

Apomorphine and the dopamine hypothesis of schizophrenia: a dilemma?

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The dopamine (DA) hypothesis of schizophrenia implicates an enhancement of DA function in the pathophysiology of the disorder, at least in the genesis of positive symptoms. Accordingly, apomorphine, a directly acting DA receptor agonist, should display psychotomimetic properties. A review of the literature shows little or no evidence that apomorphine, in doses that stimulate postsynaptic DA receptors, induces psychosis in non-schizophrenic subjects or a relapse or exacerbation of psychotic symptoms in patients with schizophrenia. After a detailed review of the literature reporting psychotogenic effects of apomorphine in patients with Parkinson's disease, an interpretation of these data is difficult, in part because of several confounding factors, such as the concomitant use of drugs known to induce psychosis and the advanced state of the progressive neurological disorder. In the context of the DA hypothesis of schizophrenia, the limited ability of apomorphine to induce psychosis, in contrast to indirectly acting DA agonists that increase synaptic DA, may be explained by the relatively weak affinity of apomorphine for the D₃ receptor compared with DA. Alternatively, enhancement of DA function, though necessary, may be insufficient by itself to induce psychosis.

L'hypothèse du rôle de la dopamine (DA) dans la schizophrénie sous-entend une exacerbation de la fonction DA dans la pathophysiologie de ce trouble, du moins dans la genèse des symptômes positifs. Par conséquent, l'apomorphine, un agoniste récepteur de la DA à action directe, devrait présenter des propriétés psychodysléptiques. Une recension des écrits n'a révélé à peu près aucune donnée probante permettant de dire que l'apomorphine, en doses stimulant les récepteurs postsynaptiques de la DA, engendre une psychose chez des sujets non schizophréniques ou une rechute ou une exacerbation des symptômes psychotiques chez des patients atteints de schizophrénie. Après une recension minutieuse des textes faisant état des effets hallucinogènes de l'apomorphine chez des patients atteints de la maladie de Parkinson, une interprétation de ces données se révèle difficile en partie à cause de plusieurs facteurs confusionnels, comme l'utilisation concomitante de médicaments connus pour provoquer la psychose et l'état avancé du trouble neurologique progressif. Dans le contexte de l'hypothèse du rôle de la DA dans la schizophrénie, la capacité limitée de l'apomorphine de provoquer une psychose, par contraste aux agonistes à action indirecte de la DA qui augmentent la DA synaptique, pourrait s'expliquer par la très faible affinité de l'apomorphine au récepteur D₃ par comparaison à la DA. Par ailleurs, l'exacerbation de la fonction DA, même si elle est nécessaire, pourrait être insuffisante pour déclencher une psychose.

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Introduction

The dopamine (DA) hypothesis of schizophrenia, which implicates an enhancement of DA function, was first proposed over 3 decades ago and remains a dominant hypothesis for the pathophysiology of this disorder,¹⁻⁵ particularly regarding the genesis of positive symptoms. Much of the evidence in support of this hypothesis is indirect and derives from information on the pharmacology of neuroleptic agents and psychotogenic psychostimulant drugs. Thus, neuroleptics, which improve psychotic symptoms, block DA neurotransmission by binding to DA D₂ receptors.² Imaging studies in patients show that at therapeutic doses all neuroleptics, with the apparent exception of clozapine and quetiapine, occupy 60%–80% of D₂ receptors.^{6,7} The apparent lower occupancy of the latter 2 drugs can be explained by looser binding to D₂ receptors⁸⁻⁹ (i.e., a comparable occupancy to classical neuroleptics does occur but is shorter lasting). Amphetamine,¹⁰ cocaine,¹¹ methylphenidate¹² and related psychostimulants,¹³ all of which enhance DA neurotransmission by presynaptic mechanisms, can induce psychosis in normal subjects that is similar to schizophrenia^{10,14,15} in cross-sectional clinical features, course and response to neuroleptics.¹⁶ Also, these agents can activate psychotic symptoms in patients with schizophrenia¹⁷ at doses that are sub-psychotogenic in non-schizophrenic subjects.¹⁸ Recent investigations show that after an amphetamine challenge, the increase in DA release is greater in patients with schizophrenia than in controls.¹⁹

