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Point of view

# Parkinson's disease, visual hallucinations and apomorphine: A review of the available evidence

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ABSTRACT

*Background:* Visual hallucinations (VH) occur in the clinical course of Parkinson's disease (PD) and are predictive for PD dementia. The genesis of VH is related to impaired bottom-up and/or top-down visual processing which can be linked to cholinergic dysfunction and mono-amine imbalance. The risk of developing VH with oral dopamine agonists seems to increase with advancing disease, while in contrast some clinical studies suggest that apomorphine does not worsen VH, or might even improve VH.
*Methods:* The aim of this study is to review the current evidence of apomorphine and its effects on VH in PD patients.
*Results:* Apomorphine is well-tolerated in PD patients with VH, also in long-term follow-up studies. Apomorphine is also suggested to have the potential to alleviate VH. Some data suggest that the positive effect of apomorphine on VH is related to its piperidine moiety, part of many anti-psychotics. Irrespective this piperidine moiety, apomorphine has a high $D_1$–like receptor affinity, and acts as a serotonin 5-$HT_{2A}$ receptor antagonist, which might explain the potential anti-hallucinogenic properties as well.
*Conclusion:* The anecdotal evidence suggesting that apomorphine has a relatively low proclivity to induce VH in PD may be due to its capacity to reduce serotonergic activity in particular. Therefore apomorphine is still an option to consider in fluctuating PD patients with VH, if they are treated properly with respect to their cholinergic deficits and existing VH.

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## 1. Introduction

Visual hallucinations (VH) occur commonly in Parkinson's disease (PD) with an estimated prevalence of 22–38%, increasing up to more than 60% after long-term follow-up [1,2]. The most significant risk factors in the development of VH include disease duration, motor symptom severity and cognitive impairment [1]. They become increasingly intrusive in many patients and are predictive for PD dementia [1].

VH have long been considered purely as a side-effect of dopaminergic medication, based on clinical experience and an early open-label trial [3]. However, despite several studies no strong link has been identified between the occurrence of VH and the dosage or duration of dopaminergic medication [1,4]. Moreover, VH have also been reported in drug-naïve PD patients [5–8]. This suggests that VH are not directly caused by dopaminergic overstimulation, but that dopaminergic treatment may act as a precipitating factor. In contrast, evidence from a number of case series and a single open-label prospective trial even suggest that apomorphine has the potential to alleviate VH [9–12].

This review will discuss the current evidence for the underlying pathogenesis of VH in PD, together with the impact of dopamine agonists in general and apomorphine in particular.

## 2. Pathogenesis of visual hallucinations in Parkinson's disease

The precise pathophysiology of VH is still not completely understood. However, many data suggest that VH are caused by disruption of either the bottom-up and/or top-down visual processing [13]. In bottom-up processing, visual information is driven by salience of visual stimuli and abstracted from the retina. Information from the retina is relayed to the primary visual cortex (V1) via the lateral geniculate nucleus. Visual stimuli reaching V1 are further processed, and coupled to specific content e.g. shape,

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colour, and motion, whereas this processing is mainly divided into two pathways. The occipito-temporal pathway or ventral visual stream is crucial for object recognition, while the occipito-parietal pathway or dorsal visual stream provides detail of the spatial content of the visual stimulus. In top-down processing, an interpretation of the visual information is generated based on perceptual expectations, prior knowledge, and attention modulation. Visual information from the inferior temporal cortex is projected to the lateral prefrontal cortex via the uncinate fascicle, and via cortico-thalamo-cortical loops. Especially the mediodorsal and reticular thalamic nuclei are essential in gating and filtering relevant visual information.

In bottom-up processing aberrant visual activity may be generated by increased neural excitability, due to f.i. deprivation, also known as the Charles Bonnet syndrome, while top-down processing can bias and even override visual stimuli due to reduced selective attention, by filtering out unwanted information and suppression of nearby distracters. This model of impaired bottom-up and top-down visual processing in PD patients with VH is supported by structural and functional imaging, demonstrating a decreased parieto-occipital and prefrontal activity in PD patients with VH [14,15], and retinal dysfunction on electrophysiological testing [16,17]. Clinico-pathological studies correlated impaired bottom-up processing to a higher Lewy body density as well as alpha-synuclein aggregation in the ventral stream area [18]. In addition, alpha-synuclein was found in the retina, however its precise role in VH needs to be determined [19].

Visual processing and VH have been linked to disrupted acetylcholine transmission [13]. The majority of cholinergic projections to the cortex originate from the nucleus basalis of Meynert (NBM), located in the basal forebrain, and from the pedunculopontine nucleus (PPN), projecting to the thalamus. Comparison of PD patients with and without VH has found greater degeneration of these regions in those with VH [20–22].

