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Insight into the Potential Factors That Promote Tobacco Use in Vulnerable Populations

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Abstract It is presently unclear why certain populations are more vulnerable to tobacco use and less responsive to smoking cessation interventions. This review considers the contribution of nicotine reward and withdrawal in populations that appear to be more susceptible to tobacco use. Our focus is on populations that have been modeled in rodents including, adolescents, females, and persons with metabolic disorders, such as diabetes. A common feature across these rodent models is heightened nicotine reward, suggesting that vulnerable populations may experience strong rewarding effects of nicotine that promote tobacco use. One distinguishing factor among these rodent models of at-risk populations is with regard to the magnitude of nicotine withdrawal, which is lower during adolescence. These groups also differ with regard to expression of the physical signs versus affective states produced by withdrawal, suggesting that these distinct facets of withdrawal differentially contribute to tobacco use in vulnerable populations. Thus, we may need to apply different diagnostic criteria and/or specialized treatments that target the unique factors that promote tobacco use in different vulnerable populations.

Keywords Adolescence · Diabetes · Females · Nicotine · Smoking · Withdrawal

This article is part of the Topical Collection on *Tobacco*

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Introduction

Epidemiological evidence has suggested that high rates of tobacco use contribute to health disparities in vulnerable populations. However, it is unclear why certain groups are more susceptible to using tobacco and are less likely to respond to cessation approaches. This review considers the different factors that may promote tobacco use in certain at-risk populations. The addictive nature of tobacco has been largely attributed to nicotine, a major alkaloid component of tobacco [1, 2]. Following chronic tobacco use, abstinence from this drug elicits a withdrawal syndrome that is believed to drive continued use and relapse behavior. This review considers clinical and pre-clinical studies that have compared nicotine reward and withdrawal in adolescents, females, and individuals with diabetes. Our assessment of the literature suggests that strong rewarding effects of nicotine promote tobacco use among vulnerable populations. Also, there are group differences with regard to nicotine withdrawal that may contribute to enhanced tobacco use in certain groups. This review also addresses the neurochemical systems that modulate group differences in nicotine withdrawal. Continued research on the biological mechanisms that promote tobacco use is important towards developing specialized medications that will target the unique factors that promote tobacco use in vulnerable populations.

Nicotine Reward and Withdrawal

Tobacco use is motivated by at least two processes involving the positive rewarding effects of nicotine and avoiding the negative consequences of withdrawal from this drug. Initially, tobacco use is largely motivated by the positive rewarding effects of nicotine that sustain continued use. Nicotine also possesses short-term aversive effects that may

limit initial use or discourage future experimentation with tobacco products. In rodents, the most common models used to study the rewarding effects of nicotine involve intravenous self-administration (IVSA) and place preference procedures involving classical conditioning between the subjective effects of nicotine and external environmental cues [3]. In rodents, nicotine produces rewarding (conditioned place preference; CPP) or aversive (conditioned place aversion; CPA) effects depending on the dose of nicotine that is used.

Following chronic tobacco use, withdrawal from nicotine produces a milieu of withdrawal symptoms including physical signs, negative affective states and cognitive deficits (see Table 1; [4]). Growing evidence suggests that the physical signs of withdrawal are mechanistically distinct from negative affective states. Early studies addressing this issue revealed that the physical signs of withdrawal are mediated via central and peripheral nicotinic acetylcholine receptors (nAChRs), whereas affective states are modulated via central nAChRs [5, 6]. A recent review summarizing the role of various nAChR subunits revealed that α2, α3, α5, α7, and β4 modulate physical signs, whereas α6 and β2 modulate affective states produced by nicotine withdrawal [7•]. Also, a recent study revealed that the physical signs of withdrawal were not correlated with high levels of anxiety or nicotine intake observed during abstinence from extended access to nicotine IVSA [8]. Together, these studies suggest that the physical versus negative affective states produced by withdrawal are modulated via distinct mechanisms. By extension, one might also predict that there are unique factors that promote tobacco use across different at-risk populations such as adolescents, females, and persons with diabetes.

