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ANALYSIS OF THE ROLE AND SIGNIFICANCE OF DRUGS ACTING ON CHOLINERGIC RECEPTORS IN MEDICAL PRACTICE

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ABSTRACT

All of the body's organs and tissues have muscarinic acetylcholine (ACh) receptors, commonly referred to as M receptors. These receptors primarily function in cholinergic nerve conduction. Although there are five distinct subtypes of muscarinic ACh receptors, it is still unclear how each of them affects cardiac function pharmacologically. Muscarinic ACh receptors may have an impact on functional myocardial disorders and myocardial traumas, including arrhythmia, myocardial ischemia, myocarditis, and myocardial fibrosis. In order to develop better strategies and provide references for further revealing and clarifying the signal transduction and mechanisms of muscarinic ACh receptors in cardiomyocytes, as well as to identify potential myocardial protective drugs that act on muscarinic ACh receptors, this article reviews the research progress on the regulation of myocardial function by muscarinic ACh receptors and related diseases. Anticholinergic medications are known to have side effects such constipation, dry mouth, and urine retention. Anticholinergic medications may cause cognitive decline and a loss of functional ability in the elderly. Numerous medications with anticholinergic properties are not members of the anticholinergic pharmacological class. These consist of antipsychotics, antidepressants, and antihistamines. An anticholinergic load results from taking several medications that have anticholinergic effects. Clinical professionals must determine which patients are at risk. The anticholinergic load can be evaluated using a variety of methods. These resources can be used by clinicians to evaluate pharmacological risk while

examining a patient's medication regimen. This can help with decisions on the continuation or cessation of anticholinergic medications. Deprescribing drugs with anticholinergic effects has several potential benefits in older people. In addition to reversing adverse effects, deprescribing may prevent problems such as falls.

Introduction. The somatic and autonomic nervous systems use cholinergic receptors for signal transduction. The ligand acetylcholine activates the receptors, thus their name. Due to distinct activation ligands that aided in their investigation, these receptors are classified as nicotinic and muscarinic receptors. Whereas muscarinic receptors react to muscarine, nicotinic receptors react to the agonist nicotine. As G-protein coupled receptors and ionotropic ligand-gated receptors, respectively, the two receptors have different functions. Nicotinic receptors are found in the neuromuscular junction and in the central nervous system. Muscarinic receptors mediate innervation to visceral organs in both the central and peripheral neural systems. Upon receptor activation, distinct physiological activities are conferred by the two receptor types' differing signal transduction [1,2,3]. Additionally, variations in receptor subtypes have distinct effects on pharmaceutical targets and disease etiology. Acetylcholine receptors in central or peripheral tissues are blocked by medications with anticholinergic properties. Either a desired therapeutic effect or an unintended negative consequence may result from this cholinergic antagonism. Many other medications have some anticholinergic effects in addition to those that are categorized as anticholinergics. These consist of antipsychotics, antidepressants, and antihistamines. Older persons frequently use medications with anticholinergic qualities to treat ailments like Parkinson's disease, melancholy, pain, allergies, and urine incontinence. Research indicates that medications with anticholinergic properties are prescribed to 20–50% of older persons. The cumulative effects of several medications that block acetylcholine receptors might be referred to as an individual's anticholinergic load. The load of anticholinergic drugs seems to be growing [4,5,6,7]. According to a recent UK study, the anticholinergic burden has increased up to nine times over the past 25 years due to increases in polypharmacy and the prescription of the majority of anticholinergic medication classes. Neurodegenerative disorders have become more prevalent in recent years; the most prevalent neurodegenerative kind of dementia, Alzheimer's disease (AD), affects roughly 17% of people over 75. According to estimates, the number of cases will increase by more than two times in Europe and three times globally by 2050. The progressive development of aggregates in brain tissue, such as senile plaques and neurofibrillary tangles, is a hallmark of AD from the very beginning. These aggregates can lead to neuronal death and degeneration, which can cause severe memory loss, cognitive impairment, language difficulties, and behavioral and personality changes [6,9]. The various conformations made it possible to identify allosteric modulators and subtype-specific agonists or antagonists by crystallography, which could lead to the development of treatment options for a variety of illnesses. Because of their significant unmet medical needs, the distinct molecular significance of muscarinic receptors, and the great potential for innovative therapeutics, we have focused on AD, cancer, and drug misuse in this study. Their role in oncogenic signaling, neurodegeneration, and dopaminergic dysfunction offers prospects for novel treatments that could transform these areas of care. The degenerative process

and trajectory of AD cannot be changed, in part because of our incomplete understanding of the mechanisms underlying its pathogenesis [10,11,12]. Additionally, efforts to find disease-modifying pharmaceutical interventions that can significantly improve cognitive outcomes have not been very successful. This is the case with antibodies that target β-amyloid oligomers, which have had significant trouble getting regulatory permission for their commercialization despite the amyloid cascade theory. However, other etiopathological ideas that can explain and help target the underlying degenerative processes must be reconsidered in the absence of considerably successful dementia treatments. In this context, the cholinergic system is linked to another generally recognized theory that explains the etiology of AD in its early stages. Cholinesterase inhibitors, which lessen the hydrolysis of acetylcholine in the synapses of cholinergic neurons, are the only known symptomatic treatment for AD [13,14,15].

