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Advances in the treatment of visual hallucinations in neurodegenerative diseases

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Abstract

Treatment of visual hallucinations in neurodegenerative disorders is not well advanced. The complexity of underlying mechanisms presents a number of potential avenues for developing treatments, but also suggests that any single one may be of limited efficacy. Reducing medication, with the careful introduction of antidementia medication if needed, is the mainstay of current management. Antipsychotic medication leads to excessive morbidity and mortality and should only be used in cases of high distress that do not otherwise respond. Education, reduction of risk factors and psychological treatments have limited evidence of efficacy, but are unlikely to cause harm.

Keywords

Alzheimer’s disease; amyloidopathy; Lewy body; Parkinson’s disease; synucleinopathy; tauopathy; treatment; visual hallucination

Neurodegenerative disorders & their relationship to visual hallucinations

Neurodegenerative disorders are a disparate group of illnesses that share the loss of CNS cells [1]. The clinical presentations reflect the different patterns and disturbances of the pathologies involved; ranging from focused loss within specific cerebral nuclei to well-distributed dysfunction involving virtually the entire cerebral cortex. Recent research has highlighted three frequent pathological processes, each associated with a signature disease,

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but which often co-exist within individual people, with the predominant pathology leading to a characteristic clinical picture [2].

Thus, disturbances in amyloid metabolism (the amyloidopathies) lead to the clinical and pathological picture of Alzheimer's disease, including its focal variants of progressive aphasia, progressive apraxia and posterior cortical atrophy [3]; abnormal tau metabolism (tauopathies) is linked to progressive supranuclear palsy, corticobasal degeneration and variants of frontotemporal dementia, for example, progressive nonfluent aphasia [4]; and synuclein dysfunction to a range of disorders including Parkinson's disease (PD) and associated Lewy body disorders (synucleinopathies) [5,6].

Of these three broad classes, hallucinations are particularly associated with the synucleinopathies.

Recognizing visual hallucinations in neurodegenerative disorders

Finding a formal definition of hallucinations that distinguishes them from veridical perceptions and other disturbances of perception has proved impossible [7]. Traditional definitions stressed perception in the absence of appropriate environmental stimuli, but these fell down with the recognition that most veridical perception is only loosely related to what is in the external world. For example, the phenomena of change blindness (in which a gorilla can dance across a basketball court unnoticed by most observers [101]) highlights the very partial nature of perception. Current models of visual perception suggest that what someone 'sees' is the output of a top–down, internal, sparse, dynamic and functional model, which acts to minimize the discrepancy between predicted and actual bottom–up input from the eyes [7]. Within these models, there can be no clear boundary between hallucinations, illusions and veridical perceptions, merely a continuum of relationships between subjective perceptions and sensory input, with hallucinations having a looser relationship than relatively accurate perception.

Despite these conceptual overlaps, it is easy enough to recognize most hallucinations in clinical practice; mainly by the disparity between patient report and the evidence of other people's senses. However, if forced to rely solely upon patient report, distinguishing true perceptions from hallucinatory ones can be challenging with what appears to be a hallucination turning out to be true and *vice versa*. Many patients are reluctant to spontaneously talk of their hallucinations because of their fear of the potential consequences [8]. Telling patients that hallucinations are common in a range of illnesses and are not to be feared before asking directly if they have such experiences very substantially increases disclosure [8]. Semistructured research interviews are available for identifying and classifying hallucinations [9]. While too time-consuming for routine clinical use, they can be a useful tool for the less-experienced clinician in guiding questions. Carers may be able to describe hallucinations that patients do not report, though the relatives of those with milder cognitive impairment tend to underestimate frequency [9]. If patients are too cognitively impaired to report their experiences, responses to invisible figures may suggest hallucinations.

Of those patients reporting visual hallucinations, a half will also have auditory and one-quarter will have tactile hallucinations, although these are almost always at different times [10]. Multisensory hallucinations in which something can be seen, heard and felt are exceptionally rare. Hallucinations commonly occur in conjunction with other visual perceptual and visuomotor disorders including senses of presence and passage, illusions and misjudgments, and motor freezing, with more severe cognitive impairment associated with greater rates of all of these phenomena [11].

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Clinical assessment

Knowledge of the classic forms of visual hallucinations in neurodegenerative disorders is helpful in recognizing them when they do occur [12].

