Section I

The Pharmacological Basis for Parkinson's Disease Treatment

Chapter 1

The pharmacological basis of Parkinson's disease therapy: an overview

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The "shaking palsy" was first recognized by James Parkinson in 1817 when he described a condition characterized by "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace [here he was referring to festination or more accurately referred to in that era as scelotyrbe festinans]: the sense and intellects being uninjured." In his writings, James Parkinson credits Galen as first noticing shaking of the limbs belonging to this disease and calling them "by an appropriate term: tremor." Parkinson further and correctly stated that "tremor can indeed only be considered as a symptom" and not a disease in itself. Since then, others have laid the foundations for the study and understanding of this condition. Freidrich Lewy described the body that now bears his name and the central focus of the science behind Parkinson's disease (PD). Froscher Tretiakoff localized the disease to the substantia nigra. Greenfield confirmed the scattered cellular changes in the locus coeruleus of the pontine tegmentum and substantia nigra. In his 1962 monograph on the *Basal ganglia*, Derek Denny-Brown described his clinical and pathological experience of PD patients, calling attention to the presence of the preponderance of thinning of the myelin sheaths as a consequence of nigral cell loss and pallor of the outer pallidum and ansa lenticularis. Arvid Carlsson, a Nobel Prize winner, recognized that the sole function of dopamine was not limited to the synthesis of norepinephrine, and, together with the work by Walter Birkmayer and Oleh Hornykiewicz, demonstrated that dopamine was decreased in the striatum in PD. George Cotzias successfully treated PD patients with levodopa (3,4-dihydroxyphenyl-L-alanine or L-DOPA), initiating the modern era of neurotherapeutics based on solid scientific data. Long gone are the days of blood letting and other treatment options that Parkinson himself recommended as the treatment of choice to "release the humors causing the condition." Recent advances in our understudying of the pathological distribution and progression in PD along with progress in genomics are constantly challenging our understanding and are providing hope for the future of the PD patient.

Since the first description and recognition of PD, many other movement disorders have been recognized. Oppenheimer first described dystonia muscular deformans in 1912, and tremor has been recognized since Galen times, and chorea was already recognized by the Romans. More recently, other abnormal involuntary movements were recognized at the turn of the 20th century. These seemingly disparate conditions were slowly recognized and were further defined and grouped conceptually into an emerging field called "movement disorders." Classically, movement disorders referred to conditions stemming from basal ganglia dysfunction. As advances in basal ganglia physiology and understanding of the underlying pathophysiology of such disorders accrued, it became clear that the term must also include conditions stemming from basal ganglia connections (reciprocal, fugal pathways, for example), along with other functionally related structures such as the thalamus, subthalamus, brainstem nuclei and pedunculopontine nuclei, and networks such as the reticular formation, cerebellum and its connections, the spinal cord and some disorders of peripheral nerve and muscle. Hence, in today's usage, the term movement disorders is quite broad, encompassing disorders of motor control, coordination, gait, abnormal involuntary movements and other seemingly "orphan" conditions such as cramps, spasms, restless legs syndrome and stiff person syndrome. Coupled with genomic

Parkinson's Disease: Current and Future Therapeutics and Clinical Trials, ed. Gálvez-Jiménez *et al.* Published by Cambridge University Press.

advances, the field is going through a renaissance requiring the mastering of a broad area of neurological disorders and basic neurosciences, and further blurring the borders between neuromuscular diseases, epilepsy, dementias, praxis and other higher cortical conditions, and genetics.

Broadly, movement disorders may be categorized into akinetic–rigid syndromes, hyperkinetic movement disorders, gait disturbances, cerebellar diseases, psychogenic movement disorders and spasticity. It is important to recognize that the observed phenomenology may be due to a variety of secondary causes, and the proper observed phenomena must be placed in the overall context in which the process is occurring. A physician interested in movement disorders thus must first recognize the category or type of movement disorder, for example whether it is tremor, chorea or dystonia. The concept or "what is it?" is the first and often most important component of determining a cause, rather than the traditional neurological approach of "where is the lesion?" This latter point cannot be overstated, i.e. defining the broad category of movement disorders in a given patient must precede the classical approach of localization to help place into perspective the alterations observed. A careful history with particular attention to family history, consanguinity, pregnancy, labor and delivery, early developmental milestones, trauma, infections, medical and psychiatric comorbidities and psychological stressors, and exposure to illicit drugs or medications for the treatment of gastrointestinal and psychiatric disorders, especially neuroleptics, are particularly important when first evaluating a patient with abnormal involuntary movements. A detailed general medical and neurological examination with emphasis on oculomotor disturbances, the presence of saccadic intrusions, Kayser–Fleischer rings (betraying Wilson's disease), fundoscopic examination looking for retinopathies and optic nerve abnormalities (papillitis, papilledema or optic nerve atrophy suggesting a space-occupying lesion, normal-pressure hydrocephalus, demyelinating diseases, metabolic or mitochondrial cytopathies), organomegaly (metabolic or storage diseases) and skin discolorations and/or deposits (phakomatosis, xeroderma pigmentosum, vitaminosis, malabsorption) may prove rewarding. Once the abnormal movements have been classified, and the neurological accompaniments documented and placed in context, the cause may become apparent and proper ancillary testing may be undertaken.

