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Mood and anxiety regulation by nicotinic acetylcholine receptors: a potential pathway to modulate aggression and related behavioral states

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Abstract

The co-morbidity between smoking and mood disorders is striking. Preclinical and clinical studies of nicotinic effects on mood, anxiety, aggression, and related behaviors, such as irritability and agitation, suggest that smokers may use the nicotine in tobacco products as an attempt to self-medicate symptoms of affective disorders. The role of nicotinic acetylcholine receptors (nAChRs) in circuits regulating mood and anxiety are beginning to be elucidated in animal models, but the mechanisms underlying the effects of nicotine on aggression-related behavioral states (ARBS) are still not understood. Clinical trials of nicotine or nicotinic medications for neurological and psychiatric disorders have often found effects of nicotinic medications on ARBS, but few trials have studied these outcomes systematically. Similarly, the increase in ARBS resulting from smoking cessation can be resolved by nicotinic agents, but the effects of nicotinic medications on these types of mental states and behaviors in non-smokers are less well understood. Here we review the literature on the role of nAChRs in regulating mood and anxiety, and subsequently on the closely related construct of ARBS. We suggest avenues for future study to identify how nAChRs and nicotinic agents may play a role in these clinically important areas.

Introduction

Nicotine consumption through tobacco products is highly co-morbid with mood disorders, including depression, anxiety and irritability; however the connection between nicotine use and behavioral regulation remains unclear and is still debated (Moylan et al., 2012). For instance, the overall incidence of smoking in depressed patients is twice as high as in the general population (Glassman et al., 1990) and the rate of smoking relapse is greater in patients with depression (Covey et al., 1998). The underlying mechanisms mediating the connection between smoking and mood alterations are not yet understood, however. Tobacco use could precipitate mood dysregulation, potentially explaining the higher incidence of depression in smokers (Boden et al., 2010); however, many studies have reported that nicotine can improve symptoms of depression under some conditions (Salin-

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Pascual et al., 1995; Tizabi et al., 1999). It has therefore been suggested that nicotine in tobacco is used in an effort to self-medicate symptoms of depression and other psychiatric disorders (Markou et al., 1998). In addition, smoking cessation and nicotine withdrawal can be accompanied by depressive episodes, stress-induced anger, and increased tension (al'Absi et al., 2007; Hatsukami et al., 1985). Taken together, these associations suggest that alterations in signaling through nicotinic acetylcholine receptors (nAChRs) might be involved in mood regulation. In this review we discuss potential mechanisms underlying the association between nAChRs and depression and anxiety.

Mood dysregulation, especially depressed mood and co-morbid anxiety states, is influential in regulating the constructs of aggression, irritability, and agitation, an interrelated triad we refer to as aggression-related behavioral states (ARBS). We review studies from both pre-clinical and clinical studies that demonstrate a key role for nAChRs in ARBS, and suggest that nAChR modulation of mood and/or anxiety might account, in part, for its effects on ARBS. Finally, we propose that further study at the pre-clinical and clinical levels might encourage development of novel nicotinic-based agents for treating mood dysregulation as well as ARBS.

Preclinical studies of nicotine on mood, anxiety, and aggression-related behavioral states

i. Depression and anxiety—While there are variable effects of nicotinic signaling on behaviors related to depression, numerous studies suggest that decreasing activity of α4β2* nAChRs can improve symptoms of depression (for reviews see Mineur and Picciotto, 2009; Picciotto et al., 2008). Chronic nicotine exposure induces up-regulation of nAChRs, but also profound desensitization of these receptors *in vitro* (Fenster et al., 1997; Grady et al., 1994). Studies in slices have shown that α4β2* nAChRs can be rapidly and persistently desensitized in the presence of nicotine, whereas α7 nAChRs can maintain their activity (Mansvelder et al., 2002). These data suggest there is decreased ACh signaling through some nAChR subtypes during ongoing smoking, but likely to be restored and potentially increased over time (because high affinity nAChRs are upregulated by chronic nicotine use as experienced by smokers (Fenster et al., 1999) as nicotine is cleared during withdrawal. This phenomenon could also underlie the cyclical mood dysregulation experienced by smokers between smoking episodes, and could therefore perpetuate smoking behavior (Watkins et al., 2000). For example, one group has proposed that a single puff of a cigarette results in occupancy of 50% of α4β2* nAChRs for more than 3 hours, that blood levels of nicotine in a smoker would saturate almost 90% of these nAChRs for hours and that desensitization of these receptors can suppress craving (Brody et al., 2006). This could explain why nicotinic signaling has seemingly paradoxical effects: low dose chronic nicotine has a comparable effect to an antagonist of high affinity β2 subunit-containing (β2*) nAChRs in a conditioned emotional response task in mice (Anderson and Brunzell, 2012), and both nicotine and the nicotinic antagonist mecamylamine can increase serotonin release in the hippocampus (Kenny et al., 2000). Several pharmacological studies have confirmed that nicotinic blockers (antagonists or partial agonists) can alleviate depression-like behaviors in mice, either alone or in combination with monoaminergic drugs (Andreasen et al., 2009; Bacher et al., 2009; Mineur et al., 2009; Mineur et al., 2011; Rollema et al., 2009). Interestingly, commonly used antidepressants can also act as α4β2* nAChR antagonists in

