suggest that substance

abuse is not only caused by motivational processes such as attentional bias, but that the combination of an overactive motivational system with reduced cognitive brain functions drives the continuation of addictive behaviors.[4,33,34] More specifically, it has been proposed that the ineffective prefrontal cognitive control circuit in substance-dependent patients[35] influences the strength of attentional bias in such a way that reduced cognitive control results in enhanced attentional bias.[4] This interaction between cognitive control–related brain functions and attentional bias provides a second plausible working mechanism to ameliorate attentional bias using pharmacological agents. Cognitive enhancing medications such as methylphenidate may therefore result in indirect beneficial effects on attentional bias–related brain activation. In line with this hypothesis, modafinil, another cognitive-enhancing medication, has been shown to have effects on both cognitive control as well on motivational aspects of cocaine dependence.[36,37]

Overall, studies using dopaminergic challenges to investigate the effects on attentional bias are promising and provide, to a certain extent, support for the dopamine theory of attentional bias. Nevertheless, the results are not always consistent, and future research is needed to further clarify the role of modulatory factors such as gender and compulsivity levels. Especially, large methodological differences such as different substance-dependent groups, dopaminergic challenges, and attentional bias paradigms in the pharmacological fMRI studies may have contributed to inconsistencies in results between these studies. In addition, all studies until now have investigated acute effects of pharmacological agents, so it is currently unknown whether chronic pharmacological treatments may reduce attentional bias in the long term.

Targeting Other Neurotransmitters to Ameliorate Attentional Bias

Only one study was identified that investigated an alternative neurotransmitter system to reduce attentional bias. Kamboj *et al*[13] investigated the effect of D-cycloserine (DCS) on attentional bias, which is a partial agonist at the glycine site of the N-methyl-D-aspartate (NMDA) receptor. The rationale for this is based in preclinical work that has suggested that DCS can have extinction-enhancing properties during cue exposure therapy.[38] Smokers in this between-group, double-blind, placebo-controlled study received two cue-extinction sessions combined with either DCS or placebo. Attentional bias was measured using a dot-probe task before and after the two cue-extinction sessions. The results did not show a beneficial effect of DCS or cue-extinction in general for smoking-related attentional bias, suggesting that DCS combined with two sessions of cue-extinction may not be a promising tool to reduce attentional bias in smokers. Despite these null results, it may be worth exploring the involvement of alternative neurotransmitters in substance-related attentional bias. Acetylcholine, for example, is known for its modulating effects on attention,[39] and a link has been proposed between the dopaminergic theory of attentional bias and the acetylcholine system.[40] For example, increases in dopamine in the ventral striatum have been suggested to be associated with increases in cortical acetylcholine release,[41] such that repeated administration of substances of abuse may also sensitize cortical acetylcholine via projections with the basal forebrain.[40] It would be worth investigating whether such a sensitization of the cortical acetylcholine system represents an integral component of attentional bias.

Another neurotransmitter system that may be worth investigating in the context of attentional bias is the noradrenaline system. Noradrenaline is mostly released from the locus coeruleus (LC), which is a nucleus in the brainstem that has strong reciprocal connections with the prefrontal cortex and the ACC. Preclinical research has shown that both tonic and phasic LC discharge activity is closely related to the overall salience and arousing properties of the presented stimuli.[42] This may suggest that the noradrenaline system could be involved in the detection of salient substance-related stimuli in the environment, probably in cooperation with the dopamine system. Atomoxetine is a noradrenaline reuptake inhibitor that increases noradrenaline levels in the prefrontal cortex including the ACC,[43] and may be a useful tool to investigate noradrenergic regulation of attentional bias in substance-dependent patients. Atomoxetine has been shown to improve cognitive functions and boost ACC activation in healthy controls,[44,45] so it may also have a beneficial effect on cognitive functioning in substance-dependent patients, and therefore may indirectly reduce attentional bias via improving cognitive control similarly to the way that has been proposed for methylphenidate. In conclusion, a focus on other neurotransmitter systems such as acetylcholine and noradrenaline could shed some new light on the pharmacology of attentional bias.

