



# The Role of Orexin Receptor Antagonists in Inhibiting Drug Addiction: A Review Article

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## Abstract

The orexinergic system and its receptors are involved in many physiological processes. Their functions in energy homeostasis, arousal, cognition, stress processing, endocrine functions, and pain modulation have been investigated. Many studies have shown that the orexinergic system cooperates with the dopaminergic system in the addiction process. Emerging evidence suggests that the orexinergic system can be effective in the induction of drug dependence and tolerance. Therefore, several researches have been conducted on the effect of orexin receptor (OXR) antagonists on reducing tolerance and dependence caused by drug abuse. Due to the significant growth of the studies on the orexinergic system, the current literature was conducted to collect the findings of previous studies on orexin and its receptors in the induction of drug addiction. In addition, cellular and molecular mechanisms of the possible role of orexin in drug tolerance and dependence are discussed. The findings indicate that the administration of OXR antagonists reduces drug dependence. OXR blockers seem to counteract the addictive effects of drugs through multiple mechanisms, such as preventing neuronal adaptation. This review proposes the potential clinical use of OXR antagonists in the treatment of drug dependence.

**Keywords:** Orexin, Hypocretin, Tolerance, Dependence, Withdrawal, Addiction

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## Introduction

Drug addiction is a reversible chronic disorder. Among the characteristics of drug addiction are the occurrence of emotional states (when access to drugs is prevented), the compulsion to use drugs, and lack of control during deprivation.<sup>1</sup> One of the major problems in the chronic use of drugs (e.g., morphine) is the formation of tolerance and dependence, which limits their clinical use.<sup>2,3</sup> Treatment for drug addiction is provided in several approaches, including pharmacological and behavioral therapies or their combination. Various medications are prescribed to manage withdrawal symptoms, treat co-occurring disorders, and prevent relapse.<sup>1,4-6</sup>

Orexin (hypocretin/OX) is a sleep-wake cycle regulating neuropeptide secreted from the lateral hypothalamus (LH). Orexin A (OXA) and OXB are two orexin neuropeptides.<sup>7</sup> Orexins are peptide products from the processing of the hypocretin (HCRT) gene, which is

responsible for encoding the prepro-orexin peptide with 130 amino acids.<sup>8-10</sup> Studies have revealed that OXA has the same affinity for both orexin receptors, while OXB selectively prefers the OX type 2 receptor (OX2R).<sup>11</sup> Although less than 100 000 orexin-secreting neurons are located in the LH, orexinergic receptors are expressed in various brain areas.<sup>7,11</sup> Research on orexinergic neurons has shown that OX neurons have different functions at different locations in the hypothalamus. For example, OX neurons (in LH) are more involved in regulating the reward cycle for addictive behaviors.<sup>12,13</sup> Also, evidence suggests that OX1R and OX2R have different functions. For example, OX1Rs are involved in the induction of dependence on morphine and cocaine.<sup>14-16</sup>

Today, various antagonists for OX receptors have been developed with the aim of therapeutic application. Some antagonists can block both orexin receptors (dual orexin receptor antagonists/DORAs), but others selectively



block one of the receptors (selective orexin receptor antagonists/SORAs).<sup>17-19</sup>

### **The role of OX in the physiological functions of the body**

Orexin has been detected in various tissues such as cerebrospinal fluid, hypothalamus, sensory ganglia, pituitary, spinal cord, enteric nervous system, adrenal, salivary and lacrimal glands, vestibular gland, testis and skin.<sup>20</sup> In general, the neuropeptide orexin is important in regulating and modulating many functions, including arousal, sleep, food and fluid intake, pain, memory, smell perception, and sexual activity.<sup>7,11,20</sup> Findings of different studies have demonstrated that the level of OXA has an inverse relationship with body mass index and is lower in severely obese patients.<sup>21</sup> Therefore, the function of orexin is not only limited to the central nervous system (CNS).<sup>22</sup> Also, orexin is involved in regulating the sleep/wake cycle.<sup>23</sup> In fact, neurons that are effective in stimulating wakefulness (such as LC noradrenergic neurons) interact with orexin.<sup>24-26</sup> Orexin also affects maternal behavior. Therefore, it can be said that orexin affects a range of motivated behaviors.<sup>12,27</sup> Interestingly, according to the available evidence, the orexinergic system is related to pathological processes in neurological diseases such as depression, narcolepsy, Alzheimer's disease, ischemic stroke, and addiction.<sup>28</sup> Currently, there is emerging evidence that implicates the role of OX in the induction of tolerance and dependence to opioids and other drugs.<sup>12,13</sup>