cell-based assays (Shytle et al., 2002; Slemmer et al., 2000), suggesting that these medications might also act in synergy with nAChR signaling to be fully effective. Rodent studies have further demonstrated that the effects of selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs) in models of depression-like behaviors can be potentiated by nAChR antagonists or partial agonists (Andreasen et al., 2009; Andreasen and Redrobe, 2009; Rollema et al., 2009), and that β2* nAChRs are required for antidepressant efficacy of at least one antidepressant medication (Caldarone et al., 2004). Conversely, mice with increased activity of α4β2* nAChRs as a result of a point mutation in the α4 subunit show increased anxiety-like behaviors (Labarca et al., 2001).

These studies suggest that limiting nAChR signaling through α4β2* nAChRs can lead to positive effects on mood symptoms, however other nAChRs also appear to be important for antidepressant responses. A recent study showed that functional β4 nAChRs are required for the full effect of buproprion, an atypical antidepressant (Radhakrishnan et al., 2013). In addition, some reports suggest that *increased* signaling at α7 nAChRs in combination with therapies that increase serotonin signaling can also improve performance in tests of antidepressant efficacy (Andreasen et al., 2012; Andreasen et al., 2013). These data suggest that a partial agonist, or a mix of agents with differing effects at heteromeric and homomeric nAChRs may be the most promising for developing nicotinic-based antidepressants, because the valence of nAChR signaling can be very different and depends on receptor subtype and brain region (Picciotto et al., 2008; Picciotto et al., 2012). These apparent discrepancies may also explain some of the controversy about the role of nicotine in mood regulation. Some models have proposed that nicotine use can, in fact, lead to negative effects on mood, for instance through HPA axis activation (Mendelson et al., 2005). Thus, because nicotine can both activate and desensitize different nAChR subtypes, resulting in differential modulation of many brain circuits, the net effect of nicotine on mood will depend on the integration of multiple nicotinic signals. The complexity of this system may suggest that a nicotinic partial agonist that selectively targets specific nAChRs involved in mood regulation could be more useful than a broad spectrum nAChR blocker.

Identifying the brain areas mediating the effects of nAChRs on depression-like behaviors will not be straightforward. nAChRs are expressed on many cell types throughout the central nervous system (Han et al., 2000), and modulate multiple neurotransmitter systems. Nevertheless, there is some evidence that nAChRs in the amygdala could be important for the antidepressant effect of nAChR blockade (Mineur et al., 2007). Cholinergic cells projecting to the amygdala exhibit high firing rates (Whalen et al., 1994) and hyperactivity of the amygdala is a hallmark of arousal and stress reactivity (Davidson et al., 2002; Drevets, 2001). Thus, decreasing amygdala cholinergic activity through α4β2* nAChR blockade could decrease stress reactivity and depression-like symptoms (LeDoux, 2003; Mineur et al., 2007). Conversely, activation of α7 nAChRs in the amygdala can also lead to an overall decrease in activity as a result of heightened GABAergic inhibition (Pidoplichko et al., 2013), suggesting a potential mechanism for α7 agonism in mediating an antidepressant-like response. This also highlights the need to consider the effects of different nAChR subtypes on specific cell-types in microcircuits throughout the brain involved in mood regulation. In the hippocampus, another brain region critical for antidepressant