The main purpose of this brief review is to analyze the role and significance of drugs acting on cholinergic receptors in medical practice, based on authoritative scientific literature.

Cholinergic receptors at the cellular level are essential for neural transmission in the autonomic and somatic nervous systems. N1 and N2 are the two subtypes of the nicotinic receptor. The peripheral or muscle receptor type is another name for N1, and the central or neuronal receptor subtype is another name for N2. The two receptors were named mainly because of their different positions in the somatic and autonomic nervous systems. Skeletal muscle has the N1 receptor at the neuromuscular junction. Both the central and peripheral nerve systems contain N2. In both the parasympathetic and sympathetic nervous systems, postganglionic neurons have N2 receptors on their cell bodies. As part of the sympathetic nervous system, they are also on the adrenal medulla. Nicotinic receptors are distributed differently from muscarinic receptors, which mediate the parasympathetic subdivision's activity mainly inside the autonomic nervous system. There are five primary subtypes of muscarinic receptors: M1, M2, M3, M4, and M5. Despite being found in the central nervous system, each subtype is restricted to distinct tissue types and encoded by distinct genes. The brain, stomach, and salivary glands are the main locations for the M1 receptor. M2 receptors are diffusely found in smooth muscle and cardiac tissue. Additionally, the salivary glands, stomach, and smooth muscle all have M3 receptors[3-10]. Although they are less well understood, M4 and M5 receptors are found in the substantia nigra and hippocampal regions. The autonomic nervous system's parasympathetic division is mediated by the widely dispersed receptors, preserving internal homeostasis (Table 1).

Table 1. Cellular Level of M-Cholinergic receptors

№	Types of M - cholinergic receptors	Location	Effects
1.	M_1	Cerebral cortex, gastric, and salivary glands.	Miosis, salivation, secretion of gastric
2.	M_2	Smooth muscle and cardiac tissue	Bradycardia
3.	M_3	Smooth muscle, gastric, and salivary glands	Spasm of intestinalis and gastric
4.	M_4	Hippocampus and substantia nigra	M4 and M5 receptors are not as well characterized
5.	**M_5**		

The CNS has nicotinic acetylcholine receptors (Table 2). Another useful component of the cholinergic system that has been thoroughly investigated in biomedical research as a possible treatment target for AD is acetylcholine receptors (AChRs). Specifically, ligand-gated ion channels called nicotinic acetylcholine receptors (nAChRs) are found in most parts of the brain. Both pre-synaptic and post-synaptic neurons express nAChRs, which regulate neuronal excitability and neurotransmitter release to influence a number of physiological and behavioral processes. The α and β subunits that make up neural nAChRs can assemble into a homomeric or heteromeric structure. Brain tissue has been shown to contain three β subunits (β2–β4) and nine α subunits (α2–α7, α9, and α10) [11-14]. In the mammalian brain, the two main subtypes of nAChRs are α7 and α4β2, which are also the subtypes most frequently implicated in neurological conditions like AD. Across vertebrate species, the distribution of nAChRs is highly conserved. The brain exhibits a wide distribution of both the α4β2 and α7 subtypes, with areas of expression that overlap. The thalamus and basal forebrain (nucleus basalis of Meynert) have a higher density of α4β2 AChRs, whereas the putamen and cerebellum have intermediate expression. The cortical regions have the lowest levels of α4β2 nAChRs. The expression of α7 nAChRs is stronger in the hippocampus, specifically in the CA1–CA3 and dentate gyrus areas, the thalamus, and the basal forebrain, whereas they are very weakly found in the cortex. It has been demonstrated that the nAChRs expressed in these regions regulate learning, memory, arousal, attention, excitability, transmitter release, and synaptic function and plasticity [7-12].