### **The role of OX in drug dependence**

Glutamate is known as the most abundant excitatory neurotransmitter in the CNS, which is involved in about 70% of synaptic transmissions.<sup>29,30</sup> Reports indicate the key role of glutamate in drug addiction.<sup>29</sup> In fact, the glutamatergic system is related to drug addiction through specific releases.<sup>31-33</sup> Another factor involved in drug addiction is dopamine (key neurotransmitter in drug addiction). Studies have shown that drugs facilitate dopamine signaling. For example, morphine increases the release of dopamine in the brain.<sup>29</sup> Interestingly, reports indicate the existence of axon-axon synapses between glutamate and dopamine neurons, providing morphological evidence for their interaction in the addiction process.<sup>34,35</sup>

It has also been revealed that dopamine (in ventral tegmental area/VTA) and OX neurons are under gamma-aminobutyric acid (GABA) inhibition.<sup>36</sup> Morphine inhibits GABA release in the nucleus accumbens (NAc), which in turn increases the release of orexin and dopamine in downstream targets (this effect persists even after stopping morphine intake).<sup>37,38</sup>

Georgescu et al in 2003 demonstrated the role of OX neurons located in the LH in the induction of morphine tolerance and morphine-induced withdrawal syndrome.<sup>39</sup> Studies have indicated that OX neurons are activated by

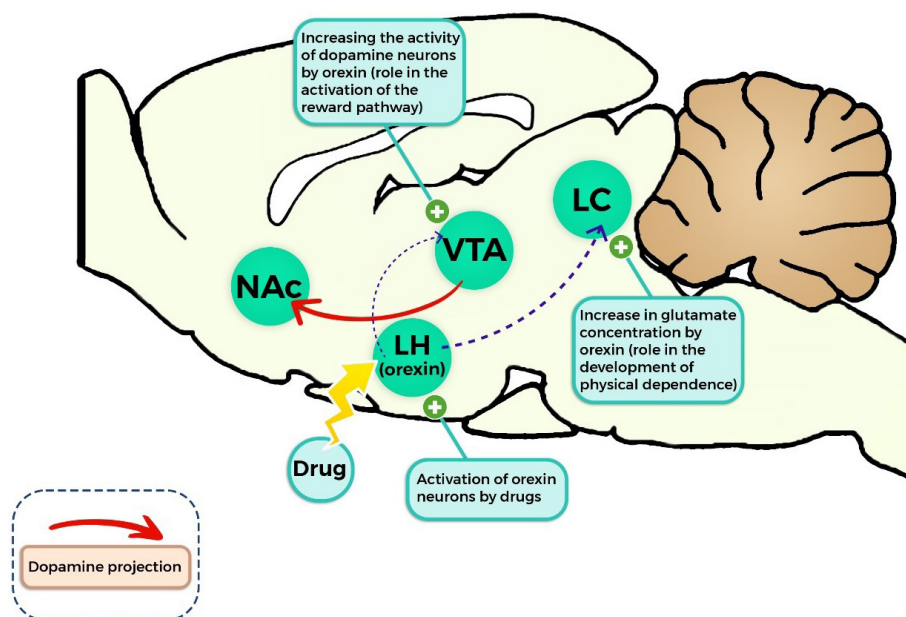
drugs. In fact, about 50% of orexinergic neurons can directly respond to opioids through the expression of  $\mu$  opioid receptors.<sup>39-41</sup> According to the results of studies, systemic injection of orexin can elevate the concentration of glutamate in locus coeruleus (LC). Also, orexin causes the release of dopamine in downstream targets by increasing the output and activity of dopamine neurons (in VTA).<sup>42-45</sup> In fact, orexin is a potent stimulatory transmitter for dopamine neurons and can cause addictive behaviors<sup>46</sup> (Figure 1).

Although there is currently little evidence of a link between orexin and addiction in humans, animal models have well demonstrated that OX neurons are important for the induction of addiction.<sup>47</sup> The studies conducted to date show a strong connection between orexin and the occurrence of addictive behaviors, which we will discuss further.

