Extrapyramidal features in Alzheimer’s disease

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Introduction

In many cases of Alzheimer’s disease (AD), extrapyramidal signs (EPS) occur at some point in the illness [1–29]. Pearce first reported EPS in pre-senile dementia in 1974 [1]. Epidemiological reports suggested that EPS in AD herald a more ominous clinical course, with a more rapid rate of cognitive [2, 7] and functional decline [3, 6], a greater risk of institutionalization [3, 8, 9] and shorter survival [3, 8, 10, 11]. We do not know whether these signs describe a distinct subset of AD patients or act as a marker of advanced disease; nor do we know if EPS are risk factors for adverse outcomes.

Earlier clinicopathological studies need to be re-examined in light of the recent clinical and pathological guidelines for the diagnosis of dementia with Lewy bodies (DLB) [30]. In order to interpret the significance of EPS in AD patients, the data need to be critically synthesized. The objectives of this review are to summarize and clarify what is known about the epidemiology, clinical relevance and pathological correlates of EPS in AD.

I therefore conducted a systematic search of MEDLINE from January 1966 until December 1997 of all studies relating to parkinsonian signs, parkinsonism or extrapyramidal features in AD. Research reports from English language peer-reviewed journals were considered for abstraction. References from these articles were also reviewed for relevant studies. I examined multiple reports from a single cohort only once and conducted a qualitative synthesis of the data from independent studies.

Clinical features

EPS refers to the following clinical features: (i) bradykinesia of extremities or face, (ii) rigidity of limbs, (iii) resting tremor and (iv) gait disturbance involving shuffling, reduced arm swing and prolonged turning. Most studies report the presence or absence of these signs. Other studies use the term ‘parkinsonism’, which is most often defined as the presence of two or more extrapyramidal features. Given that gait disturbances are common in ‘normal’ ageing, this feature is sometimes excluded from the definition [31].

Table 1 presents causes of dementia which may be associated with EPS. The examination for extrapyramidal features may be difficult in a patient with dementia due to concurrent illness, medications and impaired cognition. Nonetheless, several clinical points should be emphasized.

A resting tremor is rare in AD [6, 8, 9, 12–16]. Resting tremor is specifically associated with a pathological diagnosis of idiopathic Parkinson’s disease (IPD) [32]. It also occurs in drug-induced parkinsonism. Therefore an alternative or coincident diagnosis of IPD should be considered if a resting tremor is present.

Rigidity and bradykinesia are the signs most commonly seen in AD [6, 8, 9, 11, 13–18]. The rigidity usually found in AD is bilateral, whereas in IPD it is more likely to be unilateral [17]. The lead-pipe rigidity typical of parkinsonism should be distinguished from paratonia or gegenhalten which may be found in dementia. Paratonia is the variable resistance to passive movement that occurs when the demented patient is unable to relax.

Gait disturbance is the next most common extrapyramidal feature in AD (for those studies that include it in their definition of extrapyramidalism) [8, 17]. Although parkinsonian gait disturbances are common in older people [31], those with both a shuffling gait and impaired turning are seven times more likely to have AD than control subjects without these findings [13].
In AD, EPS usually appear after cognitive impairment has presented. If extrapyramidal features occur before the onset of dementia, then IPD should be considered. However, subtle extrapyramidal features in otherwise healthy individuals may predict the future development of AD [19, 33].

Epidemiology

The prevalence of EPS in patients clinically diagnosed with AD ranges from 12 to 92% [1–5, 8–12, 17, 20–25, 27–29]. Table 2 presents the study characteristics that relate to the wide range of reported prevalences. Cohorts that are described in multiple reports are only represented once in Table 2. Six studies did not explicitly mention the exclusion of patients on neuroleptic medication from the study or the analysis [1, 4, 20–23]. In most studies, the diagnosis of AD was based on established clinical criteria; however only 40% (eight) of the 20 studies used standardized tools for assessing EPS.

The range of prevalences can be further explained by inconsistent definitions of 'extrapyramidalism' or 'parkinsonism'. Some studies assessed only rigidity [2, 22, 24]. Others considered extrapyramidalism to be present if any one of a number of signs were found (e.g. rigidity, bradykinesia, tremor, stooped posture, gait abnormalities or poverty of facial movement). Some investigations based the 'extrapyramidalism' on a specific cut-off point on a parkinsonian assessment scale [21, 25].