According to the DA hypothesis, apomorphine, a direct DA receptor agonist in animals²⁰ and man,²¹⁻²⁴ would be expected to induce or exacerbate psychotic symptoms. However, some investigators have reported an antipsychotic effect of apomorphine and propose that this effect derives from stimulation of presynaptic DA receptors which inhibits DA neurotransmission.^{25,26} Such an explanation would be consistent with the DA hypothesis of schizophrenia but makes assumptions concerning what a presynaptic dose of apomorphine in man is.

Most of the evidence for a possible psychotogenic effect of apomorphine derives from studies using high doses of apomorphine in the long-term treatment of Parkinson's disease (PD) during which psychotic symptoms have been observed.^{27,28} Improvement of parkinsonian symptoms points to stimulation of post-

synaptic DA receptors so that these observations of emergent psychotic symptoms are compatible with the DA hypothesis of schizophrenia. Unfortunately, the observations in PD patients are confounded by many factors, such as the effect of concomitant medications and the progression of the neurological disorder, so it is unclear to what extent apomorphine is responsible for the psychosis.

This paper evaluates the evidence for a psychotogenic effect of apomorphine, with a particular focus on reports of psychotic side effects seen in PD patients treated with apomorphine. For the purposes of the latter, all papers in English and French listed in MEDLINE up to the end of 1999 in which apomorphine was used as a treatment modality for PD were reviewed. In the papers reviewed, the term psychosis is not defined but presumably implies the presence of positive symptoms, namely, hallucinations or delusions. The terms used in describing neuropsychiatric side effects remain as stated by their respective authors.

Apomorphine in non-psychotic individuals

Since apomorphine was synthesized in 1869,²⁹ an extensive body of clinical literature has been published on the use of this agent as an emetic,³⁰⁻³² as a sedative,^{33,34} in the management of alcoholism^{35,36} and in the investigation and treatment of a variety of other medical conditions^{20,37-43} including PD.⁴⁴ Despite the sizeable literature, except in PD patients (see later), the emergence of psychotic symptoms subsequent to exposure to apomorphine has not been described. Many of the investigations with apomorphine have used only single challenge subemetic doses of apomorphine varying from 0.5 mg to 1.5 mg, subcutaneously. However, such doses are sufficient to stimulate DA function in man,⁴⁵⁻⁴⁹ so that dose is unlikely to explain the absence of psychotic symptoms. Further, many researchers have used considerably larger doses. For instance, Goethe³⁰ used subcutaneous doses of 2 mg to 20 mg to evaluate antiemetic agents, and Feldmann³⁶ treated 6250 people for alcoholism over a period of 35 years with apomorphine in doses of 6 mg subcutaneously or 3 mg sublingually, administered every 2 hours for several days. White³³ reported a series of 804 subjects who received multiple doses of apomorphine while in labour, and there was no record of psychotic symptoms developing. Thus, sample size is also unlikely to have been a factor in the non-recognition of psychotic symptoms.

Until 1975, none of the studies using apomorphine were designed to evaluate psychotomimetic properties of apomorphine. However, given that apomorphine has been administered to thousands of subjects, at least incidental observations of psychotic symptoms might have been expected should they have occurred. In a double-blind, placebo-controlled, parallel design ($n = 20$ per arm), prospective study in non-psychotic subjects, apomorphine was administered in a dose of 1 mg subcutaneously 3 times a day for 14 days.⁵⁰ None of the subjects developed schizophrenia-like symptoms. Scores on the Brief Psychiatric Rating Scale (BPRS) showed a small but significant improvement with both apomorphine and placebo, but there was no significant difference between the 2 treatments.