It should be recognized that hyperkinetic and/or akinetic–rigid syndromes may coexist in different combinations, and some may be bizarre and difficult to classify properly. In these circumstances, a clear and detailed description of the observed abnormality is the best step to define what is observed and to share among colleagues. For example, the akinetic–rigid syndrome characteristic of the parkinsonian syndrome may be accompanied by tremor, early-morning foot dystonia, and medication-related abnormal involuntary dyskinesias in the same patient (see below). In addition to a careful neurological examination, a focused general physical examination must be carried out paying particular attention to the iris and sclera by fundoscopic examination looking for the presence of optic disk disease and retinopathies, the presence of hepatosplenomegaly, skin rashes or lesions, and tendon xanthomata, which may be indicators of a more systemic disorder such as lipid storage diseases, cholesterol disorders, mitochondria cytopathies, neurocutaneous syndromes, leukomyelodystrophies or other demyelinating diseases among others, all leading to parkinsonian syndrome. Many other disorders of movement have been described and are outside the scope of this work. The remainder of the discussion will center on the akinetic–rigid syndrome which is the topic of this monograph.

The akinetic–rigid syndromes are characterized by paucity of movement. Parkinson's disease and other parkinsonian syndromes are the classic examples of this syndrome, characterized by slowness of movement, stiffness or rigidity, gait disturbances and imbalance, and tremor. This can easily be recognized if the pneumonic TRAP is kept in mind – tremor, rigidity, akinesia (bradykinesia) and postural instability (gait disturbances) – which may be present in various combinations. The key symptom for defining a parkinsonian condition is the presence of bradykinesia. Many patients with PD will not exhibit a tremor. Overall, recognizing the presence of two of the four (especially two out of tremor, rigidity and bradykinesia) will help define on clinical grounds the presence of the parkinsonian syndrome in a given individual. Postural and gait disturbances usually develop late in the course of the illness. For example, early-onset postural instability and imbalance, falls and gait disturbances characterize progressive supranuclear palsy, the spinocerebellar ataxias and spastic paraplegias, whereas early-onset autonomic disturbances may herald the onset of multiple-system atrophy. Other features quite

common in the parkinsonian patient include decreased facial expression (facial hypomimia), soft and at times slurred speech with or without start hesitation, occasional stuttering, apraxia of lid opening, blepharoclonus or blepharospasm, tremor of the tongue, jaw or lips, sialorrhea, and malar and forehead seborrheic dermatitis and may be present in various combinations. Decreased blinking and micrographia are common features in parkinsonism but are not unique to PD and may be present in other parkinsonian syndromes. An astonished facial expression due to frontalis muscle contraction may also be seen. A high, raspy, high-pitched voice can also be present. When these two latter features are present, other parkinsonian syndromes such as progressive supranuclear palsy, vascular parkinsonism, some instances of drug-induced parkinsonism, bilateral basal ganglia necrosis, mitochondrial cytopathies and the nigrostriatal form of multiple-system atrophy (currently known as multiple-system atrophy-P) should be considered. A rest tremor may be evident during the initial contact and may not be restricted to the upper extremity. Not infrequently, a foot tremor may also be evident. Although a rest tremor is usually asymmetric, it may have started on the one body side affected first and not infrequently is noticed only when occurring bilaterally, with the side at onset being the most affected over time. When tremor is suspected, it can be elicited with mental exercises, maintaining the hands resting on the thighs and asking the patient to close their eyes. It is important to allow the patient to feel comfortable and relaxed when testing for the presence of tremor, as any voluntary limb movement may eliminate the rest tremor. In many patients, the rest tremor becomes evident when holding the hands outstretched, especially when the hands have been brought into position and after a short period of finger and hand quiescence allowing for "resetting or reappearance of hand rest tremor." In spite of classical teachings, cogwheeling is not unique to PD but rather is a common phenomenon in other parkinsonian syndromes and conditions in which tremor is present, such as essential tremor. The key for the cogwheeling phenomena is the presence of tremor on increased tone. When the limb is tested for tone, cogwheeling may be noticed. Stooping may be evident when sitting but quite noticeable when standing. In severe cases, marked flexion at the waist resulting in camptocormia (bent spine) may be observed. Other abnormal postures such as a striatal hand and foot may be noticed (Figure 1.1) especially in the early-morning hours or when the levels of levodopa are at their lowest ("off" stage). In some cases, severe antecollis and bent spines may ensue, betraying marked extensor muscle atrophy/myopathy with fatty infiltration. Dystonic limb posturing may be associated with other abnormal involuntary movements during the peak or "on" time of levodopa effect (see below). Many patients will demonstrate gait abnormalities consisting of start hesitation or gait ignition failure, short stride, slow cadence, decreased arm swing, turning en bloc, occasional imbalance when turning and retropulsion when tested. Rigidity is often present bilaterally but may be asymmetric in the early stages of the disease. If rigidity is suspected and is not clearly evident during the examination, it may be "brought out" by using Froment's maneuver. This is especially helpful when looking for subtle neck rigidity and limb rigidity. Other maneuvers not frequently mentioned but helpful when assessing these patients include the pillow sign, the shaking of limbs and trunk rotation.