Another reason for the discrepancy in reported prevalences is the difference in severity of AD in the subjects studied. While extrapyramidalism can be present at any stage in the course of AD [26], it is more likely in the later stages [7, 8, 17, 21, 25–27]. Thus, the investigation that included the most mild cases of AD reported the lowest prevalence of EPS [3], while the study with the most severe cases found the highest prevalence [17]. Longitudinal studies better illustrate the relationship of EPS to the stage of disease than do cross-sectional studies, as well as providing a measure of the incidence of EPS in AD [7–9, 26]. In a 3-year cohort study of 52 patients with mild–moderate AD, 39% of subjects had EPS at baseline compared with 72% at the end of the follow-up period [8]. Other prospective studies have confirmed that the likelihood of having EPS increases with advancing AD [7, 9, 26]. The incidence rate of EPS emerging during the course of AD has been estimated to be 101 per 1000 person-years [26]. Morris et al. found that 56% of AD patients without EPS at baseline developed these features over 5.5 years [7].

EPS may be found on the neurological examination of otherwise healthy people over 65 [7, 34]. Thus, the finding that EPS is common in AD may merely reflect the extrapyramidalism that can accompany ‘normal ageing’. However, several controlled trials demonstrate that EPS is more likely to be present in patients with AD than in ‘healthy’ older people [7, 13, 15, 23, 27, 28]. In a 66-month follow-up study of subjects free of EPS at baseline, extrapyramidalism developed in 36% of subjects with AD but only 5% of controls [7]. This finding is further supported by a large, population-based investigation in which elderly subjects with EPS were more likely to have a clinical diagnosis of AD compared with those without EPS [13]. Healthy elderly subjects with subtle extrapyramidal features have a greater likelihood of developing probable AD when followed-up than subjects without these features [19, 33]. Finally, patients with AD are more likely than control subjects to have subclinical extrapyramidalism detected by electrophysiological measures [15].

The effect of EPS on clinical outcomes in AD

Many investigations have found that the presence of EPS in AD is an adverse prognostic factor. These poorer outcomes include decreased survival [5, 8, 10, 11], a more rapid rate of cognitive decline [2–7], accelerated functional loss [3, 6], higher rates of depression [28] and a greater likelihood of institutionalization [5, 8, 9].