Apomorphine in patients with schizophrenia

Before the neuroleptic era, apomorphine in a dose of 1.6 mg (subcutaneously), as a single dose or in repeated doses (as many as 8 times over an 8-h period), with or without scopolamine, was used to control agitation and excitement, not only in non-psychotic patients, but also in patients with schizophrenia;⁵¹ exacerbation of schizophrenia was not reported. In numerous studies designed to evaluate DA function in patients with schizophrenia, adverse effects on the psychosis were not documented.^{20,48,52}

Few investigators have directly investigated the effect of apomorphine on the psychopathology of patients with schizophrenia. Although some studies find worsening and others improvement in the psychosis, the majority point to no change.

Open or single-blind studies

Corsini et al⁵³ reported improvement (versus placebo) after 1 mg intramuscular apomorphine in 6 of 15 schizoaffective, 8 of 24 paranoid, 7 of 12 hebephrenic and 0 of 4 catatonic patients who were unmedicated. A modified BPRS was used to assess symptoms. In a follow-up report in which the original diagnoses were reconsidered, a beneficial effect was found only in schizoaffective manic-type patients but not in patients with paranoid or disorganized schizophrenia.⁵⁴ Exacerbation of schizophrenic symptoms was not described.

In an open study of 2 patients taking neuroleptics and treated with oral apomorphine in variable daily doses (30–480 mg/day) for 5–6 days, both became

more agitated and more psychotic.⁵⁵ However, serum prolactin concentrations showed little change, which suggests that the route of administration, the dose of apomorphine, or both, were inadequate to stimulate DA receptors. In this regard, apomorphine is not well absorbed when given orally. In 5 patients given oral apomorphine (10–30 mg/day) for 3 weeks while on neuroleptics, all showed a slight decrease in BPRS scores (mean decrease 11.4%) compared with the placebo phase.⁵⁵ However, in the ensuing double-blind study by the same investigators (see below) the results were less impressive.

Meltzer⁵⁶ reported no improvement in 22 neuroleptic-free patients given 0.75 mg apomorphine subcutaneously. Details of the design and method of assessment were not provided. In 9 medicated patients, 0.375 mg subcutaneous apomorphine did not reduce BPRS scores; this dose, however, failed to decrease plasma homovanillic acid (HVA) levels (a peripheral index of DA activity).⁵⁷

Double-blind placebo-controlled studies in medicated patients

The administration of 20 mg apomorphine per day (by mouth) to 11 patients for 2 2-week periods produced no evidence of therapeutic benefit when compared with 2 placebo phases. One patient had a marked exacerbation of psychosis after taking apomorphine for 8 days, however.⁵⁵

Tamminga et al²⁶ observed significant transient improvement (lasting 20–60 min), using a modification of the New Haven Schizophrenia Scale, in 18 patients given 3 mg subcutaneously. In 9 patients, the reduction in psychosis scores was 20%–50%. In a small sample ($n = 5$), 5 µg/kg subcutaneous apomorphine decreased plasma HVA in all subjects, 2 of whom showed significant improvement and 3 no change.⁵⁸ Unfortunately, BPRS data and statistical analysis of the BPRS ratings were not provided. In contrast, Syvalahti et al⁵⁹ found no significant change in BPRS scores in 8 patients given 5 µg/kg apomorphine subcutaneously or in 7 given 15 µg/kg intravenously over 90 min. Lack of an effect on BPRS scores was also noted by Merello et al⁶⁰ in 12 patients with chronic schizophrenia who received 3 mg apomorphine (route unspecified). Likewise, Jeste et al⁶¹ found no change in BPRS scores in 11 patients given 5 µg/kg subcutaneous apomorphine, even though this dose decreased plasma HVA concentrations. However,

in 10 subjects receiving apomorphine (10 µg/kg subcutaneously), those with abnormal computed tomographic (CT) scans ($n = 6$) tended to show improvement or no change, whereas the symptoms of those with a normal CT scan tended to worsen.⁶² Thus, 3 of the patients with a normal brain CT scan showed a 25% increase and 1 a 25% decrease in placebo-corrected BPRS scores. Among the 6 patients with an abnormal brain CT scan, 2 improved and 4 showed no change. However, in 5 patients who received multiple doses of apomorphine, placebo-corrected BPRS scores showed no change after 5 µg/kg, 10 µg/kg or 40 µg/kg apomorphine.

