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Translating laboratory discovery to the clinic: From nicotine and mecamylamine to tourettes, depression, and beyond*

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Abstract

The early development of novel nicotinic drugs for Tourette's and depression was a very long journey in discovery, which began with basic behavioral neuroscience studies aimed at understanding how cholinergic and dopaminergic systems interact in the basal ganglia to control goal directed movement. These early rodent studies with nicotine and dopamine antagonists formed the basis for investigating a potentially improved treatment for children suffering from Tourette's syndrome (TS). Clinically, the research trajectory first focused on studies employing the use of nicotine gum to potentiate the therapeutic effect of the dopamine receptor antagonist, haloperidol, in patients with TS. These projects led to the discovery of a new use for a decades-old blood pressure medication, mecamylamine, a nicotine antagonist, which also appeared to provide symptomatic relief in some TS patients when used clinically and was found to reduce symptoms of mood instability and depression. This unexpected discovery led to a new hypothesis regarding the mechanism of action of antidepressants as well as a series of successful independent trials employing mecamylamine, and its active enantiomer, TC5214, as an augmenting agent in the treatment of major depression. This article is a chronological mini review of these basic and clinical translational studies on nicotinic therapeutics for Tourette's syndrome and depression over the past 25 years.

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Keywords

Nicotine; Mecamylamine; Tourette's syndrome; Depression; TC5214

Introduction

The development of novel nicotinic drugs in our lab began with basic behavioral neuroscience of nicotine in rats to search for an improved treatment for children with Tourette's syndrome (TS). Animal research began with studies of the effects of haloperidol on catalepsy and later incorporated the examination of the combination of haloperidol and nicotine and its effects on locomotor behavior. Nicotine's effects on memory, hyperactivity, and different forms of movement and performance were evaluated through studies on animal behavior and neurochemical analyses.

Clinically, the research trajectory first focused on the use of nicotine gum to potentiate the therapeutic effect of haloperidol in patients with TS. Because nicotine gum provided on short term relief, later studies, support in part with NIH funding, implemented the transdermal nicotine patch, which was found to have persistent therapeutic benefits sometimes lasting days after patch removal. Because of nicotine's short half-life, we reasoned that the persistent exposure of nicotine via the patch might be causing nicotinic receptor desensitization and that a nicotinic receptor antagonist might be a better therapeutic agent to investigate. These projects eventually led to the discovery of a decades-old blood pressure medicine, mecamylamine, which in clinical trials demonstrated beneficial effects in depression. Mecamylamine, a nicotine antagonist, also provided symptomatic relief in some TS patients.

The purpose of this article is to present a chronological mini-review of our group's basic and clinical translational studies on TS and depression over the past 25 years. The first part of the article presents a clinical description of TS and the pharmaceuticals traditionally used for the treatment of its symptoms. The second section summarizes the animal studies conducted by our group on this topic, while the third section contains a description of the clinical research performed by our group with TS patients to evaluate the therapeutic potential of nicotine and mecamylamine. The final section provides a synthesis of this research trajectory and proposes future areas of exploration.

Tourette's syndrome

Tourette's syndrome is a hyperkinetic movement disorder characterized by the expression of sudden, rapid and brief, recurrent nonrhythmic, stereotyped motor movements (motor tics) or sounds (vocal tics) [1]. These symptoms usually begin in childhood and can increase in severity during adolescence, but often subside to a tolerable level for many once they become young adults [2, 3]. These patients frequently experience behavioral and emotional problems as well as neuropsychiatric abnormalities such as Obsessive Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD), and visual-motor deficits [3–5].

Neuropathology

The pathophysiology of TS is thought to involve a dysfunction of basal ganglia-related circuits and, in particular, hyperactive dopaminergic innervation [6]. For example, most post mortem studies of TS patients have reported increased numbers of striatal [6, 7] and cortical [7, 8] dopamine 2 (D2) receptors, as well as evidence for altered dopamine metabolism in the basal ganglia [9, 10]. These findings are supported clinically because D2 dopamine receptor antagonism by neuroleptics appears to be the most efficacious approach for pharmacological intervention, with an average success rate of 70% [11]. The first neuroleptic approved for the treatment of TS was haloperidol (HALDOL®), a potent antagonist of D2 receptors [11].