Table 2. Cellular Level of N-Cholinergic receptors

№	Types of M - cholinergic receptors	Location	Effects
1.	N_N	All postganglionic cell bodies	An excitatory signal may become generated through N_N receptor activation. Depending on the strength of the signal, receptor activation may result in membrane depolarization with subsequent muscle contraction.
		Skeletal muscle at the neuromuscular junction	
		Adrenal medulla	
2.	N_M	The cell bodies of postganglionic neurons within the parasympathetic and sympathetic nervous systems Hippocampus and substantia nigra	The ionic flux generated at the postganglionic cell is responsible for excitatory signal transduction to effector organs of the autonomic nervous system.

With changes impacting major organ systems like the neurological, circulatory, respiratory, integumentary, digestive, and urinary systems, the autonomic nervous system is in charge of preserving the body's homeostatic environment. There are three divisions of the autonomic nervous system: enteric, parasympathetic, and sympathetic. Depending on where their cell bodies are located in the central or peripheral nervous systems, neurons in the parasympathetic and sympathetic nervous systems are classified as either preganglionic or postganglionic. All postganglionic cell bodies have the neuronal nicotinic receptor subtype, also known as N2. Acetylcholine triggers the N2 receptors, which then send signals from the preganglionic cell to the postganglionic cell. Transduction of excitatory signals to autonomic nervous system effector organs is mediated by the ionic flux produced at the postganglionic cell. On muscle cells that produce voluntary muscle action, the N1 or muscle nicotinic receptor is located at the neuromuscular junction. Activation of the N1 receptor may result in the generation of an excitatory signal. Receptor activation may cause membrane depolarization and subsequent muscular contraction, depending on the signal's amplitude [3,4,7,14]. Receptor activation promotes intestinal motility and the release of digestive enzymes within the digestive system. In the lungs, smooth muscle contraction brought on by receptor activation narrows the airways and increases secretion output. Additionally, muscarinic receptors have been shown to play significant roles in memory and learning and are found throughout the central nervous system. M1 receptor-deficient animal models exhibit deficits in long-term potentiation as well as cognition. Thus, synaptic plasticity and neuronal differentiation are maintained by M1 receptor activation. Muscarinic receptors play an essential function in the autonomic nervous system, as evidenced by the variety of actions they can mediate. Because receptors are so widely distributed, medicinal treatments that activate or inhibit them may have a variety of side effects in addition to their intended purpose [1,7,8,15].

Clinical Importance. A distinct pharmacologic niche is produced by the extensive distribution of cholinergic receptors in the peripheral nervous system that mediate the activity of skeletal muscle and visceral organs. Muscarinic receptors can cause bradycardia, bronchoconstriction, increased gastrointestinal motility, bladder emptying, gland secretion, and pupillary constriction for near vision when they are activated. As a result, caution is required when utilizing medications that alter acetylcholine levels. A surplus of acetylcholine can cause diarrhea, diaphoresis, urination, salivation, lacrimation, miosis, bronchospasm, and bradycardia because of the wide dispersion of receptors; on the other hand, substances that inhibit or reduce acetylcholine binding can cause tachycardia, dry mouth, dry eyes, mydriasis, decreased sweating, urine retention, sedation, hallucinations, or agitation. These side effects demonstrate how many clinical alternatives there are for agonist and antagonist medications. Nicotinic receptor agonists are used to cause paralysis at the neuromuscular junction. Nicotinic agonists accomplish this by attaching themselves to the receptor and taking up residence in the acetylcholine binding region. Tubocurarine and succinylcholine are two common medication classes [1-7]. Despite having different mechanisms for inactivating their receptors, both of these medications show specificity for nicotinic receptors at the neuromuscular junction. While succinylcholine binds and activates the nicotinic receptor, it stays attached to the receptor's active site. Because it first activates the receptor and then depolarizes the membrane, succinylcholine is known as a "depolarizing neuromuscular blocker" because of this binding, which stops the receptor from activating again while it is bound. However, the tubocurarine class of medications, which includes atracurium, rocuronium, and vecuronium, are classified as "non-depolarizing agents." By occupying the active receptor

site and blocking acetylcholine binding and activation, these substances work through competitive inhibition [8-13].

Negative consequences. Anticholinergic medications have a notable adverse effect profile. Common side effects of anticholinergic medications include constipation, dry mouth, urine retention, cognitive deterioration, and loss of the ability to carry out daily tasks. Due to age-related changes in pharmacokinetic and pharmacodynamic processes, multimorbidity, polypharmacy, and geriatric syndromes including frailty, adverse anticholinergic effects are especially significant in older persons. Serious side effects, such as falls, functional decline, delirium, and death, are associated with anticholinergic burden in older persons. According to a recent Cochrane analysis, older persons without cognitive impairment who use medications that have anticholinergic effects may be more susceptible to dementia and cognitive decline. Additionally, a number of medications that have anticholinergic effects have the potential to seriously impair older persons' dental health [4,9,10,16].