Tobacco Use in Vulnerable Populations

Adolescence There is a myriad of external factors that promote the initiation of tobacco use during adolescence, such as enhanced risk-taking, peer pressure, and concerns about weight gain [9–11]. To our knowledge, the rewarding effects of nicotine have not been directly compared in adolescent and adult tobacco users. However, it is well established that adults who initiate smoking during adolescence are more likely to continue smoking into adulthood as compared to adults that initiate smoking later in life [12, 13]. Pre-clinical studies have shown that nicotine reward is enhanced during the adolescent period of development (post-natal days 28–45; [14]). For example, adolescent rodents display greater nicotine CPP as compared to adults across a wide range of experimental protocols, nicotine doses, and routes of administration [15–22]. Studies using IV and oral SA procedures have also shown that nicotine intake is higher in adolescent versus adult rats [23–28] and mice [29]. High doses of

Table 1 Physical and affective states produced by nicotine withdrawal

	Rodents	Humans
Physical signs	Gasps	Bradycardia
	Abdominal constrictions (writhes)	Gastrointestinal discomfort
	Facial fasciculations	Increased appetite
	Eye blinks and ptosis	
	Teeth chatters	
	Escape attempts and rearing	
	Head and body shakes	
	Yawns and paw licks	
	Decreased activity	
	Hyperalgesia	Increased pain sensitivity
Affective states	Negative affective states:	Craving
	-Place aversion	Depressed mood
	-Taste aversion	Dysphoria
	-Lower brain stimulation reward thresholds	
	Anxiety-like behavior:	Stress and anxiety
	Increases in:	Irritability
	-Closed arm time (elevated plus maze)	
	-Corner time (open field)	
	-Latency to enter dark side (light dark transfer)	
	-Latency to bury (marble burying)	
Cognitive deficits	Memory and attention deficits	Difficulty concentrating

For a recent and comprehensive review of the physical and affective states produced by withdrawal in rodents and humans, the reader is referred to Hall et al. [4]

nicotine also produce aversive effects that are lower in adolescent versus adult rats [18, 30].

With regard to withdrawal, clinical studies have revealed that young smokers exhibit milder symptoms of withdrawal during abstinence from smoking [31], and they are less responsive to cessation approaches that alleviate withdrawal [32–34]. However, it is also acknowledged that young smokers display robust cue-elicited craving despite occasional cigarette use [35]. Pre-clinical studies have shown that the physical signs of nicotine withdrawal are generally lower in adolescent versus adult rats [36] and mice [16]. Also, the negative affective states elicited during nicotine withdrawal are lower in adolescent versus adult rats in intracranial self-stimulation [36] and CPA [30, 37] procedures. It should be noted, however, that nicotine withdrawal produces an increase in anxiety-like behavior that is similar in adolescent and adult mice [38]. Nicotine withdrawal also produces cognitive impairments that are greater in adolescent rats, suggesting that improved cognitive abilities may amplify tobacco use during adolescence [39]. In summary, these studies suggest that the rewarding effects of nicotine are greater, but the behavioral effects of nicotine withdrawal are lower during the adolescent period of development.

Females The rewarding effects of nicotine appear to be greater in females versus males. For example, self-reports of positive mood effects are higher in women versus men smokers [40]. Additionally, female smokers display greater responding for smoking-related cues and lower quit rates as compared to men [41, 42]. However, the rates of current smoking have been reported to be slightly higher in males (18.8 %) than females (14.8 %) according to the 2014 Morbidity and Mortality Weekly Report of the Centers for Disease Control and Prevention. Pre-clinical studies have shown that females display a more robust CPP produced by nicotine than male rats [21] and mice [38]. Also, CPP is produced following a single drug pairing in female, but not male, rats [43]. Female rats also display higher levels of nicotine IVSA following presentation of conditioned stimuli as compared to males [44, 45]. However, another study found that female and male rats display similar levels of nicotine intake and reinstatement of extinguished nicotine-seeking behavior [46]. The authors of the latter report suggest that their lack of sex differences may be related to their use of low reinforcement requirements.