Animal studies

The animal studies that were carried out prior to, and later, in parallel with clinical research in our laboratory are summarized in Table 1. The initial basic science studies in animals were conducted to better understand the behavioral pharmacology of the basal ganglia and its neurotransmitters, especially the interaction of the cholinergic and dopaminergic systems.

When rats were administered neuroleptics, they display a behavioral response known as “catalepsy”, which is characterized by active muscle tonus with the appearance of a “frozen” posture. Neuroleptic induced catalepsy in rats was abolished by kainic acid lesions of the striatum and is mediated via the blockade of striatal dopamine D2 receptors, which normally inhibit striatal cholinergic interneurons and striatopallidal γ -aminobutyric acid (GABA) output neurons [12]; [13]. Following D2 receptor blockade by neuroleptics, the globus pallidus is inhibited (via disinhibition of striatopallidal GABA projection neurons) and the motor cortex can no longer be activated via the thalamus. Using neuroleptic induced catalepsy as a model for understanding the behavioral effects of neuroleptics, it was discovered that low doses of nicotine potentiated the cataleptic effects of neuroleptics in rodents [14]. It was initially hypothesized that nicotine potentiated the actions of neuroleptics on catalepsy by activating disinhibited striatal cholinergic interneurons innervating striatopallidal GABA projection neurons, thus producing further inhibition of the globus pallidus [15]. However, the fact that nicotine also caused the presynaptic release of dopamine was paradoxical, since excessive dopamine release should counteract the cataleptic effects of neuroleptics and exacerbate tic symptoms in TS. Therefore, an alternative hypothesis was proposed that nicotine potentiates the actions of neuroleptics by producing desensitization of certain acetylcholinergic nicotinic receptor (nAChR) subtypes [16].

While nicotine acts initially as a rapid agonist at nAChRs, desensitization or a prolonged “inactivation” of these receptors occurs shortly thereafter [17, 18]; [19]. Thus, it was argued that the net functional effect of sustained nicotine exposure on many nAChR subtypes over time (its time-averaged effect) is that of an antagonist [20]. This hypothesis was also consistent with reports that mecamylamine, a noncompetitive nAChR antagonist, also potentiated neuroleptic induced catalepsy [21] presumably by blocking nAChRs involved with the tonic release of striatal dopamine [22].

The unexpected observation of nicotine potentiation of neuroleptic-induced catalepsy in the animals sparked a conversation over lunch with a colleague about the therapeutic utility of such an interaction in the treatment of hyperkinetic motor disorders such as TS.

Clinical studies on Haloperidol, Nicotine, and Mecamylamine

Table 2 contains a list of the clinical studies carried out on nicotine, TS and mecamylamine. Details on the topic, type of study, and publications are presented.

The clinical studies on nicotine and TS began with the reporting of the case of 2 TS patients (6 and 8 years old) who were not responding to treatment with haloperidol [23]. The authors found that the chewing of nicotine gum reduced the uncontrolled outbursts of the younger patient and decreased the attention deficit hyperactivity symptoms in the other case [23].

The second study was published in 1989 and it consisted of an open trial with 10 TS patients, 9 males and 1 female (mean age of 12 yrs.) [24]. The patients were receiving treatment with haloperidol at the time of the study. One piece of nicotine gum (2 mg) was given to each child three times a day. The study found that 80% of the children showed an improvement in their symptoms while chewing the gum, but 70% of the participants discontinued the gum use due to its side-effects (mainly bitter taste and stomach aches) [24].

A follow-up study was conducted with an additional 10 TS patients, eight children and two adults with a mean age of 18.7 yrs, who were receiving treatment with haloperidol [25]. The participants were asked to chew nicotine gum (2 mg) and were evaluated during two hours divided in four 30 minute periods. The results of the study showed that the frequency of tics was reduced significantly during the 30 minutes when the participants chewed gum and in the hour after chewing gum [25].