Discussion. Memory loss and a decline in other mental abilities, such as thought processing, reasoning, attention, and language, that are severe enough to impair autonomy and self-sufficiency are among the many symptoms that define the clinical picture of dementia, which is not a specific disease. Primary dementias, the most common of several illnesses affecting the central nervous system, are caused by irreversible neuronal degeneration in the intricate functional circuits of the brain. Lewy body dementia, Parkinson's disease dementia, frontotemporal dementia, and prion disorders are among the neurodegenerative illnesses that fall under this category, despite AD being the most prevalent type. plan. Clinical trials examining the possible effects of nAChRs agonists were significantly impacted by the prevalence of AD in relation to other disorders. This SR found three RCTs examining the effectiveness of the α7-selective nAChRs agonist AZD0328 and nicotine, a chemical that raises dopamine levels in the central nervous system, in reducing the cognitive symptoms of Parkinson's disease [1,4,5,7,11]. However, neither of these treatments worked well as a neuroprotective measure. Participants in the remaining trials were either diagnosed with mild to severe AD or MCI, which is characterized as a deterioration in mental and cognitive ability that is a relevant risk factor for dementia even if it does not significantly impair daily living activities. Treatments for AD are often started in the prodromal stages, according to recent clinical data. The brain, autonomic ganglia, and neuromuscular junctions all release the neurotransmitter acetylcholine (Ach). It has an impact on presynaptic neurotransmitter release, neuronal excitability, and group neuron activity coordination. Acetylcholine binds to either pre- or postsynaptic muscarinic receptors to regulate brain function. Furthermore, it has a variety of neuromodulatory roles in the developing and mature brain, including controlling cortical responses to external stimuli, determining arousal level, and guiding neuronal growth. Muscarinic acetylcholine receptors are a subfamily of G protein-coupled receptors (GPCRs) that regulate a number of vital functions in the central and peripheral nervous systems. Due to the growing demand for new therapeutic medicines, there is currently an increasing interest in delving deeper into the crystallization and pharmacology of the receptor [3,6,10,14]. However, the study's whole methodological features have not yet been published, which precludes a thorough evaluation of its quality. Future research should aim to be based on a more suitable and standardized methodology to assess the efficacy of both new and old therapeutic approaches based on the use of nAChRs agonists, including their use as adjuvants in therapies based on other agents, as the overall quality of the studies included in this review was medium to low. Bradycardia, atrioventricular block, atrial fibrillation or

flutter, hypotension, or even cardiac arrest are serious side effects that can result from cholinergic drugs since they act on the muscarinic and nicotinic receptors. Salivation, sweating, lacrimation, gastric and tracheobronchial secretions, stool evacuation, voiding of the bladder, bronchial asthma attack, and abdominal pains are additional adverse effects. Pilocarpine may result in spasms of accommodation and miosis. Depression can be brought on by certain cholinergic medications. In cases of intestinal resection or anastomosis, arrhythmias, coronary vascular disease, angle-closure glaucoma, hyperthyroidism, urinary obstruction, orthostatic hypertension, severe miosis, and pulmonary disease (COPD/bronchial asthma), cholinergic medicines should not be taken [11,12,13,15,16].

Conclusions. Accordingly, those secondary outcome measures that demonstrated encouraging outcomes in delaying the neurodegenerative pathways should be taken into consideration as endpoints in future trials. Only one clinical trial involving subjects with mild cognitive impairment treated with nicotine has published data, indicating intriguing results that require confirmation. As a result, the relationship between this class of drugs and the progression of dementia from cognitive decline to dementia has not yet been thoroughly examined. Lastly, before evidence-based conclusions regarding the safety and effectiveness of nAChR agonist candidates in dementia can be made, more research in high-quality trials is required to examine the chemical–pharmacological characteristics, functional effects, such as receptor desensitization, and dosing protocols.

Cholinergic drugs can have serious side effects, such as bradycardia, atrioventricular block, atrial fibrillation or flutter, hypotension, or even cardiac collapse, since they interact with muscarinic and nicotinic receptors. Abdominal pains, bowel evacuation, bladder voiding, bronchial asthma attack, sweating, lacrimation, gastric and tracheobronchial secretions, and salivation are additional adverse effects. Miosis and spasm of accommodation may be brought on by pilocarpine. Depression may result from certain cholinergic medications. The following conditions make cholinergic medicines contraindicated: severe miosis, intestinal resection or anastomosis, arrhythmias, coronary vascular disease, angle-closure glaucoma, hyperthyroidism, urinary obstruction, orthostatic hypertension, and pulmonary disease (COPD/bronchial asthma).

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