Double-blind placebo-controlled studies in neuroleptic-free patients

A transient decrease in psychotic symptoms (New Haven Schizophrenia Index)²⁵ was observed in 3 of 4 patients with chronic schizophrenia, 3 of whom were neuroleptic-free, after 1.5–6 mg subcutaneous apomorphine; 1 patient showed a slight increase in scores compared with placebo. Each subject was tested on multiple occasions with drug or placebo. Unfortunately, statistical data were given for only 1 subject. In 3 patients with hebephrenia who received apomorphine (1 mg subcutaneously daily for 15 days) and were evaluated using the Wittenborg Rating Scale and a variety of neuropsychological tests under double-blind conditions, there was no change.⁶³

Ferrier et al⁶⁴ investigated the effect of apomorphine (0.75 mg subcutaneously) in 15 (9 neuroleptic-naïve, 6 neuroleptic-free for 1 mo to 3 yr) patients with acute and 15 (5 neuroleptic-naïve, 10 neuroleptic-free for 1–8 yr) patients with chronic schizophrenia. Videotaped interviews were rated blindly using the Krawiecka Scale. There was no significant change in positive or negative symptoms. Levy et al⁶⁵ administered 0.75 mg apomorphine subcutaneously to 25 patients (neuroleptic-free for at least 2 wk) who had had a recent acute exacerbation of psychosis ($n = 11$), were chronically stable with persistent symptoms ($n = 10$) or who had a chronically deteriorating course ($n = 4$). There was no significant improvement or deterioration in psychopathology (BPRS) despite evidence of central activity of the drug, as measured by reduction in cerebrospinal fluid HVA and endocrine indices.

Tamminga et al⁶⁶ administered oral *N-n*-propyl-norapomorphine (NPA), an orally active apomorphine

analogue, to 18 patients with active symptoms who were neuroleptic free for at least 4 weeks. In a rising-dose design for 10 consecutive days, 9 patients received 2.5–40 mg NPA or placebo. BPRS scores showed a significant decrease as did prolactin levels (an index of DA activity). However, 9 subjects in a cross-over design in which NPA was administered for 3 weeks in increasing daily doses from 2.5–40 mg/day, showed no consistent alteration in mental status. The authors concluded that tolerance to the antipsychotic effect occurred.

Studies comparing apomorphine with indirectly acting DA agonists

In patients with acute psychosis, neuroleptic-free for at least 2 weeks ($n = 4$) or neuroleptic-naïve ($n = 9$), whereas methylphenidate (0.5 mg/kg intravenously over 90 s) ($n = 10$) increased thought disorder, 7.5 µg/kg subcutaneous apomorphine ($n = 12$) had no such effect.⁶⁷ Angrist et al¹² showed that in neuroleptic-free patients (at least 2 wk) oral administration of piribedil over 6–18 days (but not a single intravenous dose) exacerbated schizophrenic symptoms, whereas intravenous infusion of apomorphine (3.3–4 mg) had no such adverse effect. In another subject who was on the antiemetic metoclopramide (a peripheral DA receptor blocker), which only weakly crosses the blood brain barrier, an intravenous dose of 24 mg apomorphine over 52 minutes produced mild nausea but no psychotic symptoms. In a further study, Angrist et al⁶⁸ investigated the emetic threshold in 21 patients who were neuroleptic-free for 6–15 days (10 acute or subacute, 11 chronic or subchronic) and in normal controls by administering apomorphine (0.75 mg/mL) intravenously at a rate of 1 mL/min until retching occurred, which was after 1.3–5.5 mg (mean 2.8 mg). In 4 additional subjects who failed to vomit, they received 6 mg, 8.8 mg, 12 mg and 13.3 mg. Whereas amphetamine administration (0.5 mg/kg by mouth) administered to the same subjects increased psychopathology (BPRS), there was no reported change after apomorphine.