### *Orexin in cocaine and amphetamine dependence*

Cocaine addiction is characterized by loss of control over use, cocaine acquisition, and compulsive patterns of use.<sup>48</sup> After administration, cocaine enters all parts of the brain and leads to activation in the VTA, NAc and caudate nucleus, which are known as reward regions.<sup>49</sup> Interestingly, cocaine increases the number and activity of OX neurons (in LH).<sup>50</sup> According to the findings, orexin not only plays a role in maintaining hyperarousal states for cocaine seeking, but also contributes to the compulsive motivation to take cocaine.<sup>48,51,52</sup> In fact, inhibition of orexin signaling reduces several addictive effects of cocaine.<sup>39,45</sup> For example, OX1R antagonists attenuate amphetamine and cocaine-induced conditioned place preference (CPP) expression.<sup>53,54</sup> Also, evidence suggests that dual OXR antagonists (DORAs) may reduce cocaine-dependent behaviors by lowering increased dopamine levels in the ventral striatal.<sup>55</sup> One study found that suvorexant (DORA) administration could reduce the number of cocaine injections, prevent CPP in rats and reduce initial positive hedonic reactivity to cocaine. Their findings showed that suvorexant diminished the amount of extracellular dopamine in the ventral striatal.<sup>56</sup> Similarly, other studies have revealed that administration of OX1R antagonists reduces cocaine self-administration.<sup>54,57,58</sup>

Similarly, chronic administration of amphetamine induces behavioral sensitization and thus synaptic and structural adaptations in the VTA, dorsal raphe (DR) and ventrolateral preoptic area (VLPO).<sup>2,59</sup> Also, administration of methamphetamine or acute amphetamine increases Fos protein level (an indicator of neuron activation) in dorsomedial hypothalamus (DMH)/perifornical area (PFA) OX neurons.<sup>60-62</sup> These findings support the relevance of orexin signaling in drug-induced adaptation.<sup>2</sup> The results of a study showed that almorexant (DORA) does not produce conditional



**Figure 1.** The role of orexin on the reward pathway and the development of dependence caused by drug abuse (indicated based on rodent brain). NAc: nucleus accumbens, LH: lateral hypothalamus, VTA: ventral tegmental area, LC: locus coeruleus

reward effects but interferes with CPP expression and drug-induced locomotor sensitization. In fact, almorexant was able to attenuate the expression of CPP in high doses of amphetamines.<sup>63</sup> In another study, administration of SB-334867 (OX1R antagonist) dramatically decreased the effect of amphetamine on dopamine levels (in NAc shell/rat brain).<sup>64</sup> Overall, studies show that OXR antagonists are associated with decreased cocaine intake, CPP induced by cocaine or amphetamines and cocaine demand<sup>48,63,65,66</sup> (Tables 1 and 2).

#### Orexin in alcohol dependence

The orexin signaling system has an important function in generating highly salient positive reinforcement motivation.<sup>52</sup> Orexin is specifically associated with the drive toward drug-seeking, including alcohol.<sup>72-75</sup> In some animal studies orexin peptide increased following alcohol consumption, while in others it decreased.<sup>76-78</sup> Studies have revealed that the brain regions of the anterior thalamic paraventricular nucleus (aPVT), NAc and VTA are related with the OX system in alcohol abuse.<sup>79-81</sup> The findings indicate that the administration of OXR antagonists has been effective in reducing alcohol self-administration, consumption, and relapse.<sup>82-84</sup> Also, the administration of suvorexant in alcohol withdrawal syndrome reduced the latency to rapid eye movement (REM) and slow-wave sleep onset in a dose-dependent manner<sup>85</sup> (Table 3).