Despite these observations, the link between EPS and clinical endpoints in AD remains unclear. Not all studies have consistently found EPS to be an important
Table 2. Characteristics of studies reporting the prevalence of extrapyramidal signs (EPS) in Alzheimer's disease (AD)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Study design</th>
<th>Standardized assessment for EPS</th>
<th>AD diagnosis</th>
<th>AD stage</th>
<th>Subjects on neuroleptics</th>
<th>Extrapyramidalism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern [3]</td>
<td>236</td>
<td>73.1</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild</td>
<td>Excluded F, rT, B, P, V or G</td>
<td>12</td>
</tr>
<tr>
<td>Chui [2]</td>
<td>135</td>
<td>72.9</td>
<td>Prospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Mild–moderate</td>
<td>Excluded R</td>
<td>12</td>
</tr>
<tr>
<td>Burns [29]</td>
<td>178</td>
<td>80.4</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Mild–severe</td>
<td>Excluded T or R</td>
<td>12</td>
</tr>
<tr>
<td>Snowden [11]</td>
<td>136</td>
<td>78</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Excluded R with two of B, rT, G, P or F</td>
<td>15</td>
</tr>
<tr>
<td>Drachman [20]</td>
<td>42</td>
<td>66.4</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Mild–moderate</td>
<td>Not stated &gt; 2 of T, R, B, G or glabellar sign</td>
<td>26</td>
</tr>
<tr>
<td>Miller [5]</td>
<td>81</td>
<td>63.9</td>
<td>Prospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Excluded T, R or B</td>
<td>30</td>
</tr>
<tr>
<td>Girling [25]</td>
<td>75</td>
<td>82.2</td>
<td>Cross-sectional</td>
<td>Yes</td>
<td>No</td>
<td>Moderate–severe</td>
<td>Excluded &gt; 5 points on Webster scale</td>
<td>30</td>
</tr>
<tr>
<td>Lopez [9]</td>
<td>164</td>
<td>70.9</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild–moderate</td>
<td>Excluded R, B, T, G, P or D</td>
<td>31</td>
</tr>
<tr>
<td>Stern [4]</td>
<td>65</td>
<td>Not stated</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>Excluded T, R, B, G, P or F</td>
<td>37</td>
</tr>
<tr>
<td>Chui [12]</td>
<td>146</td>
<td>73</td>
<td>Cross-sectional</td>
<td>No</td>
<td>Yes</td>
<td>Moderate–severe</td>
<td>Excluded B, G or R</td>
<td>54</td>
</tr>
<tr>
<td>Bakhchine [21]</td>
<td>91</td>
<td>82</td>
<td>Cross-sectional</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate–severe</td>
<td>Included CUPRS(^{3}) &gt; 12</td>
<td>44</td>
</tr>
<tr>
<td>Samson [10]</td>
<td>198</td>
<td>61</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Not stated</td>
<td>Excluded T or R</td>
<td>44</td>
</tr>
<tr>
<td>Tyrell [24]</td>
<td>20</td>
<td>59.1</td>
<td>Cross-sectional</td>
<td>No</td>
<td>Yes</td>
<td>Moderate–severe</td>
<td>Excluded R</td>
<td>65</td>
</tr>
<tr>
<td>Leverenz [22]</td>
<td>40</td>
<td>75.7</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>Yes</td>
<td>Not stated</td>
<td>Included R</td>
<td>32</td>
</tr>
<tr>
<td>Merello [28]</td>
<td>78</td>
<td>72.4</td>
<td>Cross-sectional</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>Excluded B, R, rT, P, G or F</td>
<td>79</td>
</tr>
<tr>
<td>Molsa [17]</td>
<td>143</td>
<td>74.9</td>
<td>Cross-sectional</td>
<td>Yes</td>
<td>No</td>
<td>Moderate–severe</td>
<td>Excluded R, B, rT, P, F or D</td>
<td>92</td>
</tr>
<tr>
<td>Huff [23]</td>
<td>95</td>
<td>67.5</td>
<td>Cross-sectional</td>
<td>No</td>
<td>Yes</td>
<td>Mild–moderate</td>
<td>Not stated R, T(^{2})</td>
<td>84 (R), 9.6 (T)</td>
</tr>
<tr>
<td>Soininen [8]</td>
<td>32</td>
<td>68</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild–moderate</td>
<td>Excluded B, R, T, G, P(^{2})</td>
<td>39 (B), 11 (R), 11 (T), 52 (G)</td>
</tr>
<tr>
<td>Galasko [27]</td>
<td>135</td>
<td>72.3</td>
<td>Cross-sectional</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>Excluded T, R, B(^{2})</td>
<td>16 (T), 14 (R), 5 (B)</td>
</tr>
</tbody>
</table>

T, tremor (unspecified); rT, resting tremor; B, bradykinesia; R, rigidity; G, gait abnormality; P, stooped posture; F, facial hypominima; D, dyskinesias; V, voice changes.

\(^{3}\)Unified Parkinson's disease rating scale, Colombia University Parkinson's disease rating scale or Webster scale.

\(^{2}\)NINCDS/ADRDA or DMS III or autopsy.

\(^{1}\)Only prevalences of individual signs provided.
prognostic indicator in AD for specific outcomes (Table 3). This is probably due to inconsistent methodologies, as most studies differ in the length of the follow-up periods, methods for assessing extra-pyramidalism and definitions of endpoints.

There is controversy as to whether extrapyramidalism is truly a predictor of poor outcomes or merely a marker of disease severity [3, 9, 20, 26]. In one of the largest and more rigorously conducted studies, Stern and co-workers followed a relatively homogeneous cohort with only mild AD at baseline [3]. They also statistically controlled for any subtle differences in baseline cognitive and functional status between subjects with and without EPS. Despite these efforts, extrapyramidalism remained associated with a more rapid decline to all endpoints, supporting the notion that EPS are prognostic factors for poor outcomes in AD. Most studies that consider baseline disease severity agree with these findings [2, 4, 5, 10], although some do not [9, 20]. For example, Lopez et al. found extrapyramidalism to be associated with a greater risk of institutionalization but not with other outcomes [9].

The point at which EPS emerge in the course of AD (if at all), seems to herald an onset of a rapid decline in functional status [35]. Thus, some investigators believe that the appearance of extrapyramidalism represents a developmental stage in the course of AD that would become apparent in all patients if they lived long enough [26, 35]. Within this theory, clinical heterogeneity is expressed by the probability that these signs will manifest at varying points of the disease in different patients. This is in contrast to a competing viewpoint which suggests that AD patients with EPS represent a distinct clinical subgroup or variant of AD that portends a worse prognosis [6, 12].