In the untreated patient, five stages may be identified. Stage 1 is characterized by mild unilateral symptoms. Tremor may be mild and intermittent in the presence of other subtle symptoms such as rigidity or slowness of movement. Gait is usually normal, but a decrease in arm swing may be noticeable on the most symptomatic side, with the upper limb carried slightly abducted at the shoulder and flexed at the elbow. Facial hypomimia may be present but may be confused with "normal for the person's age." There is usually subtle reduced manual dexterity and impaired rapid repetitive movements. For example, patients may complain of having difficulties with the computer keyboard or when using a computer mouse. Micrographia may be present, with poorly formed letters. As the disease advances to stage 2, there is usually bilateral involvement with onset of mild postural changes in some, but the key is worsening of the initial symptoms with progression to bilaterality. In this stage, the more classic phenotype is observed with clear reduced facial expression, stooping when standing, reduced arm swing on walking and en-bloc turning. There are definitive alterations in rapid alternating and repetitive movements. The patient's movements are clearly slow and deliberate. Some patients may begin to complain of fatigue and weakness at this time. Commonly heard is a sense of weakness in the most affected limb but lack of objective alteration when testing muscle power on examination. Fatigue may be quite disabling in many patients thus affected. Another observation is the

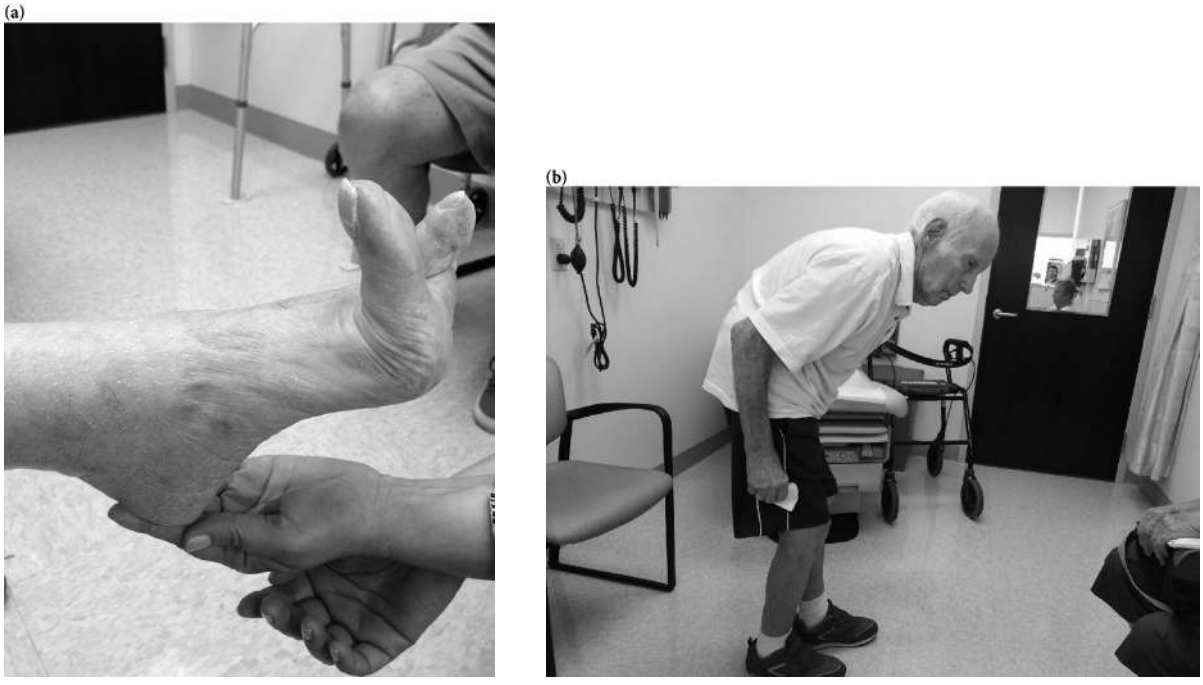

Figure 1.1 (a) A striatal foot, which may easily be confused with early-morning foot dystonia. In this particular case, there is a fixation of the joints exacerbated by a superimposed off-period worsening of great toe extension. (b) Camptocormia.

beginning of the development of the so-called striatal hand with dorsiflexion of the wrist, adducted fingers, flexed metacarpophalangeal and distal interphalangeal joints. Similarly, some patients may develop a striatal foot with clawing of the toes and varus foot posture. In stage 3, retropulsion and propulsion betray the onset of increasing impairment of postural reflexes and righting responses. Shuffling and festination of gait are noted. At this stage, the patient may require some assistance in the activities of daily living. With further progression, a more advanced stage, stage 4, is reached with severe disability, rigidity, bradykinesia and gait disturbances. Standing is unsteady, with severe retropulsion with falls if not caught by the examiner or a caregiver. Once the patient reaches an end stage with confinement to a wheelchair or bed, they are said to have reached stage 5. Drs Melvin Yahr and Margaret Hoehn carefully studied and documented the natural history of PD and developed an operational scale that bears their names arbitrarily dividing this disorder into five stages on which the above discussion was based. This scale provides a somewhat crude estimate of disease severity and progression.