Lieberman et al⁶⁹ administered apomorphine (0.75 mg subcutaneously) and methylphenidate (0.5 mg/kg intravenously) to 51 first-episode patients with schizophrenia or schizoaffective disorder who had no prior neuroleptic treatment (70%) or who were neuroleptic-free for at least 14 days (30%); 51% had eye tracking deficits. Whereas methylphenidate exacerbated psychotic symptoms (BPRS) in 59% of patients, no such

effect was reported with apomorphine.

Miscellaneous studies

In a positron-emission tomography study of regional cerebral blood flow in 12 unmedicated patients (9 neuroleptic-naive, 3 neuroleptic-free for at least 6 mo) performing a cognitive task, apomorphine (10 µg/kg subcutaneously) enhanced activation in the anterior cingulate cortex which was impaired before apomorphine administration.⁷⁰ This brain region plays a role in attentional mechanisms which are known to be impaired in schizophrenia.

Comments

The conflicting results may be related to differences in research design, heterogeneity of patient populations, dose and duration of apomorphine administration or whether the subjects were investigated while taking neuroleptics or at various intervals after neuroleptics were discontinued. Although most studies report no change in psychopathology, most of the patients in these studies were exposed to subcutaneous doses of 0.5–0.75 mg apomorphine. Three studies showing improvement used doses of 1–6 mg. Although single subcutaneous doses of 0.5–0.75 mg are sufficient to stimulate DA function in man, as measured by growth hormone increase,⁴⁵ prolactin decrease,⁴⁹ stimulation of yawning,⁴⁷ induction of penile erections⁴⁶ and decrease in cerebrospinal fluid HVA,⁶⁵ a dose effect to account for symptom amelioration cannot be excluded, especially in those studies involving medicated patients, because neuroleptics are known to antagonize the central effects of apomorphine.²²

One of the confounding factors in evaluating improvement in psychopathology after apomorphine is the nonspecific sedative effect of apomorphine. In this regard, in the study of Jeste et al,⁶² apomorphine improved scores on the anxiety syndrome subscale of the BPRS, and an improvement in anxiety was also noted by Ferrier et al.⁶⁴ Also, monitoring transient changes in psychosis with rating scales is difficult. In 2 patients with catatonic schizophrenia with catalepsy plus mutism, 1 patient with catatonia and mutism and a patient with constant formal thought disorder, the response to 2 mg subcutaneous apomorphine could be monitored objectively by directly observing the maintenance of imposed postures, ability to respond to

questions and tape recording of thought disorder.^{20,71} No improvement was observed. In the patient with thought disorder, although the voice intensity and speed of verbalizations in response to questions slowed down compared with placebo, speech remained incoherent.

The apparent therapeutic effect of apomorphine and apparent failure to worsen schizophrenia has been attributed to preferential stimulation of presynaptic DA receptors and inhibition of DA neurotransmission.^{25,26} The presumed presynaptic dose of apomorphine in man has been variously given as anywhere from 1 mg or less intramuscularly⁵³ or 1.5–6 mg subcutaneously.^{25,26,72} No evidence for this assumption has been given by the authors other than that the clinical observations conformed with the DA hypothesis of schizophrenia or could account for improvement rather than worsening of tardive dyskinesia. In a dose-response study of apomorphine-induced yawning in normal subjects, Lal et al⁷³ showed that subcutaneous doses of 3.5–5.0 µg/kg apomorphine HCl decreased yawning compared with placebo, whereas a dose of 7.0 µg/kg increased yawning (Fig. 1). These results suggest that apomorphine HCl in subcutaneous doses of 3.5–5.0 µg/kg are presynaptic but that 7.0 µg/kg subcutaneous (i.e., 0.5 mg/70 kg subject) is a post-synaptic dose. Accordingly, most investigations on the effect of apomorphine on the psychopathology of schizophrenia have used doses compatible with a post-synaptic site of action.