With regard to withdrawal, clinical studies have shown that women report that the primary reason for smoking and relapse behavior is to reduce anxiety and avoid stress [47, 48]. Indeed, women report greater levels of anxiety, depression, and stress [49–51] and they display higher levels of cortisol (a biological marker of stress in humans) during smoking abstinence as compared to men [52]. Pre-clinical studies have shown that the physical signs of nicotine withdrawal are similar in female and male rats; however, CPA produced by withdrawal is larger in female versus male mice [16, 38] and rats [53••]. Female rats also display an increase in anxiety-like behavior and plasma corticosterone levels that is larger than males [54–56]. These studies suggest that nicotine withdrawal induces similar physical signs in females and males; however, the negative affective states induced by withdrawal is larger in females. The latter effect appears to be modulated via ovarian hormones, as ovariectomized (OVX) females do not display anxiety-like behavior during withdrawal [57]. In summary, these studies suggest that both nicotine reward and withdrawal are greater in females as compared to males.

Diabetes Persons with metabolic disorders, such as diabetes, appear to be more prone to using tobacco. Much of the clinical work in this area has focused on patients with type 1 diabetes, which is a condition that produces little to no release of insulin from the pancreas. Smoking rates in adolescents with type 1 diabetes are higher than healthy controls (47 versus 38 %; [58]). Also, persons with type 1 diabetes report higher rates of current smoking (12.3 %) as compared to non-diabetic subjects (8.6 %; [59]). A recent examination of cigarette smoking trends from 2001 to 2010 revealed that smoking rates are similar in persons with and without diabetes [60]. However, the latter survey also revealed that the decline in smoking rates over this period is lower in persons with diabetes, indicating a sustained use of tobacco in persons with diabetes. Pre-clinical studies have employed two common models of diabetes involving streptozotocin (STZ) administration or a chronic high-fat diet (HFD) regimen [61]. STZ is a drug that is taken up via glucose (type 2) transporters that are concentrated on the insulin-producing beta cells of the pancreas. STZ is toxic to these cells and, as a result, produces a decrease in insulin (hypoinsulinemia) and a concomitant increase in blood glucose (hyperglycemia). The HFD model of diabetes produces insulin resistance and hyperglycemia following chronic exposure to a HFD regimen. Pre-clinical studies have revealed that STZ-treated rats display higher levels of nicotine IVSA as compared to healthy controls [62]. A subsequent study revealed that insulin resistance, produced by HFD regimen, potentiates CPP produced by nicotine [63]. This suggests that insulin resistance enhances nicotine reward via a disruption of insulin signaling. However, another report revealed that mice placed on a HFD regimen do not display nicotine CPP [64]. The discrepancy in these reports may be related to metabolic differences between rats and mice and/or different doses of nicotine and routes of administration.

With regard to withdrawal, persons with diabetes display higher rates of depression and anxiety during abstinence as compared to non-diabetic smokers [65]. Diabetic persons that smoke also display higher levels of stress, negative affect, and depression as compared to non-smokers [66, 67]. To our

knowledge, pre-clinical studies have not compared nicotine withdrawal in rodent models of diabetes. However, unpublished observations in our laboratory have revealed that STZ-treated rats display more physical signs and a larger magnitude of CPA and anxiety-like behavior produced by withdrawal as compared to controls. These studies suggest that both nicotine reward and withdrawal are greater in hypoinsulinemic rats as compared to controls.

Summary of Behavioral Studies Figure 1 depicts the factors that promote tobacco use in adolescents, females, and subjects with diabetes. A common factor that appears to promote tobacco use across all groups is the strong rewarding effects of nicotine that are unopposed by the direct aversive effects of this drug. There are group differences, however, with regard to the contribution of withdrawal. In adolescents, both the physical signs and negative affective states produced by withdrawal are lower than adults. Thus, it has been suggested that the strong rewarding effect of nicotine is a major contributing factor to enhanced tobacco use during adolescence [68–71]. In females, nicotine withdrawal produces an intense anxiety-like behavior but similar physical signs as compared to males. Hence, both the strong rewarding effect of nicotine and intense anxiety produced by withdrawal promote tobacco use in females [53••, 57, 72, 73]. In diabetes, both the physical signs and affective states produced by withdrawal are heightened as compared to controls. This is noted as a larger arrow that consists of both facets of withdrawal. As a result, it has been suggested that both the strong rewarding effect of nicotine and intense physical signs and affective states produced by withdrawal promote tobacco use in subjects with diabetes [74–76]. This review is intended to highlight the primary factors that drive tobacco use in these vulnerable groups, and future studies are needed to cross compare which populations and unique factors are most critical towards promoting tobacco use in groups that are most at risk for tobacco use. Given the different contribution of these factors, one might predict that the underlying mechanisms that modulate these facets of withdrawal are distinct.