Parkinson's disease is no longer considered only a motor disorder. It has become evident that the pathological changes are broad, and the progression seems to follow a pattern suggesting *trans*-synaptic transmission via propagation of proteins in a prion-like fashion, such that: (i) these pathological changes usually antedate by decades the motor symptoms; (ii) the process may have a portal of entry or origin at the gut or in the nasal passages; (iii) when the motor symptoms become evident the disease is fairly advanced; and (iv) any attempt to alter the natural history of the disease must be coupled with solid epidemiological data to identify those at risk before the disease becomes clinically manifest. These and other hot topics are the subject of this monograph and the editors hope the reader finds in these pages the necessary clinical and scientific foundations for an understanding of the disease, the underpinnings of the pathological processes and the foundations for solid therapeutics.

Chapter 2

Anticholinergic agents in the management of Parkinson's disease

Juan Carlos Giugni and Ramon L. Rodriguez-Cruz

Introduction

Anticholinergics had a leading role in the treatment of Parkinson's disease (PD) until the 1960s, when levodopa (L-DOPA) was introduced and proved to be a better treatment option to improve the cardinal symptoms of the disease. Since then, levodopa and dopaminergic agents have taken the leading role and have remained the most efficacious symptomatic treatment for PD. Despite the widespread use of dopaminergics drugs in PD, anticholinergics are still in use today and play a role in the treatment of PD. They are most commonly prescribed to alleviate symptoms in young patients with tremor-dominant PD and in those with PD-related dystonia. In this chapter, we describe the use, efficacy and side effects using anticholinergics for the management of PD.

Anticholinergics are substances that block the neurotransmitter acetylcholine, in both the central and peripheral nervous systems, and act on acetylcholine receptors in neurons through competitive inhibition. Anticholinergics are classified into two categories according to the receptors they act on: antimuscarinic and antinicotinic agents [1].

Antimuscarinic agents are named as such because they block muscarine, found in *Amanita muscaria*, a nonedible mushroom species. Muscarine is a toxic compound that competes with acetylcholine for the same receptors. The classic antimuscarinic agent atropine, a belladonna alkaloid, has been used for centuries to treat a variety of conditions, mainly gastrointestinal disorders. Centrally acting antimuscarinics such as trihexyphenidyl, benztropine, biperiden and procyclidine have been used in the management of PD, and were the first synthetic drugs for PD [2].

The use of anticholinergics dates back hundreds of years. In the Odyssey, Homer describes the lethal effects of *Datura stramonium*, commonly known now as jimsonweed. The antiparkinsonian effect of anticholinergics was initially described in 1867 by Ordenstein [3], one of Charcot's students, when he wrote his medical thesis on the treatment of parkinsonian tremor with belladonna alkaloids. At the time, Charcot's preferred treatment was hyoscyamine, derived from *Atropa belladonna*, for the treatment of PD [4]. As seen in a prescription located in the Philadelphia College of Physicians (Figure 2.1), the anticholinergic treatment used by Professor Charcot was usually combined with rye-based ergot products. These kinds of products are the predecessors some dopamine agonists that are currently in use [4]. In the 1940s, trihexyphenidyl (Artane®) was introduced as the first synthetic anticholinergic [2], replacing natural alkaloids.

The cholinergic system and Parkinson's disease

Some authors have postulated the theory of imbalance between acetylcholine and dopamine in the striatum as the origin of motor symptoms in PD [1, 5]. The dopaminergic and cholinergic systems are closely related and in constant balance. In PD, the degeneration of nigral neurons leads to decreased dopamine production, and this situation cause an imbalance between acetylcholine and dopamine. In PD, dopamine depletion blocks autoinhibition of acetylcholine release through muscarinic autoreceptors, leading to excessive acetylcholine release [5]. This hypothesis is supported by the fact that anticholinergics were the first treatment for PD [6].

The striatum is a nodal basal ganglia structure and is a major input station of the basal ganglia. Acetylcholine is an important neurotransmitter in the striatum based on its abundance [7]. The striatum is