A controlled study with 19 TS patients was published in 1992 with the purpose of exploring the effectiveness of nicotine in the reduction of TS symptoms in patients that were not receiving treatment with haloperidol [26]. Ten TS patients receiving haloperidol treatment and 9 untreated TS patients were included in the study. The effects of nicotine gum plus haloperidol, nicotine gum only, and placebo gum were analyzed in relation to the frequency and severity of tics. The patients were videotaped for 2 hours divided in four 30 minute periods. The results indicated that a significant reduction in tic frequency and severity was present in the TS patients being treated with haloperidol, a decrease in tic frequency during two of the periods was found in the patients only receiving nicotine gum, and no effect was produced by placebo gum [26].

The negative side-effects of the chewing of nicotine gum, the small quantity of nicotine found in the gum, and its short elimination half-life of 30 to 120 min [27] led the research team to search for a new way to test the effects of nicotine on TS symptoms [28–31]. The transdermal nicotine patch proved to be a more effective mechanism and it was implemented in the studies conducted from 1993 onward. The first publication on transdermal nicotine patch (TNP) and TS reported the case of six patients (children and adults), who after the use of a series of patches (7 mg of nicotine), showed an amelioration of symptoms [28, 32].

An open trial with 11 TS patients who were receiving neuroleptics followed [33]. Eight patients received a patch titrated to deliver 7 mg of nicotine while the remaining three patients received 14 mg of transdermal nicotine. Video tapes were used to determine the localization, frequency, and severity of tics. The severity was scored using a 5-point scale. The study found that the transdermal nicotine patch reduced the frequency and severity of tics in TS patients receiving dopamine receptor blockers. The effect of nicotine on TS symptoms became evident after three hours of applying the patch and persisted during variable time periods ranging from a couple of hours to several days following patch removal [33].

A case study of 20 TS patients (17 children and adolescents and 3 adults) who were either free of medication (2 patients) or their tic symptoms were not controlled by neuroleptics [34, 35]. Two transdermal nicotine patches (7 mg/24 hours) were administered to the patients and their motor and vocal tics were quantified using the Yale Global Tic Severity Scale (YGTSS). The study showed that each application of the patch produced a reduction in TS symptoms in 17 out of the 20 patients which lasted an average of one to two weeks after the application. The authors also reported a series of side-effects produced by the patch such as transient itching at the site of the patch application, nausea, headaches, and sedation [34, 35]. These open-label retrospective case reviews were used to secure a NIH fund grant and an investigator's IND with the FDA in order to conduct a larger well-controlled study.

The NIH funded double-blind placebo controlled trial of transdermal nicotine in 70 pediatric TS patients was conducted from 1994 to 1998 [36]. The patients received either transdermal nicotine patches (7 mg/24 hrs) or placebo patches each day for 19 days in combination with low doses of haloperidol. The frequency and severity of tics were assessed using the Clinician and Parent-rated Global Improvement Scales (CGI and PGI) and the YGTSS. The CGI and PGI scales showed an improvement in the reduction of the severity of the symptoms while the YGTSS was less sensitive in detecting a significant difference between the nicotine and placebo groups. While the patients receiving the TNP reported significantly more nicotine-related side-effects such as vomiting and nausea than the placebo group during patch exposure, there was no difference between groups in terms of nicotine related withdrawal symptoms which were monitored daily for 7 days following the last patch exposure[36].

The nAChR "inactivation" hypothesis for nicotine (as discussed earlier) was also used to explain the discrepancies between findings with nicotine gum and the TNP in patients with TS. While the beneficial effects found with the nicotine gum only lasted about 1–4 h [24–26], the response to the TNP, at least in some cases, seems to last for a much longer period of time following patch removal [16]; [32, 34]. It was therefore reasoned that an acute exposure of nicotine from chewing nicotine gum desensitized nAChRs only for a couple of hours, while a continual 24-hr exposure to nicotine as with the application of a single TNP might desensitize nAChRs for a considerable length of time following patch removal. This would be consistent with the animal literature suggesting that the duration of nicotine-induced desensitization of the nAChR is dependent on the duration of nicotine exposure. For example, it has been reported that the acute nicotine induced desensitization of prolactin [37] and behavioral responses [38] to a single bolus injection of nicotine lasted only a few

hours while a 10-day continual exposure (twice daily) to nicotine produced a nicotine induced desensitization of prolactin responses which lasted up to 8 days post-nicotine exposure. In addition, *in vitro* findings presented by Collins et al. [1996][39] and Lukas et al. [1996][40] demonstrated that certain nicotinic receptor subtypes become desensitized for several days following only a single exposure to nicotine. The increased recognition that nicotine acts both as agonist and antagonist at nicotinic receptors led to the novel exploration of the possible therapeutic effects of mecamylamine, a nicotinic antagonist, in the amelioration of TS symptoms [41, 42]