The brief, simple hallucinations of unformed dots, flashes and blobs often seen in eye disease are rare; reported in less than 10% of patients. Complex formed hallucinations are more common, though reported rates vary significantly between different pathologies from an estimated 10% in the tauopathies, to approximately 20% in the amyloidopathies (slightly higher, ~25%, in posterior cortical atrophy with its focal dysfunction of the visual system [13,14]) to over 70% in some of the synucleinopathies [7].

Most, but not all, synucleinopathies have high levels of visual hallucinations (Table 1) [15,16]. For example, in PD, particularly PD that has developed into PD dementia, point prevalence is up to 50% with lifetime prevalence around 80%. Similarly, visual hallucinations were an early identified feature of dementia with Lewy bodies with a point prevalence of 70–80% and are associated with more severe, more rapidly progressive and more disabling disease leading to earlier institutionalization and death [6]. Though they differ in clinical history, given the clinical and pathological similarities between PD dementia and dementia with Lewy bodies, we will use the term Lewy body dementia (LBD) as an umbrella term to refer to both in this article [17,18].

Within similar patient populations, the most frequent other association with hallucinations is delirium, with this accounting for more cases of hallucinations than all other causes put together [19]. Dementia is one risk factor for delirium. Hence, if hallucinations develop over hours or days in a person with a neurodegenerative disprder, particularly in the context of physical ill health, delirium should be the first possibility to consider fluctuating alertness and behavioral and perceptual disturbance [20]. Distinguishing delirium from LBD can be particularly challenging at first presentation given that fluctuations and hallucinations are characteristic of the latter disorder. In these cases, careful assessment, treatment of any physical illness and follow-up over a number of weeks may be needed to exclude delirium. The other common associations with hallucinations in later life, such as sensory disorders and functional psychosis [19], are rarely confusable with neurodegenerative disorders in practice.

Regardless of the associated disorder, the phenomenology of hallucinations tends to be consistent with the most common being of figures of people or children, followed by animals and objects [19]. The hallucination occurs within an existing visual scene rather than replacing it. Thus, patients will see a figure in a real room, rather than a hallucinatory room and figure.

Onset and offset is usually abrupt with a duration of minutes rather than seconds or hours. Most people have several hallucinations per week, but frequency varies considerably. The hallucination may move in itself, a figure waving its arms, for example, but movement in space is rarer. It will tend to have a normal visual quality and look ‘real’, though miniature and distorted figures are also reported. Unusually large eyes and teeth may be present.

Only one-third of patients realize that they are hallucinating, with greater cognitive impairment associated with poorer insight [21]. Insight may fluctuate with a reasonable understanding when calm, which is subsequently lost when the hallucination actually occurs. In consequence, over 80% try to interact in some way with what they are seeing; often then becoming upset when there is no reaction from the hallucination [22]. Approximately 50% of patients are significantly distressed by their experiences, with fear and anger being the most common responses [22]. This does not seem to be because the content of the

hallucination is inherently threatening, since most are fairly bland [23]. Reactions are more influenced by the interpretation put upon the hallucination by the patient. Approximately 50% of patients develop delusionary explanations for their experiences [24]. Carer reactions can either exacerbate or soothe patient distress.

Hallucinations within an individual tend to have a consistent form and occur in specific places at specific times. There may be a specific visual trigger in the environment; for example, a particularly patterning curtain may evoke a hallucinatory face. Top–down, internally generated processes that modulate hallucinatory risk include the transition from sleeping to waking and *vice versa*. Other times of reduced alertness are common associations, as are sleep disorders, in particular, rapid eye movement sleep behavior disorder in the synucleinopathies [25]. Moderators of bottom–up sensory processes include impoverished visual environments and poor vision [26]. Anticholinergic medication and polypharmacy, both of which are common in the older groups at high risk of neurodegenerative disorders, potentiate hallucinations [27]. The role of dopaminergic medication is less clear cut. Though hallucinations are often associated with long-term and high-dose dopaminergic medication, this may be a reflection of longstanding disease rather than medication *per se*, since pharmacologic challenge does not induce hallucinations [28,29].

The clinical course of hallucinations within disorders is variable, but they are relatively rare in early-stage disease. Within Alzheimer's disease, relatively brief hallucinatory periods of a matter of weeks may occur at any stage, often in combination with other factors, for example, an infection [30]. In the Lewy body disorders, hallucinations are more persistent, lasting for months or years rather than weeks [31]. In both, hallucinations appear to become less common in the end stages of the illness, perhaps because they are harder to communicate and so less recognized by other people, or possibly because the visual system becomes so impaired that it can not support either hallucinatory or veridical perceptions [32].