Mechanisms of Nicotine Withdrawal in Vulnerable Populations

The neurochemical systems discussed here focus on the mesolimbic pathway because this system has been shown to play a central role in modulating nicotine reward and withdrawal, and previous work comparing nicotine use in vulnerable populations has largely focused on this pathway. The mesolimbic pathway has dopaminergic fibers originating in the ventral tegmental area (VTA) that project to a series of forebrain structures within the extended amygdala, including the central nucleus of the amygdala, bed nucleus of the stria terminalis (BNST), and the shell of the nucleus accumbens

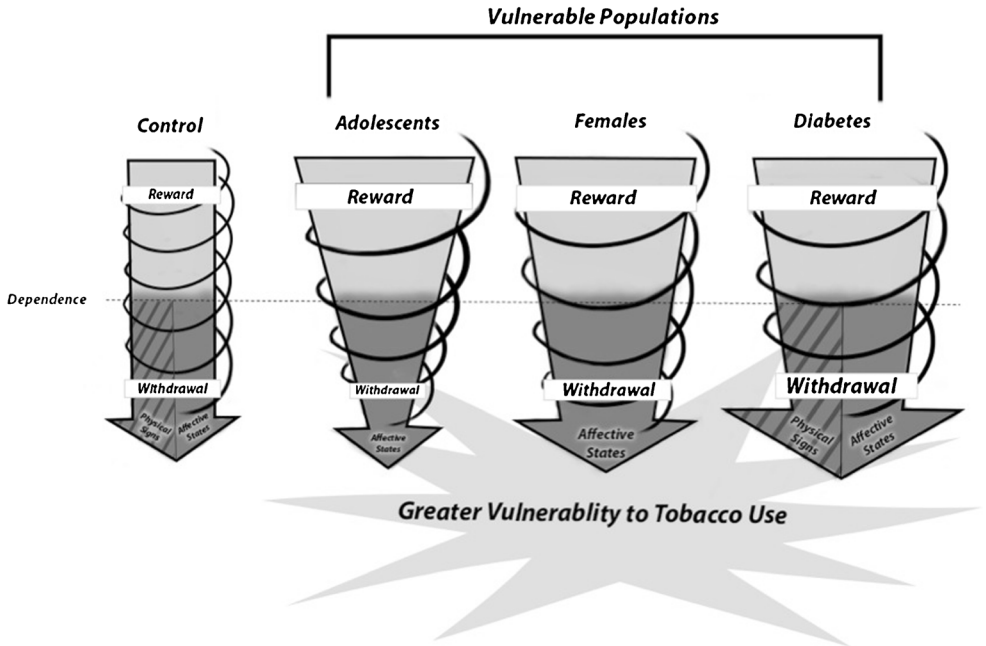

Fig. 1 The *arrows* depict the downward trajectory of nicotine dependence from the initial rewarding effects of this drug to the emergence of a withdrawal syndrome during abstinence. The contribution of nicotine reward and withdrawal is denoted in adolescents, females, and persons with diabetes. The *size of the arrow* reflects the relative contribution of these factors relative to their respective controls (i.e., adult males that use tobacco but are otherwise healthy). Across all groups, a common factor that contributes to tobacco use is the strong rewarding effects of nicotine. However, there are significant group differences with regard to the magnitude of nicotine withdrawal and the degree to which the physical signs versus affective states contribute to tobacco use in these at-risk populations

(NAcc; [77]). Much work has demonstrated that nicotine enhances dopamine transmission in the NAcc, via excitatory glutamate input from the prefrontal cortex and inhibitory gamma-aminobutyric acid (GABA) innervation from local interneurons [78, 79]. While the NAcc is a key structure involved nicotine reward, withdrawal from this drug produces a decrease in NAcc dopamine levels that is believed to serve as a biomarker of withdrawal from drugs of abuse [80–82]. The decrease in NAcc dopamine levels produced by nicotine withdrawal appears to be modulated via an increase in GABA and a decrease in glutamate levels in the VTA [27]. Given the importance of the NAcc in modulating nicotine withdrawal, the following sections focus on the changes in this structure that might explain group differences produced by nicotine withdrawal.