Mecamylamine (Inversine®) was originally used as a ganglionic blocker to treat severe hypertension at doses ranging from 25 to 90 mg/day [43]. However, later studies suggested that at lower doses (2.5 to 5 mg b.i.d.), mecamylamine functioned as a potent, broad-spectrum, centrally acting nicotinic antagonist that appeared clinically useful for treating tobacco [44, 45], cocaine [46] and alcohol dependency [47–49].

We were the first group to report therapeutic observations with mecamylamine (2.5 to 5 mg b.i.d.) as an adjunct to neuroleptic treatment of patients with TS [50, 51]. In the first study, 13 TS patients were treated with mecamylamine in doses up to 5 mg daily [50]. The severity of motor and vocal tics was assessed by the YGTSS and the Clinical Global Impressions-Severity of Illness (CGI-SI). The findings of the study indicated that mecamylamine played a role in the reduction of the severity of tics and in the improvement of other TS symptoms such as behavioral and emotional problems [50].

A retrospective open-label study of 24 patients was then conducted to document the therapeutic effect of mecamylamine on TS [51, 52]. Eighteen of these patients were not responding to treatment with neuroleptic (haloperidol, pimozide, and risperidone) and six were not receiving medication. The CGI scale was used to evaluate the patients. A significant improvement in the severity of illness was documented when looking at the data from the entire group. This improvement was seen in the patients receiving mecamylamine and their traditional medication as well as the ones who only received mecamylamine. Patients experienced a reduction in motor and vocal tics and an improvement in mood and behavioral disturbances [51, 52].

A double-blind placebo controlled study with 61 TS patients was carried out to examine the safety and efficacy of mecamylamine as a monotherapy in children and adolescents [53, 54]. The participants were administered either 2.5 to 7.5 mg/day of mecamylamine or placebo. The efficacy was measured by the Tourette's Disorder Scale-Clinician Rated (TODS-CR), CGI scale, and YGTSS. When considering the data for the total sample, mecamylamine was as effective as the placebo, but the TODS-CR indicated that mecamylamine might have reduced sudden mood changes and depression [53]. We concluded that even though mecamylamine was well tolerated by the participants; it was not effective as a monotherapy. However, an important new finding was the role mecamylamine played in the stabilization of mood and its possible role as an antidepressant [53].

A Novel Hypothesis for the Mechanism of Action of Antidepressants

In light of our prior clinical experience suggesting that mecamylamine may have mood stabilizing properties [51–53], we investigated the effects of mecamylamine in a post-hoc analysis [54] of symptom improvement in the subgroup of TS patients with comorbid Major Depressive Disorder (MDD) who participated in the former multicenter trial [53].

Of the 60 patients in the trial, eight met DSM-IV criteria for MDD, all 4 patients who received mecamylamine demonstrated reductions in depressive symptoms, while none of the placebo patients showed improvement.

The ‘monoamine’ hypothesis of depression originated following clinical observations that monoamine-elevating medications improved mood in patients with depression. The pharmacological actions of these drugs formed the basis for the monoamine hypothesis of depression postulating a functional deficiency of monoaminergic neurotransmission in the brain [55].

Following our discovery that mecamylamine had antidepressant properties in humans [56], we reviewed the literature and found that several independent groups over the years had reported an apparent common property of antidepressants was the inhibition of neuronal nicotinic receptors (nAChR) at therapeutically relevant blood concentrations [55]. The cholinergic-adrenergic theory of depression put forth in the 1970’s hypothesized a balance between cholinergic and adrenergic systems, suggesting that overactivity of the cholinergic system over the adrenergic system could lead to depressive symptoms [57, 58]. Using the cholinergic-adrenergic theory of depression as a foundation, we proposed the novel hypothesis that excessive or ‘hypercholinergic’ neurotransmission, which is associated with depressed mood states, may involve excessive nAChR activation and that the therapeutic actions of many antidepressants are mediated, in part, through inhibition of these receptors. Supporting this hypothesis, we presented our empirical evidence that the centrally acting nAChR inhibitor, mecamylamine, reduced symptoms of depression and mood instability in Tourette’s syndrome patients with comorbid major depressive disorder (MDD) [51, 53, 56] and bipolar disorder [52].