response (Santarelli et al., 2003), increasing cholinergic tone induces anxiety- and depression-like behaviors that can be reversed by systemic administration of a nicotinic antagonist (Mineur et al., 2013). Further, as mentioned above, both chronic nicotine and the nicotinic antagonist mecamylamine can facilitate serotonin transmission in the hippocampus, while the effects of monoamine depletion can be partially reversed by nicotine administration and can lead to changes in anxiety-like behavior in the elevated plus maze (File et al., 2000a; File et al., 2000b; Fu et al., 1998; Kenny et al., 2000). We recently found that serotonin depletion could prevent antidepressant-like effects induced by the nicotinic partial agonist cytisine in the forced swim and the social defeat tests, while the effects of serotonergic drugs could be potentiated by this nicotinic compound (Mineur et al., 2014). Thus, changes in nAChR signaling, and more specifically, decreasing nAChR activity, can facilitate monoamine transmission and this may mediate the ability of nicotinic drugs to alter depression-like behaviors.

Nicotinic drugs may also have effects on mood-related behaviors through actions on the mesolimbic dopamine system. Nicotine reinforcement and reward is mediated through nAChRs in the mesolimbic system (Maskos et al., 2005; McGranahan et al., 2011; Tolu et al., 2012) and numerous studies have now demonstrated that alterations of neuronal activity in the mesolimbic system can result in antidepressant-like effects (Nestler, 2014; Nestler and Carlezon, 2006; Warner-Schmidt et al., 2012). For instance, mice lacking β2* nAChRs in dopamine neurons of the VTA lack anxiolytic responses to nicotine and are insensitive to nicotine reward (McGranahan et al., 2011). This suggests that altering nAChR signaling in reward systems could also have effects on behaviors related to mood disorders.

In addition to the receptor subtype, the location of cholinergic receptors in the brain also determines the influence that nicotine can have on mood. Cholinergic signaling can have opposite behavioral consequences in different brain areas. For example, decreasing cholinergic transmission in the striatum can induce depression-like effects in mice through disinhibition of medium spiny neurons (Warner-Schmidt et al., 2012). Thus, while increased ACh transmission can increase behaviors related to depression in humans (Risch et al., 1980) and rodents (Mineur et al., 2013), the type of circuits/cell types that are modulated by ACh or nAChRs can have opposite effects on mood regulation, and the outcome on behavior depends on the sum of these effects.

The effects of genetic-, species- and sex-differences further complicate the study of nicotinic pharmacology and depression-like behaviors. Strain differences in the antidepressant effects of nicotinic agonists and antagonists have been identified (Andreasen and Redrobe, 2009) and strains of mice can show profoundly different behavioral responses to nicotine administration (Marks et al., 1983; Marks et al., 1986). This is not unexpected, since the ubiquitous expression of nAChRs means that small changes in receptor expression could alter the balance of signaling between glutamatergic and GABAergic neurons (Mansvelder et al., 2002), monoaminergic neurotransmitters (Fu et al., 2001; Seth et al., 2002) or stress hormones (Matta et al., 1998). Similarly, species differences in nicotine metabolism and pharmacology can result in different behavioral responses to nicotinic drugs in models of antidepressant-like response. For instance, while the nicotinic antagonist mecamylamine can have antidepressant-like properties in mouse models (Picciotto et al., 2008; Picciotto et al.,

2012), antidepressant effects of this drug are not observed in assays of rats (Tizabi et al., 2000). Finally, sex differences may have a significant effect on the interaction between the nicotinic system and mood regulation. Mood disorders are twice as prevalent in women than in men, and female smokers have more difficulty remaining abstinent after they quit smoking (Ward et al., 1997), particularly if they are depressed (Amenson and Lewinsohn, 1981; Borrelli et al., 1996; Cairney and Wade, 2002). Thus, it is important to keep all of these parameters in mind when interpreting the results of clinical studies of nicotinic drugs across different subsections of the population.