#### Orexin in opioids dependence

Experiments indicated that OX neurons are activated by morphine (during the CPP acquisition phase/in LH), and administration of the SB-334867 can dramatically

inhibit morphine-seeking expression.<sup>15,16</sup> Other studies have also indicated that injection of SB-334867 into VTA attenuates morphine-induced CPP in rats.<sup>46,74,88,89</sup> Studies in transgenic mice (knockout mice) also confirm that the absence of orexin reduces morphine dependence in mice.<sup>39</sup> Hooshmandi et al.'s findings demonstrated that blocking the OX1R receptor before receiving morphine could prevent dependence, but single-dose administration of the SB-334867 antagonist after dependence could not prevent the withdrawal syndrome.<sup>90</sup> Evidence suggests that orexin antagonists attenuate naloxone-induced withdrawal syndrome.<sup>91,92</sup> For example, Aghajani et al. reported that the administration of SB-334867 prevented hyperactivity of LC neurons following naloxone administration.<sup>93</sup> Interestingly, SB-334867 reduces the increased cyclic adenosine monophosphate (cAMP) concentration (in LC neurons/in morphine-dependent rats receiving naloxone).<sup>94</sup> Overall, the results propose that the activation of OX1R in the LC nucleus may be involved in the induction of morphine dependence, and OXR antagonists such as SB-334867 attenuate this effect.<sup>95</sup>

Although studies indicate a crucial role for OX1R receptor signaling in addictive behaviors,<sup>8,12,74,96</sup> it can be argued that orexin acts as a mediator in reward and drug addiction through both receptors.<sup>88</sup> For example, heroin self-administration (in rat) was dose-dependently attenuated by systemic administration of NBI-80713 (OX2R antagonist).<sup>97</sup> Therefore, it seems that DORAs can be considered in the study of drug addiction as a therapeutic potential. In another study by Esmaili-Shahzade-Ali-Akbari et al, the researchers found that suvorexant administration before each morphine injection could significantly prevent morphine

**Table 1.** Cocaine-based experiments

Addictive drug	Manipulation	Target	Subjects	Main findings/References
Cocaine	Suvorexant	dual OX1/2R	R (rat)	Attenuation of cocaine-induced impulsive behaviors (systemic or direct injection in VTA) <sup>67</sup>
	Suvorexant	dual OX1/2R	R	Attenuation of the hedonic and motivational effect induced by cocaine <sup>56</sup>
SB-334867	OX1R	OX1R	R	Counteracts the development of cocaine self-administration and attenuates the induction of amphetamine-induced CPP <sup>54</sup>
SB-334867	OX1R	OX1R	R	Administration of SB-334867 decreased cocaine intake (in a dose-dependent manner) <sup>48</sup>
SB-334867	OX1R	OX1R	M (mice)	SB-334867 blocks CPP induced by micro-injection of orexin in VTA <sup>65</sup>
SB-334867	OX1R	OX1R	M	SB-334867 injections (in VTA) attenuated impulsive-like behavior, LH self-stimulation, and cocaine self-administration <sup>57</sup>
SB-334867	OX1R	OX1R	R	Diminished the motivation for cocaine <sup>50</sup>
SB-334867	OX1R	OX1R	Female monkeys (rhesus)	Reduced cocaine self-administration <sup>58</sup>
SB-334867	OX1R	OX1R	R	Decreased demand for cocaine (in the presence of cocaine-related cues) <sup>66</sup>
SB-334867	OX1R	OX1R	R	Blocking OX1R or OX1R and OX2R together reduces the effect of cocaine on dopamine signaling and cocaine motivation, but blocking OX2R alone showed no effect <sup>55</sup>
Almorexant	dual OX1/2R	OX1/2R	R	Decrease cocaine self-administration and weaken cocaine-induced dopamine uptake inhibition <sup>55</sup>
RTIOX-276	OX1R	OX1R	R	Attenuation of cocaine-induced inhibition of dopamine uptake <sup>68</sup>

**Table 2.** Amphetamine/cannabis/nicotine-based experiments

Addictive drug	Manipulation	Target	Subjects	Main findings/References
Amphetamine	Almorexant	dual OX1/2R	R (rat)	Decreased cocaine and amphetamine-induced CPP expression but did not affect morphine-induced CPP expression/Interfered with morphine-induced locomotor sensitization but had no effect on cocaine and amphetamine-induced locomotor sensitization <sup>63</sup>
	SB-334867	OX1R	R	Decreased amphetamine-induced dopamine outflow (in NAc) and reduced amphetamine-induced sensitization <sup>64</sup>
Cannabis	SB-334867	OX1R	M (mice)	SB-334867 reduced the reinforcing and motivational properties of WIN55,212-2 (SORA2-TCS-OX2-29 had no effect) <sup>69</sup>
Nicotine	TCS 1102	dual OX1/2R	R	It had no effect on nicotine-seeking behavior <sup>70</sup>
	SB-334867	OX1R	M	Administration of SB-334867 reduced the somatic signs of nicotine-induced withdrawal but SORA2-TCS-OX2-29 had no effect <sup>71</sup>