The antidepressant properties of mecamylamine (Inversine®)

MDD has a lifetime prevalence of approximately 13.2%, and a prevalence of ~5.3% in the United States in 2005 [59]. While most MDD patients are prescribed serotonin reuptake inhibitors (SSRIs), approximately 30–45% of patients do not respond to these antidepressants [60]. Based on these findings, we reasoned that if SSRI non-response was mediated in part by nicotinic hypercholinergic presynaptic mechanisms [55], a classical nAChR antagonist such as mecamylamine (Inversine®) [61] may augment such MDD cases with inadequate response to SSRIs [62]. The first prospective clinical study designed to test this hypothesis was conducted at Yale University with mecamylamine in 21 SSRI-treated subjects diagnosed with MDD, 11 who were randomized to mecamylamine (up to 5 mg b.i.d.) and 10 who received placebo during an 8-week single blind trial [62]. There was a significant reduction in 17-item Hamilton Depression Rating Scale (HAM-D) scores in the mecamylamine treated patients that began by the fourth week of the trial and was sustained

through Week 8 when compared to placebo. Overall reductions were approximately 45% compared to baseline in the mecamylamine group, and minimal in the placebo group. Adverse events included constipation and orthostatic dizziness, but most subjects were able to tolerate the full 10 mg/day dose.

This was the first prospective clinical study designed to test the hypothesis that nAChR antagonism had anti-depressive effects [55] and supported previous clinical observations [50–52] and controlled findings [53, 56] on the use of low-dose mecamylamine in treating pediatric Tourette's patients with comorbid mood disorders. Moreover, this first “proof-of-concept” study suggested that non-competitive nAChR antagonism may augment SSRI-refractory MDD. Because many antidepressants (e.g., tricyclics, SSRIs, and bupropion) are only weak non-competitive nAChR antagonists [55], it was reasoned incomplete blockade of high-affinity nAChRs may underlie the inadequate response to SSRI's in the treatment of MDD [62].

A second larger double-blind placebo-controlled phase IIb trial in adult MDD patients was conducted in 2005 by Targacept [63]. In this study, depressed patients who demonstrated an inadequate response to an open label 6-week trial of the SSRI, citalopram, were randomized to receive 2.5–5 mg b.i.d. mecamylamine (n=92) or placebo (n=92) for 10 weeks. While a positive effect of mecamylamine ($p<0.05$) was observed on the HAM-D, an even stronger statistical advantage was reported for mecamylamine on the Sheehan Disability Scale ($p<0.005$) and the Sheehan Irritability Scale ($p<0.001$).

The antidepressant properties of S-(+)-mecamylamine (TC-5214)

Mecamylamine (InversineTM) is a racemic mixture of S-(+)- and R-(–)-enantiomers, which have therapeutically important differences for inhibition of nAChR [64–67]. For example, we demonstrated that S-(+)-mecamylamine was found to be more effective than the R-(–) enantiomer in blocking nicotine induced seizures [64] and produced less suppression of open field locomotor activity than R-(–)-mecamylamine [64]. These *in vivo* studies were supported by electrophysiological findings that S-(+)-mecamylamine had superior inhibitory actions at central human nAChRs, but less inhibitory action at muscle type nicotinic receptor than R-(–)-mecamylamine [65]. Because muscle weakness was reported as a side effect in our multi-centered controlled mecamylamine trial in TS [53], these preclinical studies suggested that S-(+)-mecamylamine had a better therapeutic profile than the R-(–)-enantiomer [64]. Based, in part, on the findings reviewed above, Targacept began further preclinical investigations of S-(+)-mecamylamine and gave it the name TC-5412 [66, 67].