These investigations are limited by a lack of control groups without AD. It is possible that extrapyramidalism is associated with poor outcomes regardless of whether a person has AD: a large, community-based investigation found extrapyramidalism to be an independent predictor of mortality in a general population of older people [34].

**Neuropathological and neurochemical correlations**

Histological and imaging studies reveal that the pathological findings in AD patients with EPS are heterogeneous [7, 11, 14, 22, 36, 37]. Definitive conclusions from these studies are limited due to retrospective study designs, inconsistent definitions of clinical ‘parkinsonism’, small numbers and failure to exclude subjects taking neuroleptic medication [22, 36]. Nonetheless, nigral degeneration with Lewy body formation, (suggestive of a coexistent diagnosis of PD) has been reported in 20–85% of autopsy-confirmed cases of AD patients with extrapyramidalism [11, 14, 22, 36, 37].

In some cases, extrapyramidalism may occur in AD in the absence of any structural nigral abnormalities [7, 11, 14, 22, 38, 39]. Leverenz et al. retrospectively reviewed the autopsies of 40 AD patients [22]. Of the 13 patients who had a history of rigidity, two had no abnormalities in the substantia nigra. Amongst the 11 with nigral changes, eight had nigral Lewy bodies, one had neurofibrillary tangles and two had cell loss alone.

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**Table 3. The association of extrapyramidalism with clinical outcomes in Alzheimer’s disease (AD)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted for baseline severity of AD</th>
<th>Decreased survival</th>
<th>Cognitive decline</th>
<th>Functional decline</th>
<th>Institutionalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soininen [8]*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Chui [2]</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lopez [9]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stern [3]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stern [4]*</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Drachman [20]</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Samson [10]</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miller [5]</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mayeux [6]</td>
<td>No</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Morris [7]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Snowden [11]</td>
<td>No</td>
<td>Trend, $P = 0.09$</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Patients with drug-induced extrapyramidalism were not excluded from outcome analyses.
In one of the only prospective studies examining this issue, 10 AD patients with extrapyramidal features were followed to autopsy where the diagnosis of AD was confirmed [7]. Of these, five had nigral abnormalities consistent with a coexistent diagnosis of IPD, three had non-specific nigral degeneration and two had no nigral lesions.

The neuropathological mechanism for EPS in AD is not well understood when nigral Lewy bodies with neuronal degeneration are absent [7, 11, 14, 22, 38, 39]. Several explanations have been suggested. First, when nigral degeneration is absent, nigral dysfunction may be present. This is supported by a case series of 28 patients with autopsy-confirmed AD, 18 of whom had EPS clinically [38]. In this study, subjects with nigral Lewy bodies were excluded from the analysis. Those with EPS had more neurofibrillary tangles in nigral neurones than those without extrapyramidalism. Nigral degeneration was not an important finding in this study.

Secondly, extranigral dopaminergic loss (e.g. mesocortical pathways) may be responsible for the extra-pyramidal features in AD for a few cases [7, 24]. Finally, increased deposition of extracellular amyloid in the striatum may explain EPS in AD in the absence of nigral pathology [40, 41].

An interesting difference in the pathological findings of AD with EPS and those of IPD, relates to the unique distribution of striatal abnormalities in these two disease states [37, 39]. In IPD the loss of dopamine and dopamine transporter sites occurs to a much greater degree in caudal striatum than in the rostral striatum [39, 42]. However, in AD with EPS, the most severe losses of dopamine transporter sites occur in the rostral striatum [39]. Murray et al. have hypothesized that a resting tremor (a predominant feature of IPD but not AD) results from loss of dopamine in the caudal putamen [39]. Therefore, the predominance of rigidity and bradykinesia, but not tremor, in AD with EPS may reflect the differential gradient of striatal dopaminergic loss compared with IPD.

Neurochemical studies have added little to our understanding of the mechanism of EPS in probable AD. In a comparison of cerebrospinal fluid concentrations of homovanillic acid (a dopamine metabolite) in AD patients with and without EPS [43], those with EPS were found to have lower concentrations, suggesting dopamine deficiency in this group. However, other investigators have reported no correlation between in the cerebrospinal fluid homovanillic acid levels in AD patients and EPS [8, 44].

**Relationship to DLB**

Recent attention has focused on dementia syndromes that are associated with Lewy bodies. DLB accounts for 14–20% of demented patients [45, 46]. Recently, consensus guidelines for the clinical and pathological diagnosis of DLB have been published [30].