Compared with single-dose challenges with the indirectly acting DA receptor agonists amphetamine and methylphenidate, a challenge dose of apomorphine does not worsen the symptoms of schizophrenia.^{67–69} Differences in pharmacological activity between apomorphine and indirectly acting DA receptor agonists may account for the differences in psychotomimetic activity (see Discussion).

Because of the short half-life of apomorphine (i.e., 33 min in man⁷⁴) compared with methylphenidate (2.1 h) or amphetamine (6.8 h), an insufficient duration of activation of postsynaptic DA receptors may account for the weak or absent psychotogenic potential of apomorphine.

Apomorphine in Parkinson's disease

Apomorphine has been used in the investigation of PD since 1951.⁷⁵ Improvement in motor symptoms after

challenge doses of 0.5–10 mg (subcutaneous)⁷⁶ points to a postsynaptic site of action. In the past decade or so, patients with PD have been exposed to short-duration high-dose apomorphine to evaluate brief-term effects as well as long-term exposure to repeated or continuous high doses of apomorphine as an adjunctive therapeutic measure. Although the development of psychotic symptoms has been described in some studies, an antipsychotic effect has been noted in others.^{77–79}

Neuropsychiatric symptoms after acute exposure to apomorphine

Before 1972, the occurrence of psychotic-like symptoms after exposure to apomorphine had not been reported.³⁹ Strian et al⁸⁰ investigated 10 patients with PD taking L-dopa and a dopa-decarboxylase inhibitor with intravenous apomorphine (1–3 mg over 2 h). One patient developed a psychosis with disorientation and paranoid symptoms. The psychosis showed a certain sexual colouring. The psychotic symptoms ceased with dose reduction. Some of the subjects (number unspecified) showed a slight euphoria with sexually coloured behaviour. However, psychosis or behavioural changes were not observed in other studies. No psychotic symptoms were reported after a subcutaneous infusion of apomorphine (30–150 µg/kg/h) over 1–6 hours ($n = 15$),⁷⁴ an intravenous infusion (100 µg/kg/h) over 6 hours or for 22–31 hours ($n = 7$),⁸¹ or when given in a dose of 150–200 µg/kg/h for 4–6 hours.⁸² Similarly, no

such side effects were observed by Obeso et al⁸³ who administered apomorphine intravenously in a dose of 5–10 mg/h, up to a maximum of 30 mg/h, for 4–7 hours ($n = 9$), or by Hughes et al⁸⁴ who administered 10–17 subcutaneous injections of apomorphine (mean dose 2.7 mg) over 10 hours ($n = 7$). Likewise, psychotic symptoms were not described by Grandas and Obeso⁸⁵ or Van Laar et al.⁸⁶

Psychotic symptoms after treatment with apomorphine

In patients receiving oral NPA for PD for approximately 9 weeks, PD symptoms improved in all 24 patients studied, but 6 patients developed transient mental aberrations (description not given) and 1 developed agitation, garrulity, hallucinations and confusion.⁸⁷ The latter had experienced a similar reaction in the past to L-dopa.

In 2 single case reports on the treatment of PD with apomorphine lasting 18 months⁸⁸ and 12 months,⁴⁴ respectively, no psychotic symptoms were described. Courty et al⁸⁹ described 4 case reports of patients taking levodopa and other dopaminergic agents who, when treated with the addition of daily subcutaneous apomorphine for 3 months or more, developed excessive sexual preoccupation, increased sexual activity and mood changes. In addition, 3 of these subjects developed delusional ideas of jealousy which resolved when the dose of apomorphine was reduced.