TC-5214 demonstrated robust efficacy in rodent models of anxiety (social interaction and light/dark chamber) and depression (forced swim and behavioral despair) and, again, showed a superior preclinical safety profile when compared to that of either the racemic compound or the (R)-enantiomer [66, 67]. In addition, TC-5214 was well tolerated in both acute and chronic toxicity studies with no mutagenic potential detected, and possessed a pharmacokinetic profile suitable for clinical development as a pharmacotherapy for neuropsychiatric disorders.

In 2009, Targacept conducted a double blind, placebo controlled phase IIb trial with TC-5214, as an adjunct treatment in MDD patients who had failed to respond adequately to a six week trial with citalopram. TC-5214 demonstrated superiority ($p < 0.001$) over placebo on the primary outcome measure, the Montgomery-Asberg Depression Rating Scale (MADRS) [68, 69], with less side effects than that observed with the racemate (InversineTM) in the previous MDD trials.

Future directions

The positive outcome of Targacept's phase IIb trial led to a license agreement in late 2009 with AstraZeneca for the global development and commercialization of TC-5214 [70]. In June, 2010, AstraZeneca and Targacept announced the initiation of a large phase III trial of TC-5214, which included four phase III studies of TC-5214 as an adjunct treatment for patients with inadequate response to standard SSRI therapy. [70]. Unfortunately, these efficacy and tolerability studies did not meet the primary endpoint of change on the Montgomery-Asberg Depression Rating Scale (MADRS) total score after eight weeks of adjunct treatment with TC-5214 as compared to placebo. In all four studies, every dose group (TC-5214 and placebo) showed at least a 40 percent improvement in MADRS total score after eight weeks of adjunct treatment. TC-5214 was overall well tolerated in these studies with an adverse event profile generally consistent with prior clinical trials. These phase III studies concluded the AstraZeneca/Targacept joint development program for TC-5214. Based on the totality of the results, AstraZeneca and Targacept did not pursue a regulatory filing for TC-5214 as an adjunct treatment for patients with MDD.

While the future of TC-5214 remains uncertain, there are several indications in the realm of neuropsychiatric disorders that may provide a better fit for this well tolerated and well-characterized nAChR inhibitor [71–73].

The future clinical results from such studies will help demonstrate the fruition of two and half decades of research in our laboratories. However, no matter the result, there is no doubt that the understanding of nicotine on brain-behavior relationships and in drug development for neuropsychiatric disorders will have been advanced for the next generation of researchers.

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Highlights

- The article presents a mini-review of studies on TS and depression over the past 25 years
- It summarizes the studies on the behavioral biology of the basal ganglia and its neurotransmitters
- It describes research with TS patients to evaluate the therapeutics of nicotine and mecamylamine