ii) Aggression-related behavioral states—Depressive disorders are frequently co-morbid with the psychological and behavioral states of aggression, agitation, and irritability, both in adults and children (Fava and Rosenbaum, 1998; Messer and Gross, 1994; Snaith and Taylor, 1985; Weiss and Catron, 1994). The role of nAChRs in the modulation of aggression and related behaviors has been studied in both animal models and human studies. As detailed below, human studies of aggression, agitation, and irritability are complicated compared to animal models because of the inconsistent definition of these concepts and application to human behavior. In animal models, aggression is frequently divided into offensive and defensive aggression, especially examining attack behavior. The effects of acetylcholine, cholinomimetics, and acetylcholinesterases, as well as specific nicotinic drugs have been studied in animal models of aggression for several decades. As acetylcholine, cholinomimetics, and acetylcholinesterases can affect function of both muscarinic and nicotinic AChRs, we have not included these studies within this focused review, however, studies of these agents have been conducted on forms of aggression in cats (Allikmets et al., 1969) and rodents (Bandler, 1969, 1970; Igic et al., 1970; Yoburn and Glusman, 1984). With respect to nicotinic drugs, in 1971, Silverman reported that acute injection of a low dose of nicotine (0.025 mg/kg) reduced aggression in rats, as measured in a brief social isolation assay (Silverman, 1971). In this study, a single nicotine injection reduced aggression from baseline, and four days of repeated daily injection reduced aggression even further. Nicotine reduces aggression in rats in many different paradigms, including shock-induced fighting (Driscoll and Baettig, 1981; Rodgers, 1979; Waldbillig, 1980), frustrative non-reward (reaction to the inability to obtain rewards following repeated efforts; (Schechter, 1974), and a muricide model (Waldbillig, 1980). Importantly, effects of nicotine in the muricide study did not stem from a general sedating effect, were not affected by peripheral nAChR blockade with hexamethonium, and were blocked by mecamylamine (Waldbillig, 1980). It is also interesting that increasing doses of nicotine not only reduced the proportion of fighting episodes in rats after footshock, but also replaced that behavior with posturing (an intermediate aggressive behavior), suggesting that nicotine might act to scale social and agonistic behavior (Driscoll and Baettig, 1981) shifting the curve in a similar way as does increasing the activity of a subset of neurons in the mouse ventromedial hypothalamus (Lee et al., 2014).

In cats, nicotine reduced aggression in a dose-dependent manner in a rat-biting assay, and doses that were highly effective at reducing aggression did not cause changes in food intake, suggesting a specific effect on aggression (Berntson et al., 1976). Cats specifically reduced biting, an aggressive behavior, while pawing and cuffing, non-aggressive behaviors,

remained stable or increased, supporting the idea that nicotine had specific effects on behaviors related to aggression. Results from experiments in mice have been more variable than in rats. In a footshock-induced aggression paradigm, nicotine increased aggression in mice (Rolinski and Herbut, 1981). Further, in an isolation-induced aggression model, one study found no effect of acute nicotine on aggression but an anti-aggressive effect of lobeline, an agent with complex pharmacological properties at nAChRs (Redolat et al., 2000). This finding is in contrast to a more recent study assessing both target-biting and standard resident-intruder tests in mice, which found a dose-dependent reduction in aggression by nicotine in mice (Johnson et al., 2003). These two studies employed different strains of mice, OF1 and Swiss Webster, respectively, and mouse strain is a well-known variable affecting behavior in aggression models (Crawley et al., 1997). The scoring methodology of the encounters also differed substantially. Despite these species differences, studies across behavioral paradigms suggest that nicotine can reduce aggressive behavior.

Mice with genetic deletion of different nAChR subunits will be valuable for dissecting the mechanism by which nicotine influences aggressive behavior (Changeux, 2010; Stoker and Markou, 2013). A recent study investigating how social behavior is regulated by cholinergic and norepinephrine transmission in the prefrontal cortex (PFC) used β2 subunit knockout mice ($\beta2^{-/-}$) in a social interaction task, which included a measure of aggressivity (Coura et al., 2013). At baseline, $\beta2^{-/-}$ mice exhibit increased levels of norepinephrine, dopamine, serotonin, and acetylcholine within the prelimbic region of the PFC, yet display similar levels of aggression compared to control mice both before and after global norepinephrine depletion. Specific norepinephrine depletion in the prelimbic region of the PFC markedly increased aggression in control, but not $\beta2^{-/-}$ mice, a finding that suggests aggression was modulated by the balance of monoamines and acetylcholine in the prelimbic cortex, and requires functional β2 nAChRs (Coura et al., 2013).