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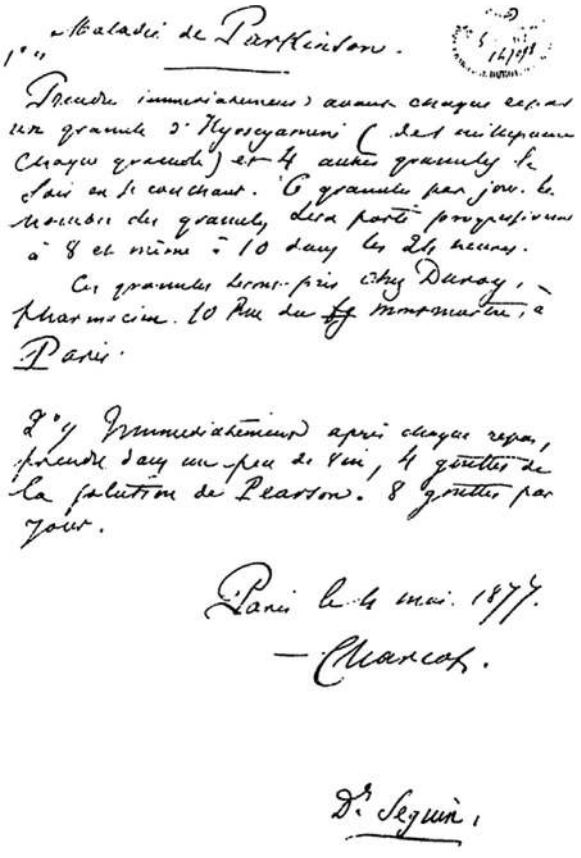

Figure 2.1 Prescription of anticholinergic treatment used by Professor Charcot, dated 1887 from the College of Physicians of Philadelphia Library.

subdivided into two regions, the matrix and the striosomes. Both compartments contain medium spiny neurons, which comprise nearly 95% of striatal neurons, and affect the direct and indirect pathways [8, 9]. The remaining striatal neurons are interneurons and only 1–3% are giant aspiny cholinergic interneurons. These interneurons have multifold arborizing axons [10, 11], and this explains the high expression of cholinergic markers in the striatum [7]. In the striatum, acetylcholine acts via muscarinic and nicotinic receptors, in postsynaptic and presynaptic targets, and contributes to the activity of the medium spiny neurons [12]. The primary effect of acetylcholine on medium spiny neurons is depolarization via muscarinic receptor M1. This facilitation occurs primarily on medium spiny neurons of the indirect pathway [13].

Multiple studies in PD have shown loss of cholinergic neurons in the pedunculopontine nucleus (PPN) in PD [14–16]. The PPN is located in the mesencephalic tegmentum and contains cholinergic, GABAergic and glutamatergic neurons [17]. Effects on the PPN in PD are narrowly related to gait disturbance, and the severity of cholinergic neuronal depletion in the PPN correlates with the severity of motor symptoms [14]. Another cholinergic system change in PD is an increase in the muscarinic binding sites in the globus pallidus internus, probably due to a compensatory upregulation in response to a decrease in cholinergic activity [18]. These changes result in elevated peaks of acetylcholine in the striatum, and may affect the indirect pathway [5]. Some authors believe that anticholinergics can correct this imbalance in PD, thereby reducing the degree of neurotransmission mediated by neostriatal acetylcholine [19].

Nicotinic receptors also play a role in PD. Nicotinic receptors are located at presynaptic terminals. Substantial evidence from studies of epidemiologic and animal PD models suggest a protective effect and an inverse relationship on the development of PD [20]. However, clinical trials have not shown similar results [21, 22].

Pharmacokinetics and pharmacodynamics

The anticholinergic drugs available for use in the treatment of PD provide a different mechanism of action, which is an alternative to relieve some of the bothersome motor symptoms, especially tremors.

The anticholinergic drugs used in the treatment of PD are competitive antagonists of muscarinic receptors. The most commonly used worldwide are trihexyphenidyl (Artane®), benztropine (Cogentin®), biperiden (Akineton®) and procyclidine (Kemadrin®).

The mechanism of action of anticholinergics is still not fully known but is suspected to be a result of blocking of the muscarinic receptors in the striatum, acting as strong inhibitors of the presynaptic carrier-mediated dopamine transport mechanism [23]. In addition to the muscarinic blockade, anticholinergics act as agonists at the noradrenergic synapse, and also have *N*-methyl-D-aspartate (NMDA) antagonist receptor activity [24].

In general, most anticholinergic drugs have good and rapid oral absorption through the gut. The average the time to maximal plasma concentration (T_{max}) is 2.5 h (1.5–3.5 h). The maximum plasma concentration (C_{max}) is dose dependent and is different for each drug,

Table 2.1 Properties of major anticholinergics used in Parkinson's disease

Drug	C_{max} (μg/l) for dose (mg)	T_{max} (h)	$t_{1/2}$ (h)	Preparations[a]	Initial daily dosage	Titration	Final daily dosage
Trihexyphenidyl	7 (10)	1.3	33	2–5 mg 0.4 mg/ml	1 mg	Increase 2 mg every 4–5 days	6–10 mg (2–3 mg tid)
Biperiden	4–6 (4)	1.5	18–24	2 mg 5 mg/ml	1 mg	Increase 1 mg every 4 days	6–9 mg (2–3 mg tid)
Benztropine	2.5 (1.5)	7		0.5, 1, 2 mg 1 mg/ml	0.5 mg	Increase 0.5 mg every 5–6 days	2–6 mg (1–2 mg tid)
Procyclidine	116 (10)	1	8–16	2.5–5 mg 2.5 mg/5 ml	2.5–3 mg		15–30 mg (5–10 mg tid)

Tid, three times daily.