Table 1

Animal studies on Haloperidol, Nicotine, and Mecamylamine

Topic	Study	Findings	Publications
Haloperidol-induced catalepsy	Catalepsy was induced in rats using haloperidol.	The cataleptic effects of haloperidol are mediated by dopamine receptors localized postsynaptically on striatal neurons	[6]
Haloperidol induced Catalepsy	Rats were injected with haloperidol, morphine or NaCl. Catalepsy was measured using the Digiscan-16 Animal Activity Monitoring System by focusing on the duration of the period of vertical movements and the latency to the first vertical movement.	With repeated testing, the animals showed a progressive increase in their catalepsy scores.	[7–9]
Dopaminergic and Cholinergic systems and motor behavior	Rats were assigned to a kainic acid striatal lesioned or control group. Examined the responsiveness of rats to pilocarpine, haloperidol, scopolamine, and d-amphetamine.	The kainic-acid induced striatal lesions potentiated the locomotor response to the dopaminergic agonist, d-amphetamine, and scopolamine, attenuated the cataleptic response to haloperidol and potentiated the cataleptic and convulsive responses to pilocarpine.	[10]
Dopaminergic and Cholinergic systems and motor behavior	Chickens were used to examine the effects and interactions of apomorphine, haloperidol, scopolamine, and pilocarpine on stabilimeter activity and tonic immobility. Tonic immobility was assessed in a BRS sound attenuating chamber and stabilimeter activity was assessed in 4 activity platforms.	In birds and mammals, the dopaminergic and cholinergic systems are intimately involved in the expression of motor behavior.	[11]
Haloperidol-induced emotional defecation	First study: Rats randomly assigned to 4 morphine dose groups. Second: 5 groups of rats were randomly assigned to one dose of domperidone Third: the effect of benzodiazepam on defecation was examined	Haloperidol produced increased defecation in laboratory rats.	[12]
Amphetamine or scopolamine-induced hyperactivity	Rats were injected with d-amphetamine or scopolamine and studied with Digiscan Animal Activity Monitors	Activity measures of horizontal, vertical, stereotypic, and rotational behaviors differed depending on dose and drug	[13]
Catalepsy and quinolinic acid	Rats were injected with QA or a phosphate-buffered saline vehicle. They were then tested for cataleptic responses to haloperidol and SCH23390.	D ₁ -dopamine and D ₂ - dopamine receptors which mediate the cataleptic response are restricted to QA-sensitive neurons.	[15]
Scopolamine, Haloperidol, and emotional defecation	Rats were randomly assigned to one of four dose groups of scopolamine Rats were randomly assigned to one of four dose groups of n-methylscopolamine	A decrease in fecal excretions and an attenuation of haloperidol-induced defecation was found following administration of scopolamine. n-Methylscopolamine reduced defecation at all doses and when combined with haloperidol, both fecal number and mass decreased significantly.	[16]
Pimozide, Apomorphine, Haloperidol and emotional defecation	Three groups of six rats were randomly assigned to one of three dose groups of pimozide Rats were assigned to receive one of four doses of apomorphine	Apomorphine and pimozide were both found to increase levels of fecal boli excretions. When apomorphine was combined with haloperidol, defecation levels increased, showing that this phenomenon is not directly mediated by dopamine receptors.	[17, 18]

Topic	Study	Findings	Publications
Nicotine and locomotor behavior	Rats were injected with nicotine and evaluated by ten indicators of locomotor behavior	Nicotine decreased measures of vertical movement in a dose-related fashion	[14]
Nicotine, Haloperidol and Catalepsy	The rats received nicotine alone or in combination with haloperidol and then evaluated with the Digiscan-16 Animal Activity Monitor System	Nicotine alone did not produce catalepsy. Nicotine's potentiation of haloperidol-induced catalepsy could be related to striatal D ₂ receptor mechanisms.	[19]
Nicotine, Haloperidol and Catalepsy	The rats received an injection of either haloperidol or saline and one hour later received an injection of either nicotine or saline	Nicotine could not potential haloperidol-induced catalepsy without an intact striatum. The behavioral effect of nicotine and haloperidol cotreatment was not due to any change in dopamine turnover.	[20]
Nicotine and memory	Aged rats received either an injection of nicotine or saline while young rats received an injection of saline. Their acquisition and retention different types of mazes was evaluated	Aged rats pretreated with nicotine made fewer errors over the entire test period than the aged controls. Nicotine induced an enhancement in learning and reference memory, but not in working memory.	[21, 24, 25]
Nicotine and Kainic Acid	Rats were either pretreated with saline or nicotine and were then administered kainic acid	The rats pretreated with nicotine exhibited a marked reduction in the number of wet dog shakes. Little visible brain damage was seen in these rats when compared to the ones pretreated with saline.	[22, 23]
Prenatal and postnatal nicotine exposure and locomotor behavior	Rat offspring were exposed to nicotine prenatally and postnatally	A higher percentage of deaths were seen in those with nicotine exposure. Hyperactivity was documented in two of the doses of nicotine.	[26]
Nicotine and microglial activation	RT-PCR, western blot, immunofluorescent, and immunohistochemistry analyses.	Acetylcholine and nicotine pre-treatment inhibit lipopolysaccharide (LPS)-induced TNF- α release in Muriel-derived microglial cells an effect that was attenuated by $\alpha 7$ selective nicotinic antagonist, α -bungarotoxin. The inhibition appears to be mediated by a reduction in phosphorylation of p44/42 and p38 mitogen- activated protein kinase (MAPK). Negative regulation of microglia activation was linked to nicotine's neuroprotective properties.	[32]
Anxiolytic effects of Mecamylamine	Saline and mecamylamine groups were used. The rats were evaluated in the Elevated Plus-Maze and stress chamber.	Mecamylamine has anxiolytic properties under stressful conditions.	[27, 29]
Mecamylamine	Mecamylamine and its stereoisomers were evaluated as inhibitors of human nAChRs, mouse nAChRs, and rat NMDA receptors expressed in <i>Xenopus</i> oocytes.	nAChRs showed a prolonged inhibition after exposure to low micromolar concentrations of mecamylamine. NMDA receptors were only transiently inhibited by higher micromolar concentrations.	[28]
Mecamylamine, Haloperidol, Catalepsy and Defecation	Rats were injected with either saline or mecamylamine followed by saline or haloperidol. Catalepsy was evaluated by the bar test.	Only the rats treated with mecamylamine showed significant haloperidol-induced catalepsy.	[30]