The causes of hallucinations

A wide range of explanatory models for visual hallucinations have been proposed [19]. Early, single-factor theories (cortical release, cortical irritation, top–down activation) have been replaced by interactive models that suggest that distributed dysfunction within perceptual and attentional systems is necessary for hallucinations to occur. Imaging and the distribution of pathology in neurodegenerative hallucinators suggest that primary and secondary visual pathways, the ventral visual stream and its frontal projections together with brainstem and thalamic regulatory systems are key areas; possibly in conjunction with pathology in medial temporal structures [33,34]. Collerton and colleagues' general Perception and Attention Deficit model [19] and Lewy body-specific theories in Diederich and colleagues' Interactive model [35], as well as Shine and colleagues' Attentional Control model [36], are consistent with evidence that combinations of impaired attentional and perceptual processes are needed if hallucinations are to occur [37–44].

Treatment targets: what improvements are possible?

There is a lack of strong evidence on the effectiveness of interventions for visual hallucinations. Most reports are of single cases or small case series that do not specifically target visual hallucinations [45,46]. Potential benefits might include reducing the hallucinatory experience itself, either in frequency or duration, or if this is not fully possible as is often the case, reducing its impact upon the patient and the people around them. Owing to the limited effectiveness of treatments on the occurrence of hallucinations, and the

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potential costs of interventions, focusing efforts on the half of patients who are distressed by their experiences may be the most effective strategy.

Treatment options for visual hallucinations

Reducing risk factors—One set of strategies is based upon reducing factors that are thought to increase the frequency of visual hallucinations. Thus, improving lighting, reducing visual triggers – if they exist – and improving visual function with glasses or cataract operations are all worth trying; though mainly because they are useful in themselves or are of minimal cost, than because they have demonstrated efficacy [45]. If hallucinations are associated with specific times of day, targeting social contact at that time may be effective in reducing frequency or duration.

Consistent with the risk-reducing strategy, reducing existing medication is a sensible first step. A very wide range of medications have anticholinergic effects and can induce or exacerbate hallucinations; particularly when multiple medications are taken concurrently [27]. A careful consideration of the risks and benefits of each medication followed by systematic reduction or elimination of nonessential drugs and monitoring of the effects on hallucinations takes time and effort, but can be very effective. Titrating doses of dopaminergic medication to the minimum and testing the relative benefits of levodopa and direct dopaminergic agonists may reduce hallucination in the synucleinopathies but at the cost of increasing motor disability [47].

Pharmacological treatments

Recommending appropriate pharmacological treatments for the management of visual hallucinations is difficult given the diversity of neurodegenerative diseases in which these phenomena arise. Just about all evidence for pharmacological interventions comes from studies in PD, and LBDs (see Table 2) [48–58] though, even here, primary (or even secondary) outcomes in these trials do not specifically target visual hallucinations and any effect is often conflated with other psychiatric symptoms and behaviors. Thus, there is little evidence to suggest differential treatment responses in different pathologies.

The neuroleptics and atypical antipsychotics, which are the pharmacological mainstay of the management of hallucinations in younger people with psychosis, can, however, worsen the motor signs of synucleinopathies because of their anti-dopaminergic effects, precipitate a neuroleptic malignant syndrome (particularly in LBDs) and they are associated with increased mortality from stroke in dementia and parkinsonism [59]. For these reasons, they are best kept as reserve treatments to be used if hallucinations are particularly distressing and disturbing, and other treatments have been ineffective. If antipsychotics are required, quetiapine has been reported to reduce psychosis in PD, though it may have a narrow therapeutic window with excessive sedation at higher doses limiting its use. The best evidence appears to be for clozapine with two double-blind randomized control trials of clozapine suggesting that this agent might have a benefit on visual hallucinations in PD. However, clozapine has a significant side-effect profile and requires regular patient monitoring and for this reason is not regularly prescribed in frail older patients.

The cholinesterase inhibitors may stabilize cognition and neuropsychiatric symptoms in Alzheimer’s disease and LBD. There is some suggestion that treatment response is greater in patients with LBD who have hallucinations than in those who do not, but this may reflect changes in other factors associated with hallucinations, particularly impairments in alertness and attention, rather than a direct effect on hallucinations. Recently, there has been interest in the use of higher than normal doses of cholinesterase inhibitors in the treatment of cognitive symptoms in Alzheimer’s disease [60]; whether similar dose levels may be helpful

in the treatment of visual hallucinations in LBD is unknown, although one might expect significantly more side effects at higher dose levels, which could offset any treatment benefit. There are case reports that memantine may cause or exacerbate visual hallucinations, but since it is a well-tolerated drug it may be worth trialing in a hallucinating patient.