Until the generic term ‘DLB’ was recommended, the nosology used to describe the Lewy body syndromes was confusing. The terms used included ‘diffuse Lewy body disease’ [47], ‘the Lewy body variant of AD’ [45] and ‘senile dementia of the Lewy body type’ [48]. This lack of consensus on terminology reflects the clinical and pathological spectra associated with the various Lewy body disorders. Lewy bodies are the pathological hallmark of IPD, where they are mainly confined to subcortical structures (e.g. substantia nigra, locus coeruleus, dorsal vagal nucleus and nucleus basalis of Meynert). The term ‘diffuse Lewy body disease’ has been used to describe a state whereby Lewy bodies are widely distributed throughout the cerebral cortex and subcortical structures, with little or no accompanying AD pathology. When Lewy bodies are found in the cortical and subcortical structures coexistent with the pathological findings sufficient to meet a diagnosis of AD, then term ‘the Lewy body variant of AD’ has been used. Whether that situation represents two separate disease processes or a variant of AD is uncertain.

Clinically, there are similarities, but also important differences to distinguish AD with EPS from DLB. There is a male predominance in DLB compared with AD [49–51]. In both processes, the extrapyramidalism is typically the symmetrical rigid-kinetic variety [52–54] and a resting tremor is uncommon. However in AD, the EPS tend to occur later in the dementing process than in DLB, where these signs may be among the presenting features [51, 54]. This is particularly true of the parkinsonian gait abnormalities, which generally occur late in the course of AD but early on in DLB [54].

While both AD and DLB are progressive dementias, the pattern of cognitive deficits may differ. The deficits of AD (amnesia, apraxia and agnosia) are often present in DLB. However, DLB is more likely to also involve impaired visuo-spatial skills, executive functioning, attention and verbal fluency [45, 55, 56].

 Neuropsychiatric disturbances presenting early in the course of the dementia are the most prominent characteristics that help distinguish AD from DLB. Visual hallucinations are more likely to be present in DLB than in AD [30, 46, 48–51]. Fluctuating mental status with impaired attention is also a diagnostic feature of DLB [50, 48–50, 52, 53]. In the absence of a delirium, demented patients with repeated fluctuations in mental status may have DLB.

What proportion of cases with a clinical diagnosis of probable AD with extrapyramidalism actually have DLB? Many epidemiological studies of AD with EPS were carried out before the characterization of DLB. Therefore, it is possible that many subjects diagnosed as AD with extrapyramidalism actually had DLB. This is important when considering reports of AD patients...
that linked extrapyramidalism with psychotic features [2–4, 6, 19].

From an anatomical perspective, early studies that attempted to define the pathological basis of EPS in AD patients did not specifically look for cortical Lewy bodies [22, 57]. Those that did examine the cortex probably underestimated the number of cortical Lewy bodies due to inadequate staining techniques [7, 14, 27]. Ubiquitin immunoreactive staining is needed to enhance the detection of cortical Lewy bodies, particularly in the presence of AD pathology [57]. This technique was not in widespread use until the late 1980s, when studies of AD patients with EPS started to report higher number of cortical Lewy bodies [36].

Considering all neuropathological data available to date, it is likely that most cases of AD patients with extrapyramidalism have Lewy bodies, either in the subcortical structures alone (e.g. IPD) or in the cortex as well (DLB) [11, 14, 22, 36, 37, 45]. Hansen et al., demonstrated this indirectly by retrospectively reviewing the clinical features of patients with pure AD on autopsy (e.g. no Lewy bodies) separately from those with the Lewy body variant of AD [45]. They found that very few of the ‘pure’ AD patients had EPS clinically. However, in a few cases, extrapyramidalism can occur in AD patients without any Lewy bodies on pathological examination [7, 11, 14, 22, 38, 59].

**Therapeutic considerations**

**L-dopa replacement**

Whether or not the extrapyramidalism that accompanies AD will respond to L-dopa replacement depends on the underlying pathology. L-dopa responsiveness reflects that sufficient damage has occurred in the substantia nigra to cause a critical deficiency of striatal dopamine [58]. Given that many patients with AD and EPS have neuropathological abnormalities in the substantia nigra, some of these will improve with L-dopa. In support of this, Rajput found three out of five AD patients with coexistent pathological findings of IPD responded clinically to L-dopa [58]. Similarly, Byrne et al., found that most patients with DLB had documented improvement in EPS with L-dopa [55]. The interpretation of these investigations is limited due to retrospective design and lack of controls.