A detailed discussion of the neurocircuitry and neuropharmacology of aggression is beyond the scope of this review (for detailed reviews, see Anderson, 2012; Nelson and Trainor, 2007; Siegel et al., 1999; Takahashi et al., 2012a), but published studies provide potential avenues for future studies of nAChRs in brain regions critical for aggressive behaviors. In rats, a hypothalamic “aggression area” (HAA) has been implicated in aggressive behavior by stimulation paradigms, and efferents from this region have been mapped, with substantial connection throughout the brain, including thalamic nuclei, septal nuclei, and the periaqueductal gray (Roeling et al., 1994). Using optogenetic and *in vivo* recording methods, a distinct region within the HAA, the ventrolateral subdivision of the ventromedial hypothalamic nucleus (VMHvl), was recently shown to be necessary and sufficient for offensive aggression in mice (Lin et al., 2011). Afferents to the VMH are also numerous, and include other hypothalamic nuclei, the bed nucleus of *stria terminalis*, lateral septum, and amygdala (Berk and Finkelstein, 1981; Chen et al., 2011; Luiten and Room, 1980). The substantial connections of the VMH suggest that there are multiple nodes of neuromodulatory control over agonistic behaviors. Equilibrium binding studies have also demonstrated expression of α7 nAChRs in the VMH in adult rats (Morganstern et al., 2013; Tribollet et al., 2004), while both α7 and β2 subunit-containing nAChRs are present in the

VMH of late embryonic and early postnatal rats (Huang and Winzer-Serhan, 2007; Tribollet et al., 2004).

Substantial research has focused on the influence of serotonin neurotransmission in regulating agonistic behaviors, including evidence of involvement of serotonin disruption in humans in aggressive states and traits, but dopaminergic, norepinephrinergic, and GABAergic neurotransmission have all been implicated in aggression (Nelson and Trainor, 2007; Takahashi et al., 2012b; Yanowitch and Coccaro, 2011). Nicotine, signaling through nAChRs, can influence serotonergic transmission in a complex manner, generally acting to increase serotonin release in many brain regions (reviewed in Seth et al., 2002), including the hypothalamus (Ramos et al., 2004). Nicotine influences the rate of dorsal raphe nucleus (DRN) neuron firing, and can increase serotonin release in rat midbrain slices (Mihailescu et al., 1998), an effect that appears to be largely mediated by presynaptic enhancement of both norepinephrine (Li et al., 1998) and glutamate release (Garduno et al., 2012). At the behavioral level, nicotine's effects on DRN neurons mediate anxiogenic and anxiolytic effects following nicotine administration and during nicotine withdrawal (Cheeta et al., 2001; Picciotto et al., 2002).

Effects of nicotine on mood, anxiety, and aggression-related behavioral states in human and clinical studies

i) Depression and anxiety—The relevance of nicotine in both depression and anxiety has been studied extensively (Laje et al., 2001; Morissette et al., 2007; Picciotto et al., 2002). Recent imaging studies have shown that availability of β2* nAChRs for tracer binding was greatly decreased in actively depressed patients but was intermediate in remitted subjects (Saricicek et al., 2012). Post-mortem studies confirmed that a higher level of acetylcholine competing for receptor binding was the likely reason for the decrease in nAChR availability, and this has been confirmed in studies using a cholinesterase antagonist to increase acetylcholine levels dynamically (Esterlis et al., 2013). These results indicate that abnormal nicotinic signaling may underlie depression symptoms (Mineur et al., 2013; Tizabi et al., 2000), and raise the possibility that β2* nAChR availability could be a biomarker of depression, correlated with severity of the symptoms.

Clinical studies have demonstrated an increased rate of smoking in individuals with depression (Diwan et al., 1998), a tendency for depressive symptoms to develop in the context of smoking cessation (Laje et al., 2001), and the capacity for nicotine to improve depressive symptoms, even in non-smokers (McClernon et al., 2006; Salin-Pascual et al., 1996). Clinical data on the role of nicotine in anxiety is more complex, with the most consistent findings being the development of anxiety symptoms in the context of withdrawal, and the observation that these symptoms may improve with nicotine replacement (Picciotto et al., 2002).