[a]Available tablet and liquid forms are given.

with the exception of procyclidine as its plasma concentration is high even in small doses [25]. The half-life ($t_{1/2}$) is also different in each drug; for example, trihexyphenidyl has a C_{max} of 7 μg/l for a 10 mg dosage with a $t_{1/2}$ of 33 h, and biperiden has a C_{max} of 4–6 μg/l for 4 mg dosage with a $t_{1/2}$ of 18–24 h. The results for these and the other two commonly used drugs are illustrated in Table 2.1.

The bioavailability of anticholinergics ranges from 30 to 90%; for example, procyclidine and biperiden have an absolute bioavailability of 75% and 33%, respectively [25, 26]. The tissue distribution of anticholinergics has been observed in laboratory animals and has been reported to be large. For biperiden, a brain/plasma area-under-the-curve ratio of 7–12 ng/(h ml) has been reported [27]. These authors also showed that with an intravenous infusion of biperiden, maximal brain concentration was obtained within 3–10 min. The high concentrations of these drugs in the brain could be explained by their intensely lipophilic properties. Lipophilic biomolecules in the brain serve to promote the uptake of anticholinergics, and for trihexyphenidyl and biperiden, the uptake is also related to intralysosomal uptake of the drug [28]. The protein binding of anticholinergics has not been elucidated in humans, but in rats the binding of biperiden to plasma protein is approximately 90% [29].

For the most part, all anticholinergics are metabolized in the liver, and the pathways of excretion are urine and bile. There are some differences for each of these drugs. For trihexyphenidyl and procyclidine, the metabolism is due to hydroxylation of the alicyclic groups, and excretion is through urine and bile for trihexyphenidyl and through urine for procyclidine [30]. Benztropine is metabolized by *N*-oxidation, *N*-dealkylation and ring hydroxylation [31].

Table 2.2 Commonly used drugs with secondary anticholinergic effects

Name of drug	Use
Diphenylhydramine	Antihistamine
Ipratropium bromide	Bronchospasm
Clozapine	Antipsychotic
Quetiapine	Antipsychotic
Olanzapine	Antipsychotic
Amitriptyline	Antidepressant
Nortriptyline	Antidepressant
Paroxetine	Antidepressant

The dosage and titration vary for each drug (Table 2.2), but in general, to avoid the adverse effects of these kinds of medication, initiation of treatment should be with low dosages and slow titration, especially in the older population.

Beyond the anticholinergic drugs, there are many others drugs used for different conditions in PD, especially psychiatric symptoms (such as depression, psychosis and hallucinations), as well as drugs used for general conditions like allergies that also have anticholinergic properties acting on cholinergic receptors [32].

Current use of anticholinergic drugs in the management of Parkinson's disease

While anticholinergic drugs were initially the most important drugs for treating PD, their use declined after the development of levodopa and most recently

dopamine agonists. The occurrence of adverse effects also caused a decline in their use but to a much lesser extent. The current use of anticholinergics has been limited to the treatment of a PD resting tremor that is not responding satisfactorily to dopaminergics and PD-related dystonia [33]. One of the reasons beyond the advent of dopaminergic drugs and the presence of adverse events is the lack of clinical trials with anticholinergic drugs in recent years. The majority of studies in this class of drug were performed several decades ago, and most were conducted before the use of current clinical diagnostic criteria such as the UK Parkinson's Disease Society Brain Bank criteria [34] for idiopathic PD, and also before the use of the Unified Parkinson's Disease Rating Scale (UPDRS).

In the last Cochrane review of anticholinergics for symptomatic management of PD, the authors evaluated the efficacy and tolerability of anticholinergic drugs in the motor treatment of PD compared with placebo [35]. In the review, they included randomized controlled trials comparing anticholinergic drugs versus placebo or no treatment in new-onset or advanced PD, either as monotherapy or as adjunctive therapy. Initially, there were 14 potentially qualifying studies published from 1954 to 1986, and five were excluded for technical or methodological issues. The remaining nine studies, with a total of 221 patients participating, were included. The duration of the studies was between 5 and 20 weeks. Different drugs were investigated (benzhexol, orphenadrine, benztropine, bornaprine, benapryzine and methixine), and one study used two different anticholinergics drugs. All the studies reported improvement from baseline in at least one outcome measure with the exception of one study. Five studies reported both tremor and other parkinsonian motor manifestations as outcome measures, while the rest of the studies used disability and other parkinsonian signs but no tremor. All studies demonstrated anticholinergics to be better than placebo for improving motor symptoms as adjunct therapy or monotherapy. Neuropsychiatric and cognitive adverse events were described in six studies. Side effects, in particular cognitive and neuropsychiatric, were the most common reason for withdrawal. There is insufficient available data to compare efficacy or tolerability among anticholinergics.

