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Motor and non-motor effects of apomorphine infusion

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Chapter 4

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 D₁-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.

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.

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, 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 an 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 pedunclopontine 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

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

a) 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

b) Apomorphine

No worsening of VH has been reported in advanced PD patients receiving apomorphine treatment with long-term follow-up in descriptive studies³⁸⁻⁴¹ 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

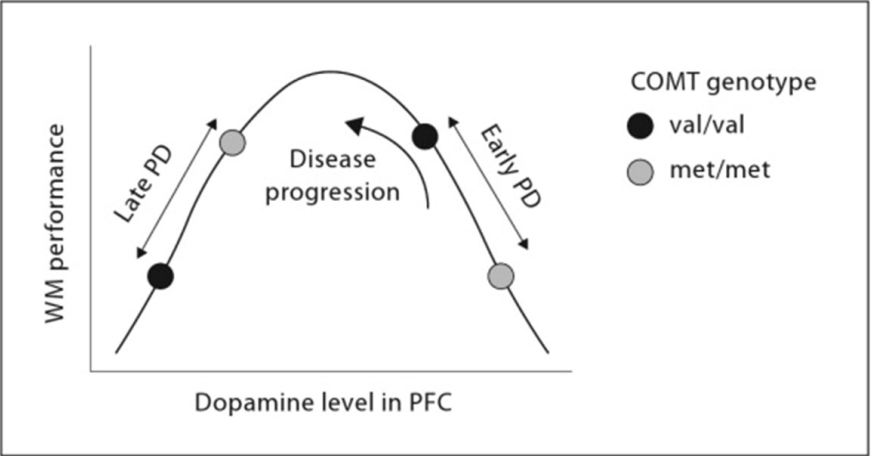
In spite of this evidence, the common clinical perception remains that apomorphine has the proclivity like other dopamine agonists to worsen VH in patients with PD.⁴⁵ This may be in part due to those early anecdotal descriptions of worsening neuropsychiatric symptoms and the absence of a randomized controlled 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,^{49,50} suggesting that overstimulation of retinal or cortical dopamine receptors may result in reduced lower-order visual perception. The absence of a positive effect on higher-order perceptual functions in PD patients with VH might be related to a dosing- or a ceiling effect. Conflicting results have been reported in the effect of apomorphine on attention, this variability potentially being related to the clinical stage of PD, although distinct outcome measures and lack of adjunctive clinical data (e.g. use and dosing of other medical therapies) may also have contributed.^{39,40,51,52}

Chemical structure and receptor binding profile of apomorphine

The molecular structure of apomorphine is closely related to dopamine (Figure 4.2), sharing a benzene ring with two hydroxyl groups, but it also contains a piperidine

FIGURE 4. 2 | Relationship between prefrontal functioning and dopamine level in prefrontal cortex



WM : working memory. Val/val: high-activity COMT genotype. Met/met: low-activity COMT genotype. Note that moderate dopamine levels in the prefrontal cortex (PFC) yields optimal prefrontal performance. Adapted from Williams-Gray and colleagues.⁶⁷

moiety ((CH₂)₅NH), which may be crucial for its proposed antipsychotic effect.⁵³ This piperidine moiety is also incorporated in the chemical structure of many antipsychotic medications, including piperidine phenothiazines, haloperidol, risperdone, bulbocapnine and other aporphines.^{54,55} Based on the structural similarities, it has been argued that the antipsychotic potential of apomorphine is due to the specific action of this piperidine moiety in binding to dopaminergic and serotonergic receptors (particularly 5-HT_{2A}-receptors), producing an antagonistic effect.^{9,12,55-57}

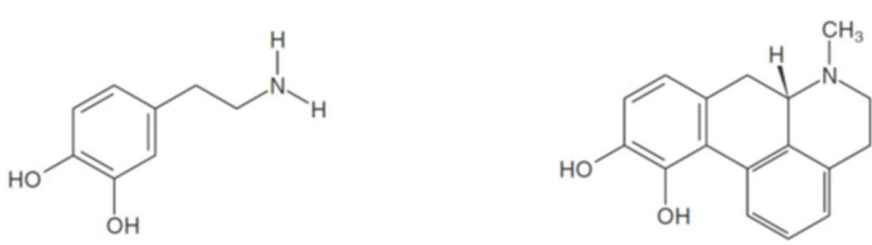
Apomorphine is a strong dopamine agonist possessing high affinity for both D₁-like (D₁ and D₅) and D₂-like (D₂, D₃, and D₄) receptors.⁵⁸ It also possesses antagonist activity at 5-HT_{2A} receptors and agonist activity at norepinephrine receptors, although affinity at both receptors is relatively weak.^{59,60}

The role of dopamine and serotonin in the development of visual hallucinations

a) Dopamine

The rich expression of D₁-like receptors in the prefrontal cortex suggests a key role in top-down processes related to attention, a feature supported by a number of animal studies.^{61,62} Absence of selective D₁ agonists and antagonists has complicated the study of these specific receptors in humans. However, genetic variation in the breakdown of prefrontal dopamine by the catechol-O-methyltransferase (COMT) gene has made it possible to compare high-activity (low dopamine levels) and low-activity (high dopamine levels) COMT genotypes. Results from both animal and genetic studies suggest an inverted U-shaped relationship between D₁-like receptor activity and prefrontal function (Figure 4.1), with both low and high dopaminergic activity impairing function of the prefrontal regions, clinically manifesting as reduced working memory and attention.^{63,64} In other words, the optimal prefrontal performance is achieved with intermediate dopaminergic activity and whether stimulation or inhibition of D₁-like receptors yields

FIGURE 4.1 | The chemical structure of dopamine (left) and apomorphine (right). Note the piperidine moiety ((CH₂)₅NH) of apomorphine.