It has been proposed that nicotine use and anxiety disorders share common neurobiological substrates. This idea is consistent with epidemiological data suggesting that a greater risk for nicotine dependence exists in patients with anxiety disorders (Kushner et al., 2012). The regular use of nicotine could contribute to dysregulation of the neuronal substrates that modulate anxiety and stress response, thereby contributing to the maintenance of anxiety

symptoms and abnormal response to behavioral challenges (Koob and Le Moal, 2001). Conversely, as has been described for other addictive disorder such as alcohol abuse, predisposition to addiction may be triggered by abnormal development or maladaptive changes in common systems regulating anxiety and nicotine use (Kushner et al., 2011; Pervanidou, 2008). Some studies have suggested that anxiety disorders increase nicotine consumption and lead to a higher likelihood of nicotine addiction(Kushner et al., 2012); however, as noted in the Kushner study, it remains unclear whether the anxiety disorder itself or neurobiological processes that predispose an individual to an anxiety disorder promotes susceptibility to nicotine dependence. Further human imaging and pharmacological studies are clearly needed to determine the mechanistic connections between nicotine intake and the development and expression of anxiety disorders.

Available therapies for smoking cessation mainly target the nicotinic system through replacement therapies (gums, patches, e-cigarettes), or with nicotinic partial agonist able to curb withdrawal symptoms by moderately activating nicotinic receptors (i.e. varenicline (Coe et al., 2005; Oncken et al., 2006; Rollema et al., 2007)). It has been postulated that these approaches could have positive effects on mood in smokers trying to quit. Nicotine delivered through skin patches can also improve mood in non-smokers (Salin-Pascual et al., 1995; Salin-Pascual et al., 1996), potentially through sustained desensitization of nAChRs (Mineur and Picciotto, 2010; Picciotto et al., 2008). Recently, a clinical trial of a nicotinic-based antidepressant that blocks nAChRs (dexmecamylamine) failed to show efficacy in patients who were resistant to SSRIs (Vieta et al., 2014), however, similar compounds have shown promising effects in smaller clinical trials, and enhanced the effects of SSRIs in human depressed subjects (George et al., 2008; Philip et al., 2009), suggesting that a subset of patients may be more responsive to these medications or have an underlying alteration of cholinergic signaling. Although the failure of this large clinical trial suggests that using dexmecamylamine will not be clinically useful for major depressive disorder, more selective antagonists or partial agonists may decrease signaling through specific nAChR subtypes while sparing others, and may be more effective or well-tolerated. Thus, future clinical trials with targeted nicotinic antagonists or partial agonists could be of interest.

ii) Aggression-related behavioral states—As noted above, the study of ARBS in human subjects is complex, and requires precise definition. Here we consider the triad of aggression, agitation, and irritability to represent three distinct, but related, psychological and behavioral states in human subjects that we refer to as ARBS. Aggression refers to behaviors that are intended to be destructive to the self, others, or property (Swann, 2003). Agitation, which generally refers to excessive motor or verbal behaviors, frequently, though not always, co-occurs with aggression. Likewise, aggressive behaviors need not include an agitated component, but frequently do. Finally, irritability, the most nebulous of the three, has been defined as “(...) a feeling state characterized by reduced control over a temper which usually results in irascible verbal or behavioural outbursts, although the mood may be present without observed manifestation (...)” (Snaith and Taylor, 1985). Thus, irritability may predispose one to aggression, especially when irritability and agitation are present, but all three concepts may exist independently. In clinical practice, however, the three concepts are frequently used interchangeably, and generally define similar psychological and

behavioral domains. Furthermore, while clinical trials generally identify one of these terms as an outcome, rating scales for their measurements might capture aspects of all three. A demonstration of this interplay is the Agitated Behavior Scale, a commonly used clinical rating scale for patients with brain injury (Corrigan, 1989). The scale includes measures of violence, excessive motor behavior, and irritability, as well as an assessment of mood lability, thereby encompassing all three terms along with a mood component.

ARBS are observed across numerous neuropsychiatric disorders, including depressive, bipolar, psychotic, neurocognitive, neurodevelopmental, stress-related, substance use and personality disorders (American Psychiatric Association, 2013). Many of the above disorders include a prominent mood component in addition to other symptoms. Indeed, mood is a critical modifier of psychological states that might predispose individuals to ARBS. A recent paper illustrated this concept in patients with schizophrenia, in whom the construct of “urgency”, defined as the tendency to act rashly in the context of positive or negative emotion, correlated strongly with aggression, and was inversely correlated with functional connectivity in a cortical circuit believed to modulate impulsivity (Hoptman et al., 2014). It is possible, therefore, that alterations in nAChR signaling that can modulate mood and anxiety states may influence the development of ARBS.