There have been a few studies using anticholinergic drugs for PD in recent years, with most focusing on the management of sialorrhea and bladder dysfunction in PD. A randomized, double-blind, placebo-controlled study with ipratropium bromide in 17 patients with PD and troublesome drooling showed a mild improvement on a subjective measure of sialorrhea, without significant adverse events, although it did not affect objective measures of saliva production [36]. Most recently two randomized, double-blind, placebo-controlled crossover studies, one with glycopyrrolate for sialorrhea in 23 patients with PD, showed that 1 mg three times daily of glycopyrrolate, an anticholinergic drug with poor permeability across the blood–brain barrier, is safe and effective for sialorrhea in PD [37]. Another pilot study comprised 19 patients taking a single dose of oral, slow-dissolving thin films containing tropicamide. The results showed that 1 mg tropicamide resulted in a significant saliva reduction when compared with placebo, and without adverse events [38]. A 12-week dose-titration trial of controlled-release oxybutynin for neurogenic bladder concluded that controlled-release oxybutynin was safe and effective for this condition [39].

The first report of anticholinergics improving tremors was in 1949 [40], and this was followed by other studies confirming the benefits of anticholinergics [41, 42]. In our experience, we have seen improved tremor in similar PD patients with good tolerability, especially in young PD patients (under 60 years old). In those patients with medication-refractory tremors, we believe it is a good option to try anticholinergics before considering surgical interventions, although there is no evidence to argue in favor of a preferential effect of anticholinergics on tremor rather than other motor symptoms [35].

Another use of anticholinergic drugs in PD is to treat dystonia. Dystonia in PD, which occurs in different stages of the disease, is common in the early stage of young-onset PD and is most often seen as either a "wearing off" or a dyskinetic phenomenon, especially at peak dose, but also as biphasic dyskinesia in advanced PD [43]. End-of-dose dystonia is present most often as an early-morning and generally painful foot dystonia but can involve any part of the body. Dystonias as a dyskinetic phenomenon are most common as a facial dystonia. Anticholinergics are useful in the treatment of dystonia, especially DYT1 dystonia [44]. For PD dystonia, there have been no randomized trials with anticholinergics. There is a report of benefit from anticholinergics in wearing off of foot dystonia [45].

The benefits of anticholinergics to treat axial symptoms in PD were reported in a few trials [42, 46, 47]. A recent study showed that the anticholinergic agent

trihexyphenidyl improved axial symptoms after deep-brain stimulation of the subthalamic nucleus [48]. Only a few reports have been published comparing dopaminergic therapy and anticholinergics directly with objective measures. In a small study, Koller [49] compared trihexiphenidyl and carbidopa/levodopa taken for 2 weeks and found improvement of tremors. Another study by Parkes *et al.* [50] demonstrated improvement of resting tremor, rigidity and bradykinesia with levodopa when compared with benzhexol. There was a more robust improvement of rigidity and tremors using levodopa after 6 months but only mildly after using benzhexol. Akinesia responded better to levodopa, with only a negligible improvement with benzhexol. In another single-dose study, Schrag *et al.* [51] compared biperiden intravenously and apomorphine on two consecutive days and found that both drugs were effective in reducing tremor in PD, although without evidence for selective anticholinergic responsiveness of parkinsonian tremor.

It is still unclear if there is a synergistic effect between levodopa and anticholinergics. One study found that combining anticholinergic drugs with levodopa could affect the profile of the levodopa concentration in plasma. Levodopa absorption was reduced because there was a delay in gastric emptying of levodopa, but the fluctuation in the plasma concentration was less after anticholinergics, which could be beneficial in fluctuating patients [52]. This synergistic effect has been reported by others authors [47, 50]. However, other reports found that the chronic use of anticholinergic agents may have a negative impact in levodopa absorption [53]. The same authors commented that patients stabilized on levodopa often present a severe deterioration after withdrawal of anticholinergics. In these patients, addition of benzhexol will produce improvement [54].

Adverse effects and contraindications of anticholinergic drugs

As we know, anticholinergics act by blocking the muscarinic receptor, in both the central and peripheral nervous systems; hence, they may be responsible for peripheral or nonneurological and central or neurological side effects (Table 2.3). Current evidence has shown that anticholinergics, when compared with other antiparkinsonian drugs, are associated with a higher risk of adverse effects, especially in the elderly, who seem to be more susceptible. Many factors may contribute to this, including increased permeability of the blood–brain barrier, pharmacodynamic changes related to aging, the fact that the aging brain is particularly sensitive to these medications, and the risk of polypharmacy and drug–drug interactions [55]. Although the use of anticholinergics in PD is low, there are many other drugs with anticholinergic properties (e.g. antidepressants, amantadine) [32] that PD patients receive that may cause anticholinergic side effects, mainly neurological side effects. These side effects may be uncomfortable for younger patients, but the effects in older patients could be devastating. The central adverse effects could be a serious problem too. Cognitive impairment and dementia are common problems observed in patients with PD [56]. Cholinergic deficits play an important role in the cortical neurochemical alterations in cognitive impairment [57]. Central anticholinergic side effects may be subtle but bothersome, such as sedation, the inability to concentrate and confusion, or more severe, such as agitation, hallucinations and cognitive decline. Ehrt *et al.* [58] reported a significant association of anticholinergic properties and the incidence of cognitive decline in a large cohort of PD patients followed for 8 years, with a rate of cognitive decline 6.5 times higher