Medication may also be effective in reducing mood disturbance in patients with visual hallucinations with anxiolytics and antidepressants both having a potential, if limited, rolen [61,62].

For all prescribing, starting with low doses and slowly increasing until a therapeutic response or limiting side effects occur minimizes the risk of a poor outcome, but this approach does need effective monitoring systems, which are often not present.

Psychological management—All patients and carers can potentially benefit from information on hallucinations. Key messages to get across are that hallucinations are common, to be expected in neurodegenerative diseases, usually spontaneously reduce or disappear over time, can be controlled, and do not have to be distressing [22,27]. Helpful information can be found on disease related charities such as the Alzheimer's, Lewy body and Parkinson's Disease Societies [102–104].

Four factors seem to be associated with the distress which arises with hallucinations [63]:

- For those patients without insight, the sense that they make of the hallucination is important – for example, whether a figure is seen as a benign visitor or a malign intruder;
- For those with insight, the effect of recognizing oneself as a person who hallucinates and consequently fears of madness or loosing one's mind can be a source of upset;
- The reactions of other people, particularly family and healthcare staff can either exacerbate or reduce these concerns;
- Finally, the effectiveness of the patient's coping strategies moderates their level of distress with more effective control associated with less distress.

Patients spontaneously use a wide range of coping strategies [64]. Increasing cognitive impairment reduces, but does not eliminate their use, suggesting that they may be effective even in advanced disease. There are a number of strategies that aim to increase insight into the unreality of the hallucination by testing its agreement with other senses (i.e., 'can it be heard or felt'), or looking for incongruities in its appearance, location or movement. These can be effective when the patient is troubled by an individual hallucination and is already aware of, and is not distressed by, the fact that they hallucinate. For those who may be distressed by that insight, control techniques which disturb visual processing – looking at or away from the hallucination, putting on or turning off lights, or closing eyes – may be effective in reducing the duration of the experience.

Cognitive behavioral treatments, adapted from those developed to treat auditory hallucinations in younger people with psychosis, are starting to be applied to manage distress in neurodegenerative disorders [65]. Distress is posited to be maintained by a combination of dysfunctional beliefs and behaviors, which keep the patient more distraught than is necessary. Treatment depends upon collaboratively developing more functional beliefs and behaviors [27]. This approach requires well-trained and experienced therapists who are in short supply. Thus at present, it is within the realm of research rather than routine treatments.

Practical management

Owing to the lack of strong evidence to guide practice, practical management of hallucinations is largely pragmatic. Since hallucinations usually occur within a complex of cognitive and other symptoms, some of which may be worsened by treatment of the hallucination, plans need to balance potential costs and benefits across a range of areas. Close working with patients and carers can prioritize change in those areas which are most disabling or distressing, even at the cost of increasing problems in other areas [66].

In the absence of extreme distress, 'wait and see' is a legitimate tactic. In any event, regular monitoring of hallucination, consequences and other symptoms is helpful.

Conclusion

Treatment of visual hallucinations in neurodegenerative disorders is not well advanced. The complexity of underlying mechanisms provides a number of potential avenues for developing treatments, but also suggests that any single one may be of limited efficacy. The widespread pathology of these illnesses with consequent disturbances in many cerebral systems makes it difficult to attack one target without producing unwanted effects elsewhere; most obviously in the synucleinopathies in which treatment of hallucinations may worsen motor symptoms and *vice versa*.

Future perspective

Looking to the future, new therapeutic approaches are needed, as well as better evidence for the effectiveness or otherwise of existing treatments. Improved ways of measuring hallucinations will make it easier to track treatment response, while better understandings of the mechanisms which underlie hallucinations may open up new treatment avenues. In this regard, neuroimaging, neurophysiological and neuropathological/neurochemical studies have begun to provide powerful insights in the etiology of visual hallucinations [67–71]. For example, postmortem and neuroimaging studies in LBD patients have found that alterations in both nicotinic and muscarinic receptors are associated with visual hallucinations [45,71]. New pharmacological agents that target these receptor systems may therefore be useful future treatments. The serotoninergic system may also be a viable target; serotoninergic receptor dysfunction has been reported in Lewy body diseases [72,73] and it is well-established that activation of this system occurs with, for example, hallucinogens such as lysergic acid diethylamide. Agents that influence this system have been tried in PD-associated psychosis and include ondasetron (a 5-HT_3 antagonist) [74] and pimavanserin (selective 5-HT_{2A} receptor inverse agonist) [75], both of which have been reported to possibly improve visual hallucinations. However, the ondasetron study was only reported in a small cohort and positive effects were not observed in a subsequent study [76], similarly the beneficial effect of pimavanserin was not observed in a subsequent larger Phase III trial.