Emerging data suggest that nicotinic agents may have a significant role in addressing ARBS across a variety of diagnoses. Few clinical trials have been designed to explore nicotinic agents for the specific management of agitation, irritability, and aggression specifically; however, evidence supporting a significant but complex role of nicotine and nicotinic receptors in these syndromes can be gleaned from a variety of clinical studies with different primary outcomes that also report on these data (Arnold et al., 2012; Conners et al., 1996; Drusch et al., 2013; Newhouse et al., 1994), as well as well-conducted case series (Mayer et al., 2001; Rosin et al., 2001). A second line of evidence comes from a number of studies describing the prominence of ARBS in the context of nicotine withdrawal (Lucidarme et al., 2010), and the tendency for these symptoms to resolve following administration of nicotine (Schechter, 2011).

A role for nicotinic agents as a treatment for ARBS is suggested in a recently published double-blind, placebo controlled trial of transdermal nicotine in adult smokers with schizophrenia (Allen et al., 2011). In this study, participants in the active arm experienced a 33% reduction in agitation as measured by the Agitated Behavior Scale (Corrigan, 1989), versus a 23% reduction for the placebo arm. This is a small difference, but one that the authors note as being similar to the drug-placebo differences in trials of antipsychotics for the same indication. In addition, there were significant differences in the positive and negative symptoms of schizophrenia scale (PANSS) excited component subscale, with participants in the intervention arm showing more significant reductions than those who received placebo. Notably, these differences were larger in patients with less severe nicotine dependence as measured by the Fagerstrom scale (Fagerstrom, 1978), a finding the authors suggest could be related to a higher dose requirement in this subgroup than the 21 milligram patch that was used in the study. In contrast, a recent study involving a human laboratory model of psychosis did not find nicotine to be different from placebo when assessing both positive and negative symptoms and cognitive effects (D'Souza et al., 2012). Other work has

found nicotine to be similarly ineffective in improving social cognition and subjective stress responses (Drusch et al., 2013).

At least one way to interpret these findings is to suggest that nicotinic agents may reduce ARBS not by influencing the core symptoms of schizophrenia, but via a parallel mechanism that only becomes apparent in individuals with suprathreshold levels of aggression. This is supported by data from a case series in which transdermal nicotine was an effective treatment for agitation in four patients with severe dementia (Rosin et al., 2001). Similarly, transdermal nicotine was used successfully as adjunct treatment in a further series of two patients with dementia (Carmel and Sheitman, 2007). These studies were both small and uncontrolled, but contribute to an increasing base of clinical data justifying further exploration of nicotinic agents for management of ARBS across a variety of diagnostic categories.

A number of studies involving treatment with nicotinic agents evaluated changes in agitation as a secondary outcome. Two studies used transdermal nicotine to treat attention deficit hyperactivity disorder (ADHD), and included assessments using the Profile of Mood States (POMS) questionnaire (McNair et al 1971). The first small study (n = 17) found that although nicotine was effective for overall symptoms, it had no effect on subscales associated with agitation or aggression (Conners et al., 1996). More recently, a larger study (n = 40) found on *post-hoc* analysis that patients in the treatment arm experienced a statistically significant improvement in irritability with no improvement in any of the other 12 measures on the POMS. The role of nicotine in affecting irritability in this population therefore remains unclear. A retrospective case series of 24 patients with Tourette's Syndrome reports on the investigators' experience with the nicotinic receptor antagonist mecamylamine (Silver et al., 2000). Although no relevant scales were used, the authors describe qualitative improvement in aggression, anger and irritability in a number of the cases, as well as overall improvement on the Clinical Global Impression scale (CGI). The same authors completed a double-blind, placebo controlled trial of mecamylamine (n = 61) in Tourette's Syndrome and found no difference from placebo in terms of overall symptoms (Silver et al., 2001a; Silver et al., 2001b); however, there was a significant difference in terms of 'sudden mood changes', with a marked decrease in the treatment arm that was statistically different from the placebo group. The conceptual overlap between 'sudden mood changes' and ARBS is intuitive, although not definitive, and further work would be required to confirm the nature of this effect. Even more preliminary findings come from a trial of mecamylamine in autism (Arnold et al., 2012). This small study reported no clinically or statistically significant benefit, but provided anecdotal evidence of decreased irritability in four cases. This was spontaneously reported by parents, and was sufficiently convincing that treatment was continued in these cases. Clearly additional studies are needed to establish the validity of the findings in trials designed to assess ARBS-specific outcomes, as both nicotine and mecamylamine have been described as effective for aggression and agitation in studies where they had no effect on the primary outcome (D'Souza and Markou, 2012; Silver et al., 2001b). Finally, studies should include both nicotinic agonists and antagonists, which might identify a preferred agent for a given indication.