this optimum depends on the baseline dopaminergic activity in the prefrontal cortex. Enhanced dopamine levels are found in early PD patients resulting in impaired prefrontal functioning,⁶⁵⁻⁶⁷ presumably due to a relative overstimulation of the mesocortical frontal loops, which are relatively spared in the early phases of PD.⁶⁸ Therefore during early PD, with this relative dopaminergic overstimulation in the prefrontal cortex, apomorphine could potentially worsen top-down processing. However in late PD, the relative shortage of dopamine in the prefrontal cortex might be corrected by apomorphine administration, because disease progression is accompanied by a reduction in the number of prefrontal D₁-like.⁶⁷⁻⁷⁰

Dopamine may also play a role in bottom-up visual processing. It is well recognized that dopamine deficiency in the occipital cortex, lateral geniculate nucleus and retina impairs lower-order visual functions, such as colour discrimination and visual contrast sensitivity, as well as playing a role in higher-order visual functions, such as motion perception, visual acuity, and colour vision.^{16,17} Dopamine appears to play a more specific role in retinal function with concentrations sensitive to light intensity and a circadian rhythm with lower dopamine concentrations at night and higher levels during the day.¹⁷ Therefore, dopamine seems to be essential in mediating light-adaptive mechanisms in retinal function.^{71,72} These deficits can be reversed with the administration of levodopa¹⁷ and apomorphine,⁵¹ suggesting a compelling link between dopamine and visual perception.

b) Serotonin

The serotonergic receptor 5-HT_{2A} is suggested to play a role in the pathogenesis of VH, based on the hallucinogenic potency of 5-HT_{2A} agonists like LSD (potent ergoline), and association with schizophrenia. The 5-HT_{2A} receptor is widely expressed in the neocortex including prefrontal, parietal, and occipital cortex, receiving projections from dorsal and, to a lesser extent, the medial raphe nucleus.⁷³ In addition, serotonergic projections target 5-HT_{2A} receptors in the ventral tegmental area, where they potentially could modulate dopaminergic activity.

Positron emission tomography (PET) studies comparing PD patients with and without VH demonstrated an increased 5-HT_{2A} binding in prefrontal and visual processing areas of the VH patients.^{74,75} A potential explanation for these findings is compensatory post-synaptic up-regulation due to pre-synaptic serotonergic neuronal loss. Neurochemical studies using the 5-HT_{2A} receptor agonist, psilocybin, have also demonstrated a dose-dependent reduction in prefrontal functions (e.g. attention and working memory) and in visuo-perceptive functions (e.g. high-level motion perception) as well as inducing VH in healthy volunteers.⁷⁶⁻⁷⁹ Interestingly, functional imaging studies have demonstrated similar activation patterns in healthy volunteers with psilocybin-induced hallucinations and those seen in PD patients with VH with reduced activity in the occipital cortex and visual pathways, as well as increased activation in the prefrontal cortex.⁸⁰⁻⁸² Subsequent studies have made use of the 5-HT_{2A} receptor antagonist ketanserin, used to block

the effects of psilocybin in healthy volunteers.^{77,78,83} These findings, together with the successful use of clozapine in the treatment of PD-related VH (due to predominant 5-HT_{2A} receptor antagonist activity), suggest a pivotal role of these receptors in reducing VH.⁸⁴ This is confirmed by the effectiveness of the selective 5-HT_{2A} antagonist pimavanserin, recently introduced in some countries, which has been reported to have a beneficial effect on VH in PD patients.⁸⁵ Therefore, part of the possible anti-hallucinogenic activity of apomorphine could be explained by its 5-HT_{2A} antagonism.⁶⁰

Based on receptor profiles, other mixed D₁-like and D₂-like dopamine agonists, such as pergolide, cabergoline, and rotigotine, could exert similar anti-hallucinogenic effects to apomorphine. However, the evidence to date suggests a totally distinct effect on VH for the ergolines pergolide and cabergoline, because these drugs have serotonin agonist activity, in contrast to the serotonergic antagonistic properties of apomorphine's piperidine moiety.³⁵ The relatively high potential for inducing VH of rotigotine might be explained by the absent piperidine moiety and perhaps also related to activation of serotonergic receptors, but that needs to be confirmed.⁸⁶

Conclusion

The beneficial effect of apomorphine in the treatment of VH is based on limited available data and lacks prospectively designed randomized controlled trials. However, it does appear that unlike oral dopamine agonists, apomorphine does not exacerbate symptoms in PD patients with pre-existing VH.^{12,38-40}

Deficient cholinergic and imbalanced mono-aminergic systems may induce VH in PD. Therefore, the treatment of VH in PD will very likely require a combination of therapies dependent on the balance of mono-amines and cholinergics. Therefore, a combination of apomorphine, clozapine perhaps combined with pimavanserin and cholinesterase inhibitors should be considered in patients who have developed refractory VH on oral dopamine agonist therapy and who cannot withdraw them without substantial deterioration in motor performance.

TABLE 4.1 | Receptor affinity of dopamine agonists.

	D ₁ -like	D ₂ -like	5-HT _{2A}
Aporphines			
Apomorphine	++	+++	-
Ergot derivatives			
Bromocriptine	-	+++	++
Cabergoline	+	+++	+++
Lisuride	-	+++	++
Pergolide	+	+++	+++
Nonergoline derivatives			
Pramipexole	0/+	+++	0/+
Ropinirole	0	+++	0/+
Rotigotine	++	+++	NA

D = dopamine receptor; 5-HT = serotonin receptor; NA = information not available; - indicates antagonist activity; 0 indicates no affinity; + indicates low affinity; ++ indicates moderate affinity; +++ indicates high affinity.

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Part III

Apomorphine and cutaneous adverse events including subcutaneous nodules