**Table 3.** Alcohol-based experiments

Addictive drug	Manipulation	Target	Subjects	Main findings/References
Alcohol	Suvorexant	dual OX1/2R	R (rat)	Reduced the latency to REM sleep and sleep and slow-wave-sleep (SWS) onset in a dose-dependent manner/produced REM sleep and SWS fragmentation <sup>85</sup>
	Almorexant	dual OX1/2R	Healthy humans	Almorexant did not affect the pharmacokinetics of ethanol and did not synergize its effects <sup>86</sup>
Almorexant	dual OX1/2R	OX1/2R	R	Diminished alcohol self-administration (Systemic or VTA administration) <sup>79</sup>
Almorexant	dual OX1/2R	OX1/2R	R	It did not enhance the sedative effect of alcohol <sup>87</sup>
SB-334867	OX1R	OX1R	R	Reduced alcohol intake and preference (Intra-NAc infusions) <sup>80</sup>
SB-334867	OX1R	OX1R	R	Decreased alcohol relapse drinking <sup>83</sup>
SB-334867	OX1R	OX1R	R	Attenuated ethanol self-administration and the cue-induced reinstatement of ethanol-seeking in highly motivated rats <sup>82</sup>
GSK1059865	OX1R	OX1R	M (mice)	Significantly reduced alcohol consumption in ethanol-dependent Mice <sup>84</sup>
TCS-OX2-29	OX2R	OX2R	R	Microinjections of TCS-OX2-29 (into the aPVT) reduced intermittent-access ethanol drinking <sup>81</sup>

dependence and tolerance. This study revealed that suvorexant administration reduces the increased levels of p-ERK and cAMP response element-binding (CREB) proteins.<sup>98</sup> In the only clinical study conducted in this field, Huhn et al. found that suvorexant can reduce opioid withdrawal symptoms in opioid use disorder (OUD) patients. Suvorexant also increased the total sleep time of study participants. The results indicate that suvorexant

may have therapeutic potential in treating opioid withdrawal<sup>99</sup> (Table 4).

#### *Orexin in cannabis and nicotine dependence*

Studies on the effect of OXR antagonists on cannabinoid and nicotine abuse have yielded different results. For example, administration of SB-334867 attenuated the motivational and reinforcing properties of WIN55,212-

**Table 4.** Opioids-based experiments

Addictive drug	Manipulation	Target	Subjects	Main findings/ References
Opioids	Suvorexant	Dual OX1/2R	M (mice)	Decreased morphine tolerance and dependence / decreased increased levels of CREB and p-ERK proteins <sup>98</sup>
	SB-334867	OX1R	M	Administration of SB-334867 prevented morphine-induced sensitivity to locomotor activity in mice <sup>100</sup>
	SB-334867	OX1R	R (rat)	Significantly reduced naloxone-induced withdrawal syndrome physical symptoms in morphine-dependent rats <sup>92</sup>
	SB-334867	OX1R	R	Microinjection of SB-334867 into LC dramatically suppresses glutamate-induced morphine withdrawal <sup>101</sup>
	SB-334867	OX1R	M	Attenuated the symptoms of naloxone-induced withdrawal <sup>91</sup>
	SB-334867	OX1R	R	Attenuation of morphine-induced CPP (acquisition and expression/micro-injection into VTA) <sup>89</sup>
	SB-334867	OX1R	R	Intra-DG (dentate gyrus) administration dose-dependently reduced morphine priming-induced reinstatement <sup>102</sup>
	SB-334867	OX1R	R	Decreased motivation and the cue-induced reinstatement of remifentanyl-seeking <sup>103</sup>
	SB-334867	OX1R	R	Inhibition of increased activity of LC neurons following naloxone administration in morphine-dependent rats <sup>93</sup>
	SB-334867	OX1R	R	Prevention of naloxone-induced neuronal activation within the LC in morphine-dependent rats/ Decreased cAMP concentration in LC neurons <sup>94</sup>
	SB-334867	OX1R	R	Significant reduction of physical symptoms of morphine withdrawal syndrome induced by naloxone <sup>95</sup>
	TCS-OX2-29	OX2R	R	Intra-DG (dentate gyrus) administration dose-dependently reduced morphine priming-induced reinstatement <sup>102</sup>
	TCS-OX2-29	OX2R	R	Attenuation of morphine-induced CPP (acquisition and expression/micro-injection into VTA) <sup>89</sup>
	NBI-80713	OX2R	R	Dose-dependently reduced heroin self-administration (systemic administration) <sup>97</sup>