Topic	Study	Findings	Publications
Mecamylamine, nicotine, and seizures	Rats received saline, (±)-mecamylamine, R-(−)-mecamylamine, or S-(+)-mecamylamine prior to nicotine injection.	Mecamylamine and each of its stereoisomers block nicotine-induced seizures in a dose-related manner. S-(+)-mecamylamine has inhibitory properties more similar to the racemic than the R-(−)-mecamylamine isomer.	[31]

Table 2

Clinical studies on Haloperidol, Nicotine, and Mecamylamine

Topic	Study	Findings	Reference
Nicotine gum, haloperidol, and TS	Reporting on the case of two TS patients undergoing treatment with haloperidol who were given nicotine gum to chew	Chewing nicotine gum reduced outbursts and attention deficit hyperactivity symptoms	[33]
Nicotine gum and haloperidol and TS	Open trial with 10 TS patients who received treatment with haloperidol and were given nicotine gum to chew	Patients showed an improvement in symptoms	[34]
Nicotine gum and haloperidol and TS	Follow-up study with 10 additional TS patients receiving treatment with haloperidol and were given nicotine gum to chew	The frequency of tics was reduced during the chewing of gum and afterwards	[35]
Nicotine gum and haloperidol and TS	Controlled study with 19 TS patients. One group was receiving treatment with haloperidol while the other was not. The effects of nicotine gum and placebo gum were examined.	A significant reduction in the frequency and severity of symptoms was present in the group treated with haloperidol, decrease in frequency in those receiving only nicotine gum and no effect in the use of placebo gum	[36]
Transdermal nicotine and TS	Reporting on the case of six TS patients who received the nicotine patch	The patients showed an amelioration of symptoms	[37]
Transdermal nicotine and TS	Open trial with 11 TS patients receiving dopamine receptor blockers and received nicotine patches.	The patch reduced the frequency and severity of tics	[38]
Transdermal nicotine and TS	Case study of 20 TS patients who received transdermal nicotine patches. Their tics were quantified using the YGTSS	The patch produced a reduction in TS symptoms during the use of the patch and 1 to 2 weeks after application	[39, 40]
Transdermal nicotine and TS	Double-blind placebo controlled trial with 70 TS patients receiving treatment for haloperidol. The patients received nicotine and placebo patches. CGI, PGI and YGTSS scales were used to assess the symptoms	CGI and PGI scales showed a difference in the reduction of the severity of symptoms between the nicotine and placebo groups, but YGTSS did not	[41]
Mecamylamine and TS	13 TS patients were treated with mecamylamine. CGI-SI and YGTSS scales were used to assess symptoms	Mecamylamine played a role in the reduction of the severity of the symptoms and improved behavioral and emotional problems	[42]
Mecamylamine and TS	Retrospective open-label study of 24 patients not responding to neuroleptics or not receiving medication. CGI scale was used to assess the symptoms	Improvement in the severity of the symptoms was seen in patients receiving mecamylamine and medication as well as in those only receiving mecamylamine. Improvement in mood and behavioral disturbances was also documented	[43, 44]
Mecamylamine and TS	Double-blind placebo controlled study with 61 TS patients who received mecamylamine or placebo. The symptoms were assessed using TODS-CR, CGI and YGTSS scales	Mecamylamine was as effective as the placebo. The TODS-CR scale pointed to mecamylamine's role in the reduction of mood changes and depression	[41, 45]