Bottom-up and top-down visual pathways are modulated by acetylcholine. Low cholinergic activity following the use of anticholinergic drugs impairs attention [23,24] and visual processing [25], and can sometimes induce delirium with VH, even in individuals without clinical evidence of PD [26]. In contrast, use of cholinesterase inhibitors improves attention, thalamic function and visual processing in a dose-dependent manner [23,27–29]. There is little *in vivo* clinical data of cholinergic activity in PD patients with VH [30]. PD patients with dementia (PDD) together with VH had a greater reduction in cortical cholinergic activity compared to those without VH, and a greater clinical response to cholinesterase inhibitors in these patients with VH compared to those without [31–33]. An ongoing randomized, placebo-controlled, double-blind phase IV study is currently investigating the effect of rivastigmine in PD patients with VH without dementia (NCT01856738).

Although the majority of the pathophysiological evidence for VH involves disruption of the cholinergic system, there is also support for a dysbalance in mono-aminergic neurotransmitter systems, especially related to dopamine and serotonin [34].

## 3. Clinical evidence for the risk of development of visual hallucinations related to dopaminomimetics

### 3.1. Oral dopamine agonists and rotigotine transdermal patch

Anecdotal clinical experience and a number of clinical trials have suggested that oral dopamine agonists may exacerbate and unmask VH. In a 2010 meta-analysis the use of dopamine agonists including pergolide (relative risk (RR) 4.80, 95% confidence interval (CI): 2.24, 10.29), rotigotine (RR 4.02, 95% CI: 1.23, 13.11), pramipexole (RR 3.36, 95% CI: 2.41, 4.68), ropinirole (RR 2.84, 95% CI: 1.34, 5.99), cabergoline (RR 1.56, 95% CI: 0.47, 5.21) and bromocriptine (RR 1.10, 95% CI: 0.37, 3.26) was associated with a higher RR of VH compared to placebo [35]. However, no adjustment was made for disease duration, age or cognition, all of which are likely to impact on the development of VH. Studies have shown that use of dopamine agonists in patients >70 years of age is associated with an increased risk of developing VH compared to younger patients [4], while a recent meta-analysis demonstrated that the RR of developing VH increased to 5.24 (95% CI: 2.42, 11.35) in advanced PD patients (age of 61–66 years, disease duration of 5.9–8.9 years) using dopamine agonists on top of levodopa treatment [36].

In contrast to the possible increased risk of dopamine agonists, infusion of high-dose levodopa failed to precipitate VH in non-demented PD patients [37]. In addition, low-dose dopaminergic treatment is rarely complicated with the development of VH in other disorders, such as hyperprolactinaemia, raising the possibility that cholinergic and/or serotonergic dysfunction is an essential prerequisite for their occurrence.

It is therefore recommended that in the absence of systemic illness, the dose of dopamine agonist should be reduced if VH develop and that they should be prescribed with caution in PD patients with significant cognitive impairment [30].

### 3.2. Apomorphine

No worsening of VH has been reported in advanced PD patients receiving apomorphine treatment with long-term follow-up in descriptive studies [38–41] and apomorphine has even been suggested to have a beneficial effect on VH [9,12]. The antipsychotic potential of apomorphine was first reported in patients diagnosed with schizophrenia [42,43]. In a double-blind, placebo-controlled trial 3 mg subcutaneously-administered apomorphine reduced psychotic symptoms in 18 patients with longstanding schizophrenia [43]. This reduction in psychotic symptoms has also been replicated in several open and controlled trials of the management of acute psychosis patients diagnosed with schizophrenia [44].

The beneficial effects of apomorphine in the treatment of neuropsychiatric symptoms (predominantly VH) in patients with PD have been reported in a number of case series [9–11]. Altogether these case series describe long-term follow-up (8–72 months) of 16 PD patients, from which 12 patients had VH. Eleven described a dramatic reduction in visual symptoms with only mild persistence in the remaining case [9]. Support for these observations has come from a more recent open-label clinical trial, in which treatment with oral dopamine agonists was replaced with apomorphine [12]. PD patients with VH ($n = 8$) demonstrated an improvement in neuropsychiatric symptoms, as measured by the Neuropsychiatric Inventory Questionnaire. The improvement in VH severity became already evident after only a week of apomorphine treatment and persisted during the trial, which lasted six weeks. These findings suggest at least that apomorphine may be prescribed in PD patients with VH, provided there is concomitant reduction of oral dopamine agonists and/or adequate treatment of existing cognitive deficits [12].

In spite of this evidence, the common clinical perception remains that apomorphine has the proclivity like other dopamine agonists to worsen VH in patients with PD [45]. This may be in part due to those early anecdotal descriptions of worsening neuropsychiatric symptoms and the absence of a randomized controlled trial of the impact of apomorphine on VH [46–48].

Apomorphine appears to increase lower-order visual perception (e.g. contrast sensitivity), while higher-order perceptual functions (e.g. colour perception, visual acuity, visual object, and space perception) remain unchanged. A decrease in contrast sensitivity was found after infusion of apomorphine in healthy volunteers

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