2 (synthetic cannabinoid agonist), but administration of TCS-OX2-29 (selective OX2R antagonist, SORA2) had no effect.<sup>69</sup> It was also shown that administration of TCS 1102 (DORA) had no effect on nicotine seeking in rats, but administration of SB-334867 could reduce nicotine withdrawal (somatic signs)<sup>70,71</sup> (Table 2).

### Possible mechanisms of orexin involvement in the induction of drug dependence

Although the role of OX in increasing the levels of neurotransmitters (glutamate and dopamine) involved in addiction has been indicated in many studies,<sup>42–45,55,56</sup> the cellular mechanisms related to the involvement of OX in the induction of addictive behaviors have not been fully investigated. Evidence has indicated that cocaine, amphetamines, and other addictive substances strongly activate the ERK (extracellular signal-regulated kinases) pathway through the signaling system initiated by activating either dopamine or glutamate receptors, or both.<sup>104–106</sup> Indeed, N-methyl-D-aspartic acid (NMDA) receptors increase ERK phosphorylation by increasing Ca<sup>2+</sup> permeability and activating several Ca<sup>2+</sup>-dependent kinases.<sup>29</sup> Also, OXA and OXB can increase ERK phosphorylation<sup>107,108</sup>. In fact, orexin activates the p38-MAPK signaling pathway and increases ERK1/2 phosphorylation by interfering with the Gq/PLC/PKC signaling pathway.<sup>28</sup> Since OX neurons respond to opioids,<sup>39–41</sup> consumption of opioids increases orexin levels, which can eventually lead to increased ERK phosphorylation. Esmaili-Shahzade-Ali-Akbari et al. demonstrated that suvorexant administration with morphine reduces the level of p-ERK (in mouse brain).<sup>98</sup>

It is possible that antagonists of orexin receptors, such as suvorexant, may reduce the level of p-ERK by blocking orexin receptors and preventing the activation of the MAPK signaling pathway.

CREB transcription factor has been widely demonstrated in forms of cellular adaptation and it has been reported that its expression changes in drug addiction.<sup>109,110</sup> Studies on the pathways involved in morphine dependence have demonstrated that chronic administration of morphine alters the cAMP system. In general, chronic morphine use increases CREB, PKA (cAMP-dependent protein kinase) and cAMP.<sup>29</sup> Also, it has been demonstrated that the administration of OXR antagonists leads to a significant reduction in CREB protein levels in morphine-dependent animals.<sup>98,111</sup> Therefore, orexin appears to help in the induction of drug addiction by increasing the level of CREB protein, which is inhibited by orexin receptor antagonists.

### Conclusions and future perspectives

Addiction is a chronic health-related disorder; research suggests a role for the OX receptors in drug addiction. Hitherto, most studies have focused on the OX1R, while the OX2R also appears to play a role. OX2R is generally involved in sleep arousal, but in specific regions of the brain, it can play a role in expressing and regulating addiction and negative emotions. There is a relative lack of studies on OX2R in drug dependence in the literature. Although the mechanisms by which OX may be involved in drug addiction are not yet fully understood, it has been reported that orexin can alter dopamine levels and affect the levels of p-ERK and CREB proteins. Animal

and clinical studies on the orexinergic system show a valuable therapeutic potential for OXR antagonists in the treatment of drug dependence and the alleviation of withdrawal symptoms. Nevertheless, the development of OXR antagonists with better pharmacological properties (for example better solubility, faster distribution, higher functional power, and more bioavailability) can improve their clinical application.

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#### Competing Interests

The authors declare none.

#### Data Availability Statement

Data are contained within the article and are available from the corresponding authors upon reasonable request.

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Not applicable.

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