Adolescence Initial studies comparing age differences produced by nicotine withdrawal revealed that adolescents display a smaller decrease in NAcc dopamine levels than adults [27]. Subsequent studies revealed that this neurochemical resistance is modulated via enhanced glutamate and reduced GABA release in the VTA [83]. Adolescent rats were also resistant to the decreases in NAcc dopamine levels produced by administration of a kappa agonist in nicotine-dependent rats [84]. Subsequent studies revealed that adolescent and adult rats display similar increases in ACh levels [85] and stress-associated genes [57] in the NAcc during nicotine withdrawal. Taken together, these studies suggest that age differences produced by nicotine withdrawal are modulated via NAcc dopamine systems.

Females The NAcc appears to also modulate sex differences in nicotine withdrawal. Initial studies comparing sex differences produced by nicotine withdrawal revealed that adult females display an increase in the expression of CRF mRNA in the NAcc that is larger than males [56]. CRF is thought to undergo a dynamic shift from facilitating hedonic states to promoting aversive states produced by chronic stress. This is based on the finding that intra-NAcc infusions of CRF produce CPP and an increase in local dopamine levels in naïve rats [86]. However, intra-NAcc CRF administration produces CPA and a reduction in dopamine levels in chronically stressed rats. Recently, we postulated that nicotine withdrawal induces a larger increase in CRF and, as a result, a larger decrease in dopamine in the NAcc in females as compared to males [57]. This hypothesis is based on our finding that adult females display a larger increase in dopamine (D1) receptor mRNA levels in the NAcc than males [57]. The latter result is believed to serve as indirect evidence that dopamine levels are lower in the NAcc of females versus males during withdrawal. In our mechanistic hypothesis, we also postulated that the decrease in NAcc dopamine is modulated via a CRF/GABA interaction. This is based on the finding that activation of CRF-R1 receptors in the NAcc increases GABA and decreases dopamine levels in this region [87]. Thus, we postulate that females display heightened CRF release and activation of CRF-R1 receptors that increases GABA and decreases dopamine levels in the NAcc. In support of our working hypothesis, unpublished observations have revealed that nicotine withdrawal produces an increase in NAcc GABA levels that are higher in female versus male rats. Work in other laboratories has also shown that females display overactivation of CRF stress systems. For example, Bangasser et al. [88] demonstrated that female rats display higher levels of CRF and a larger ratio of CRF-1 receptor coupling to G-proteins as compared to males. Female rats also display lower levels of beta-arrestin2, a protein that modulates CRF-R1 receptor internalization [53••, 89]. Taken together, it is suggested that the ability of CRF to modulate NAcc dopamine via GABA is disproportionately greater in females as compared to males.

Diabetes To our knowledge, no one has compared the neurochemical mechanisms of nicotine withdrawal in rodent models of diabetes. Previous studies have shown that STZ-treated rats display a profound suppression of dopamine release and D1 receptors in the NAcc [62]. Also, STZ-treated rats display a suppression of dopamine release in the dorsal striatum [90–94]. Based on the finding that STZ-treated rats display a general suppression of dopamine transmission, one might predict that hypoinsulinemic rats would display a larger decrease in NAcc dopamine levels during nicotine withdrawal. Future studies are needed to examine this important question, especially given that diabetic patients may self-medicate their deficits in dopamine with substances, such as nicotine.

Summary To date, our work has focused on the underlying factors that play a central role in promoting tobacco use in populations that are at greater risk for using tobacco. Although it is not possible at this time to provide a unifying hypothesis to explain why certain populations are more vulnerable to tobacco use, we have taken important steps towards understanding the unique factors that promote tobacco use in certain groups. Namely, in adolescents, our work suggests that a heightened regulation of dopamine in the NAcc promotes the rewarding effects of nicotine and protects from the decreases in dopamine produced by withdrawal. In females, the strong rewarding effects of nicotine and intense stress produced by withdrawal are modulated via enhanced CRF systems that regulate dopamine release in the NAcc. In diabetic rodent subjects, hypoinsulinemia produces a profound suppression of dopamine systems in the NAcc that may lead to profound reductions in dopamine during withdrawal. Future studies are needed to more fully understand the complex

network of brain systems that promote tobacco use in vulnerable populations.