Treatment Implications

In summary, some of the reviewed pharmacological attentional bias studies in substance-dependent individuals show evidence that attentional bias and related brain activation can be modulated by dopaminergic agents, although the results are not always consistent. In addition, it may be that cognitive enhancing agents

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will be able to indirectly reduce attentional bias via boosting cognitive control. However, we should be very careful with generalizing these positive attentional bias–related findings for particular drugs to beneficial treatment effects for several reasons. First, it is unknown whether chronic treatment with dopaminergic agents will result in a long-term reduction in attentional bias, and whether this in turn will improve clinical outcome measures such as relapse or reduced substance use. There is one study that showed that attentional bias was reduced in opiate-dependent patients after chronic treatment with methadone or buprenorphine as compared to current users[46]; however, the same effect was found in a group of patients receiving nonpharmacological treatment, suggesting that prolonged abstinence in general may have caused the reduction in attentional bias. As the study was not double-blind and did not include a placebo, it is particularly difficult to attribute the reduction in attentional bias to the chronic pharmacological treatment. Further studies are needed to show if chronic pharmacological treatment will lead to a reduction in attentional bias.

Clinical application of positive findings for certain dopaminergic agents to reduce attentional bias is further complicated by the fact that attentional bias is not the only dopaminergic-mediated process involved in addiction. While attentional bias and craving are supposed to have mutual reinforcing associations in theoretical models,[3,4] none of the studies discussed in this review found beneficial effects of the dopamine challenges on subjective cravings. This may be explained by the original concept of the dopaminergic incentive sensitization theory of attentional bias, implying that dopamine release following exposure of substance-related cues may occur independent of neural mechanisms that mediate withdrawal and related withdrawal-induced cravings.[11,17] While a phasic dopaminergic response in response to conditioned substance-related cues may trigger the enhanced attentional processing of these substance-related cues, other dopaminergic deficiencies such as tonic dopamine depletion may induce withdrawal-related craving and can motivate drug-seeking behavior.[47] Besides attentional bias and craving, there is also accumulating evidence that prefrontal dopamine levels can modulate cognitive control–related brain functions. An inverted U-curve theory of dopamine and cognitive control suggests that there is an optimal prefrontal dopamine level for cognitive performances, and that either too low or too high levels may reduce cognitive control[31]; this is further confirmed by findings that the effects of dopaminergic agents on cognitive functioning are modulated by dopaminergic genotypes.[48] In this context, it is interesting to mention that the same group of smokers in which normalized attentional bias–related brain activation was found after the dopamine antagonist haloperidol was administered also performed a Go/NoGo task to measure inhibitory control under placebo and dopamine-deprived conditions.[8] In contrast to the beneficial effects of the dopamine antagonist on attentional bias–related brain activation, reduced inhibitory control and prefrontal brain function was found after haloperidol relative to the placebo condition.[49] Besides the unpleasant side effects, these differential effects of dopaminergic agents on different processes that are all involved in the continuation of substance-related behaviors may be one of the reasons why dopamine antagonists do not seem to be successful in the treatment of cocaine dependence.[50] Future research therefore faces the challenge to investigate the effects of pharmacological agents on the multiple processes involved in addictive behaviors. Pharmacological agents that may be able to restore the balance between motivational processes and controlling processes may eventually succeed to more effectively treat substance dependence.

Besides pharmacological interventions, attentional bias modification training may provide an alternative way to reduce attentional bias in addiction. While attentional bias modification (ABM) training could probably constitute a treatment obstacle for some substance-dependent patients, it is worth investigating nonpharmacological interventions to reduce substance-related attentional bias. While some of the initial proof-of-concept studies yielded promising findings, others did not,[51–57] and evaluations of ABM in substance abusers who are motivated to change their behavior have either been underpowered,[53] or have failed to include appropriate control conditions.[57]

Conclusions

The findings of the current review show that pharmacological challenges with antagonistic dopaminergic properties were able to decrease attentional processing of substance-related stimuli when substance-dependent individuals were confronted with these conditioned cues. These findings should, however, be interpreted as a proof-of-principle concerning the role of dopamine in attentional bias rather than as a finding with direct clinical relevance. Future research is necessary to evaluate the effects of chronic pharmacological treatment on attentional bias, as well as its effects on other important processes involved in addiction, such as craving and cognitive control. These future research suggestions are necessary to find out whether the net effect of a pharmacological intervention will be beneficial in the treatment of addictive behaviors.

Disclosures

The authors do not have anything to disclose.

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