Table 2.3 Common side effects and contraindications of anticholinergics

Central adverse effects	Peripheral adverse effects	Contraindications	Precautions
Sedation	Dry mouth	Bladder neck obstruction	Cardiovascular disease
Inability to concentrate	Sore throat	Myasthenia gravis	Gastrointestinal obstructions
Confusion	Anhidrosis	Uncontrolled arrhythmias	Glaucoma
Agitation	Tachycardia	Uncontrolled narrow-angle glaucoma	In the elderly
Cognitive decline	Urinary retention		Cognitive decline
Delirium	Constipation		Prostatic hyperplasia
Hallucinations	Increased intraocular pressure		
	Weakness		
	Blurred vision		

in the group using drugs with anticholinergic properties compared with those who were never exposed to them. The cognitive issues induced by anticholinergics are more related to executive function [59] and short-term memory [60].

Neurological signs of anticholinergic toxicity include ataxia, blurred vision, diplopia and in severe cases delirium, hallucinations, seizure coma and rarely death. This neurotoxicity is termed acute anticholinergic syndrome. This syndrome is usually reversible once all of the toxin has been excreted and usually no specific treatment is necessary, but in some severe cases use of physostigmine is necessary.

The peripheral adverse events of anticholinergics are due to parasympatholytic effects. These include dry mouth, which is very common but usually tolerated as many PD patients also have sialorrhea, and a sore throat due to decreased mucous production and cessation of perspiration (anhidrosis) leading to increased body temperature, which may be severe. One therapeutic option is to increase hydration and avoid hot weather and extreme exercise. Tachycardia is another possible side effect, and therefore it is good practice to have a cardiovascular evaluation and electrocardiogram before the onset of treatment. Urinary retention can happen, so elderly patients should be cautious, especially those with prostatic issues. Constipation is a common problem, and because it is almost always present in PD, it could be a problem for this population leading to discontinuity in the treatment with anticholinergics. Another potential severe side effect of anticholinergics is elevated intraocular pressure, which patients with narrow-angle glaucoma, or symptoms of, must avoid. In large doses or in susceptible patients, anticholinergics may cause weakness. Patients taking anticholinergics can also have blurring of vision due to accommodation problems and mydriasis.

Contraindications to the use of these drugs include patients with urinary retention due to bladder neck obstruction, patients with a diagnosis of myasthenia gravis, uncontrolled cardiac arrhythmias and narrow-angle glaucoma.

Future use of anticholinergic drugs

There are a few ongoing trials using anticholinergic agents in PD that are focused on the treatment of urinary issues and sialorrhea. However, there is increased interest in the cholinergic system, especially in the PPN for the axial symptoms in PD and the potential therapeutic use. Other interesting areas of research are the nicotinic receptors and their role in PD. Epidemiological and animal models in PD studies have shown substantial evidence that nicotine has a protective effect and an inverse relationship on the development of PD; despite this, clinical trial results have been negative. This is especially evident considering the modulation of dopamine release due to the α6 nicotinic acetylcholine receptor [61]. In another study with six PD patients who underwent ^{123}I-FP-CIT imaging prior to and at multiple intervals after nicotine therapy, imaging showed no significant decrease in binding potentials in the striatum over 1 year. This was slower than expected in parkinsonian patients and was inversely correlated with UPDRS-III, possibly representing a deceleration of neuronal loss [62].

Conclusions

There is evidence that anticholinergics can still play a role in improving motor function in PD, as monotherapy or as an adjunct to other antiparkinsonian drugs, but their use is limited by neuropsychiatric and cognitive adverse effects. In our experience, they are still an option to treat PD patients, mainly younger patients and those with severe tremor. The elderly population should be careful when using them, due to the presence and possibility of various adverse events. Future research may provide further insight about the better-tolerated drugs and optimal dosing.

References

1. Standaert DG, Roberson ED. Treatment of central nervous system degenerative disorders. In: Hardman JG, Molinoff PB, Ruddon RW and Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw-Hill, 1995; 503–19.
2. Schwab RS, Tillmann WR. Artane in the treatment of Parkinson's disease; a report of its effectiveness alone and in combination with benadryl and parpanit. *N Engl J Med*, 1949; **241**: 483–5.
3. Ordenstein L, *Sur la Paralysie Agitante et la Sclérose en Plaques Generalisée*., 1867; Paris: Martinet (two leaves of color plates).
4. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. *Cold Spring Harb Perspect Med* 2011; **1**: a008862.
5. Aosaki T. Miura M, Suzuki T, Nishimura K, Masuda M. Acetylcholine-dopamine balance hypothesis in the striatum: an update. *Geriatr Gerontol Int* 2010; **10** (Suppl. 1): S148–57.
6. Duvoisin, RC. Cholinergic-anticholinergic antagonism in parkinsonism. *Arch Neurol* 1967; **17**: 124–36.