Alternative Systems That May Modulate Group Differences in Withdrawal

Recent evidence suggests that nicotine withdrawal is also modulated via the habenula-interpeduncular (Hb-IPN) pathway [95••, 96, 97]. Microinjections of a nAChR antagonist in the habenula or IPN elicit physical signs of withdrawal in nicotine-dependent mice [98••]. However, the latter effect was not observed following injections in other regions, such as the VTA, cortex, or hippocampus. Also, intra-IPN infusions of a glutamate antagonist facilitate marble burying produced by nicotine withdrawal, and this effect is reversed following administration of a CRF-R1 antagonist [98••].

Recently, it has been suggested that the Hb-IPN and mesolimbic pathways play a distinct role in modulating the physical versus affective components of withdrawal [99••]. Indeed, there is a high density of α5 and β4 nAChR subunits in the Hb-IPN pathway, and mice lacking these subunits display fewer physical signs and heightened hyperalgesia produced by withdrawal [97, 100]. On the other hand, there is a higher density of α6 and β2 nAChR in the VTA as compared to the habenula or IPN, and mice lacking these subunits display reduced anxiety-like behavior but no differences in physical signs produced by nicotine withdrawal [100]. Furthermore, intracerebroventricular injections of an α6 antagonist attenuated CPA and anxiety-like behavior but had no effect on the physical signs of nicotine withdrawal in wild-type mice [101].

With regard to vulnerable populations, we have observed that the physical signs and affective states produced by withdrawal are separable. Namely, adolescents display fewer physical signs but similar affective states as compared to adults experiencing nicotine withdrawal [20, 36]. Also, female adult rats display greater negative affective states but similar physical signs of withdrawal than males [21]. These data suggest that there are group differences in the physical versus affective states produced by withdrawal. These group differences are likely modulated within distinct circuits in the brain, such as the mesolimbic and/or Hb-IPN pathway. Indeed, the habenula is a sexually dimorphic nucleus with regard to sexual behavior and the distribution of androgen and estrogen receptor mRNA in this region [102, 103]. Future research is needed to examine the unique contribution of the mesolimbic and Hb-IPN pathways in promoting tobacco use in different vulnerable populations. There are also connections between the mesolimbic and Hb-IPN pathways that may modulate different aspects of nicotine withdrawal. Indeed, the IPN receives heavy glutamatergic input from the medial habenula and dense CRF innervation from the VTA [98••, 104•]. This suggests that there is likely cross communication between the mesolimbic and Hb-IPN pathways that form a larger brain construct that modulates nicotine withdrawal.

Conclusion and Clinical Implications

The information provided here offers some clinical implications to consider. First, we may need to focus our efforts of providing a better understanding of the mechanisms that modulate the unique factors that promote tobacco use in at-risk groups. This will help guide the development of more specialized and effective treatments for smoking cessation in vulnerable populations. Second, a common factor that promotes tobacco use in vulnerable populations is the strong rewarding effect of nicotine. Thus, it is important to educate populations that may be more susceptible to initiating tobacco use, especially given that marketing strategies target certain groups, such as young females that are particularly susceptible to tobacco use. Third, our findings suggest that group differences in withdrawal may alter our approach to smoking cessation in different groups. In adolescents, we may need to apply different diagnostic criteria or smoking cessation medications in young persons that may not experience strong nicotine withdrawal and/or deficits in dopamine. In females, our results suggest that the most effective smoking cessation treatments may need to target stress that plays an important role in tobacco use and relapse behavior in women. As a whole, our work implies that health care professionals should assess the demographic and health background of their patients in order to deliver more specialized treatments that might be more effective in certain vulnerable populations.

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Compliance with Ethical Standards

Conflict of Interest Luis M. Carcoba, Oscar V. Torres, Joseph A. Pipkin, Tiahna Ontiveros, and Laura E. O'Dell declare that they have no conflict of interest.

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- •• Of major importance

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