Clinical studies reporting on ARBS in the context of nicotine withdrawal provide further support for the involvement of nicotine and the nicotinic system in these syndromes. Studies that describe symptom resolution after nicotine replacement are particularly helpful. Nicotine withdrawal has been described as causing increased anger and tension as measured on self-report scales (Gilbert et al., 1998). Increased irritability and physical aggression was reported in a study of 35 male smokers following initiation of abstinence (Parrott and Zeichner, 2001). The concept of nicotine withdrawal has been codified in the DSM-5 and irritability is described as a characteristic symptom (American Psychiatric Association, 2013). A large prospective trial (n = 144) of patients admitted to an intensive care unit found that smokers had a significantly higher rate of agitation (nicotine replacement therapy was not permitted) that was almost double the rate in the control population (Lucidarme et al., 2010). The authors highlighted the need for studies exploring the utility of nicotine replacement therapy in these instances, an approach that has been reported as effective in a prior case series of four patients admitted to a neuro-ICU (Mayer et al., 2001). Cumulatively, this work supports the idea that nicotine withdrawal may increase agitation across a variety of contexts, and that this agitation is reversible following the administration of nicotine. More broadly, this work suggests that nicotine and nicotinic receptors may have the capacity to influence ARBS.

A number of important questions regarding nicotine and aggression remain. Given the prevalence of chronic nicotine use in the population by tobacco smoking, it is important to determine the effect chronic nicotine exposure itself has on aggressive behavior outside the context of withdrawal. In addition, many conditions involving impulsive aggression are chronic disorders that require long-term treatment, such as neurodevelopmental or neurodegenerative disorders. Thus, the utility of chronic nicotine to treat ARBS must be determined if nicotinic-based medications are to be useful in managing pathological impulsive aggression in these populations. If chronic nicotine is not effective, acute administration of nicotinic agents might be envisioned for “as-needed” uses in emergency departments or inpatient units, but not for chronic use. Well-conducted clinical trials might shed light on whether nicotine administration in this setting is effective, and perhaps identify specific etiologies of ARBS for which nicotine is uniquely therapeutic. Nicotine withdrawal and its affective consequences have been studied extensively (Stoker and Markou, 2013), yet the effects of nicotine withdrawal on aggressive behavior needs further exploration both in animal models and in humans. Finally, attempting to clarify how nicotine's effects on mood and anxiety influences its effects on aggression may help elucidate its mechanism of action, as well as provide guidance as to optimal clinical uses of nicotinic agents in disorders with pathological aggression.

Conclusions

The mechanisms underlying nicotinic modulation of mood and anxiety regulation are only beginning to be understood, due to the complex pharmacology of nAChRs, their broad distribution, their desensitization in response to agonists, and the multiple neural systems modulated by nAChRs. However, changes in nAChRs could provide relevant biomarkers for at least a subset of depressive symptoms, and may help with the diagnosis and characterization of the pathophysiology of depression.

Clinical investigation of nicotinic agents for management of ARBS is in its early stages. Nevertheless, considerable progress has been made. Robust descriptions of ARBS in the context of nicotine withdrawal suggest the involvement of nicotine and nicotinic receptors in these syndromes. Furthermore, a number of studies suggest that nicotinic agents are effective for the management of ARBS, and we hypothesize that the ability of these agents to modulate mood and anxiety might be one mechanism underlying these effects. Notably, these studies have occurred across a variety of diagnostic categories. These findings are conceptually important, as they suggest that future studies of nicotinic agents may benefit from deliberate assessment of these constructs, rather than overall outcomes. Current clinical literature does little to clarify whether nicotinic agonists or antagonists are most helpful for treating ARBS. Likely, this will ultimately be found to vary according to underlying diagnosis and perhaps also smoking status. Despite the complexity, the lack of currently available agents to effectively treat aggression, irritability, and agitation without significant side effects means that further study in this promising area is strongly indicated.

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- There is high co-morbidity between smoking and mood disorders.
- Clinical trials have shown effects of nicotine on aggression-related behaviors.
- Few trials of nicotine study aggression-related outcomes systematically.
- Further studies nicotine and nAChR effects on aggression are necessary.