Clinical pharmacological studies are less supportive of the benefit of L-dopa replacement to treat EPS in AD [28, 44]. In a randomized, double-blind, placebo-controlled trial, Duret et al., treated 14 patients with clinical AD associated with rigidity with L-dopa [44]. The rigidity remained unchanged in all patients regardless of treatment. Despite the lack of response, there was a rise in L-dopa metabolites (homovanillic acid) in the cerebrospinal fluid of subjects while taking L-dopa. Thus, if a deficiency of striatal dopamine had caused EPS, these patients should have improved. Merello et al., conducted apomorphine tests on 11 patients with AD and EPS, none of whom responded [28]. An apomorphine challenge tends to predict responsiveness to L-dopa and may be a marker for presynaptic nigrostriatal dysfunction [59]. It is usually positive in patients with IPD.

A judicious limited trial of L-dopa may be reasonable in patients with probable AD in whom the extrapyramidal features are causing functional impairment. Patients may be more likely to respond if the extrapyramidalism is suggestive of coexistent IPD (e.g. resting tremor, unilateral). In suspected cases of DLB one must be cautious as L-dopa may precipitate or worsen the neuropsychiatric symptoms.

**Use of neuroleptic medication**

Behavioural complications often accompany the later stages of AD when EPS are more common. Caution is needed in treating the psychotic features with neuroleptic medication. There is little evidence that these medications are effective in controlling behavioural complications in AD [60]. Most neuroleptics may exacerbate extrapyramidalism. Some patients with DLB are at risk for neuroleptic sensitivity syndrome [61]; this involves an acute reaction to a neuroleptic drug, with increased confusion, immobility, decreased food intake and sometimes death. Therefore neuroleptic drugs for behavioural complications in a demented patient with EPS are best avoided. If drugs are necessary, than an atypical neuroleptic, such as clozapine (which has fewer EPS side effects), should be tried [62, 63].

**Anticholinesterase inhibitors**

Trials of anticholinesterase inhibitors have shown mild to modest cognitive improvement in selected patients with AD [64, 65]. The rationale for these drugs is based on the theory that the cognitive impairment in AD is due to declining cortical cholinergic activity.

Patients with DLB may be particularly responsive to cholinergic therapy [66, 67]. The prominence of hallucinations and fluctuations of mental status in DLB are similar to delirium and anticholinergic toxicity, suggestive of relative cholinergic deficiency. This possibility is reinforced by the finding that cortical choline acetyltransferase is much lower in AD patients with cortical and subcortical DLB than in those with AD pathology alone [66, 67]. Thus, patients with AD and EPS who are clinically suspected to have the Lewy body variant, may derive benefit from this new class of drugs. One theoretical concern is that cholinergic agents could worsen extrapyramidal motor dysfunction. Clinical trials to test directly the
use of anticholinesterase inhibitors in probable DBL have not yet been reported.

**Conclusion**

Methodological differences between epidemiological studies preclude a precise estimation of the prevalence of EPS in clinically diagnosed AD. Criteria to define EPS of AD need to be standardized so that data from different investigations can be synthesized. However, controlled studies show that EPS are more likely in AD patients than in the general population of older people. Furthermore, EPS are more likely in the later stages of AD.

The neuropathological findings in patients with probable AD and extrapyramidalism are heterogeneous. However, most cases are associated with subcortical Lewy bodies (with or without concomitant cortical involvement). The mechanism of EPS in the absence of Lewy bodies remains unclear. The new diagnostic categorization of DBL necessitates reinterpretation of earlier epidemiological and pathological studies of presumed AD with EPS. An awareness that some of these patients may have DBL has important therapeutic implications, specifically the avoidance of neuroleptic medications and a possible increased responsiveness to cholinergic therapy.

Most evidence supports the notion that EPS in AD implies a worse prognosis: the point at which the extrapyramidalism emerges heralds an onset of functional decline. Extrapyramidalism is associated with a higher mortality probably relating to falls and impaired mobility [34]. Thus, regardless of the underlying aetiology, extrapyramidalism may place an additional burden on an already frail patient.

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**Key points**

- Extrapyramidal signs are common in patients with Alzheimer’s disease and are more likely to be present in the later stages of the illness.
- Extrapyramidal signs herald a more ominous clinical course in patients with Alzheimer’s disease.
- Most Alzheimer patients with extrapyramidal signs have Lewy bodies in the subcortical structures, with or without cortical involvement.
- There are important prognostic, diagnostic and therapeutic considerations for Alzheimer patients who have extrapyramidal signs.

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**References**

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