Other compounds may ameliorate visual hallucinations in LBD; a case report suggested ramelteon (selective MT_1/MT_2 melatonin receptor agonist) [77] was of benefit in two LBD patients and an open-label study found that yokukansan, a traditional Japanese medicine, reduced the occurrence of neuropsychiatric symptoms, including visual hallucinations in dementia with Lewy bodies patients [78]. Further work is needed to validate these findings.

Looking further into the future, better prevention of the illnesses, which are particularly associated with hallucinations will be more beneficial than treating them once they arise [79,80], but the challenges in achieving this are formidable [81,82].

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Executive summary

Hallucinations & neurodegenerative disorders

- Complex visual hallucinations of people, animals and objects are common, distressing and disabling features of neurodegenerative disorders, particularly the synucleinopathies.
- Disturbed alertness, sleep disorders and impairment of visual perception and attention are common associations.

Treatment targets & selection

- The evidence base for treatment selection is poor.

Nonpharmacological interventions

- Low-cost interventions (education and environmental change) with little risk of harm are common, but lack evidence of efficacy.
- Psychological treatment for distress associated with hallucinations may supplement other approaches.

Pharmacological management

- Pharmacological management uses reduction of potentiating medication as the first approach, with additional medication as a secondary strategy. Antidementia drugs are relatively safe, but lack evidence for specific treatment effects on hallucinations. Antipsychotic medication leads to significant excess morbidity and mortality.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the clinical features of complex visual hallucinations in neurodegenerative disorders, based on a review
- Describe the nonpharmacological and pharmacological management of complex visual hallucinations in neurodegenerative disorders, based on a review

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Table 1

Rates of complex visual hallucinations in parkinsonian syndromes.

Disorder	Cross-sectional prevalence of complex visual hallucinations (%)
Dementia with Lewy bodies	60
Parkinson's disease	38
Vascular parkinsonism	20
Unclassified parkinsonism	11
Corticobasal degeneration	5
Progressive supranuclear palsy	<5
Multisystem atrophy	0

Data taken from [15,16].

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Table 2

Examples of pharmacological interventions used in treating visual hallucinations in Parkinson's disease and Lewy body dementia.

Drug	Typical daily oral dosage	Comment
Quetiapine	25–200 mg	There have been a number of trials examining quetiapine in PD psychosis with and without dementia [47,48]. Reported efficacy has been variable and specific effects on visual hallucinations have not been reported. Quetiapine is probably less effective than clozapine, but is better tolerated, although higher doses are associated with hypersomnolence and sedation
Clozapine	25–50 mg	Low doses appears to improve visual hallucinations in PD psychosis [49,50]. However, it is associated with significant and serious side effects and requires active monitoring
Cholinesterase inhibitors	Donepezil (5–10 mg), galantamine (8–24 mg) and rivastigmine (3–6 mg)	Well established for the treatment of cognitive symptoms in dementia. The evidence is less clear for the treatment of visual hallucinations In PDD patients, in the EXPRESS study, the presence of visual hallucinations predicted a better response to rivastigmine [51], although a significant reduction in hallucinations was not found In DLB, rivastigmine has been reported to reduce visual hallucinations and in part this may be mediated by improved attentional function Open-label studies have also supported the possible benefits of donepezil and galantamine in the treatment of visual hallucinations in LBD, but the evidence is relatively weak
Memantine	5–20 mg	Evidence for memantine in the treatment of visual hallucinations has been conflicting and limited to LBD A number of case reports [52–55] have suggested that memantine may led to a worsening of hallucinations in DLB, although this is contradicted by another report [56], suggesting memantine reinitiation in a patient led to amelioration of their visual hallucinations There have been two major double-blind RCTs in DLB and PDD examining the global effect of memantine [57,58]; one of the trials failed to find any benefit with memantine in terms of overall neuropsychiatric symptom although the second trial reported that visual hallucination severity was reduced in DLB (but not PDD)

DLB: Dementia with Lewy bodies; LBD: Lewy body dementia; PD: Parkinson's disease; PDD: Parkinson's disease dementia; RCT: Randomized controlled trial.