In 30 investigations involving 560 patients with PD (Table 1), no neuropsychiatric symptoms were reported in 10 studies, and in 4, emotional lability and euphoria but no psychotic symptoms were recorded. In the remaining 16 studies, 51 patients may be broadly considered to have experienced psychotic symptoms while taking apomorphine, (i.e., 9.1% of 560 patients), namely, those in whom the respective authors mention delusions, hallucinations, pseudo-hallucinations, illusions, psychosis, paranoid ideas (or paranoid symptomatology). The breakdown of the symptoms in these 51 patients was visual hallucinations ($n = 15$), visual hallucinations plus confusion ($n = 4$), visual pseudo-hallucinations ($n = 1$), visual delusions ($n = 9$), visual illusions ($n = 1$), intermittent illusions ($n = 1$) and paranoid psychosis with confusion and visual hallucinations ($n = 2$). Of the remaining 18 patients, in 3 the type of hallucination was unspecified, 7 were described as being psychotic but no details were provided, 1 had

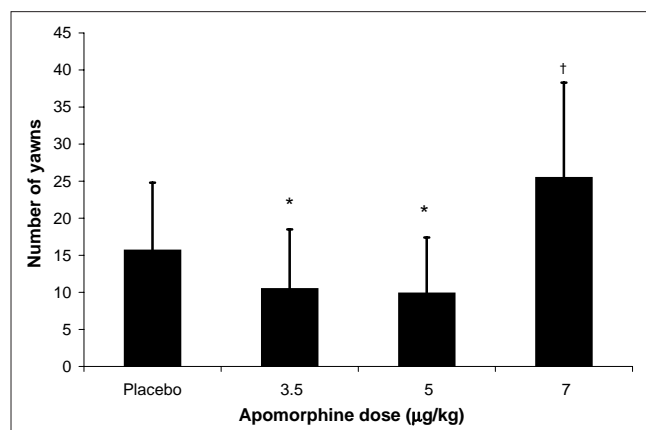


Fig. 1: Dose–response effect of apomorphine administration on yawning in normal men. Apomorphine HCl was injected subcutaneously into 5 men and yawns were counted. Data are means and standard deviations. (Based on Lal et al.⁷³) *Significantly less than placebo ($p < 0.05$). †Significantly greater than placebo ($p < 0.05$).

hallucinations plus delusions, 1 had auditory hallucinations and 6 had paranoid symptomatology with or without other psychotic features.

The mental status of these 51 patients before apomorphine treatment was initiated was unspecified in 18 cases; 6 had experienced psychotic symptoms on other anti-PD medications and 1, prior febrile hallucinations; 1 patient had visual hallucinations plus paranoia, and 1 patient had nocturnal confusion. In 9 subjects in the studies of Hughes et al¹⁰⁸ and Steiger et al,²⁸ it is unclear how many of these patients are included among those with prior psychosis, similar psychiatric side effects before apomorphine or neuropsychiatric disturbance on DA agonists. In 15 subjects, it would appear there were no psychotic symptoms before apomorphine treatment.

Unfortunately, most of the studies in patients with PD have focused primarily on motor symptoms of apomorphine; the mental side effects either before or while taking apomorphine have been described in little detail, at times with unusual terminology such as “visual delusions,” and mostly as an aside. Accordingly, the occurrence of psychotic symptoms with apomorphine administration may be an underestimate.

In all of the studies, subjects had been receiving L-dopa for many years and most continued on L-dopa when placed on apomorphine. In addition, most were concomitantly receiving other dopaminergic agents such as bromocriptine, lisuride, pergolide and amantadine, and others were also taking antiparkinsonian anticholinergic agents and selegiline. These drugs are known to induce psychosis,^{115–120} or, in the case of selegiline, to potentiate the psychiatric complications of L-dopa.¹²¹ Sanchez-Ramos et al¹²² reported 55 of 214 patients investigated for PD experienced visual hallucinations. Dementia, age and duration of disease were strongly associated with the hallucinations. Peyser et al¹²³ reported that psychotic symptoms (hallucinations, delusions or thought disorder) occurred in up to 40% of patients with PD usually, but not exclusively, in the context of pharmacological treatment.

Interestingly, in the study of Scarzella et al,¹¹⁰ subjects were off all prior medications during apomorphine treatment and none developed psychotic symptoms. However, the treatment duration was only 2 weeks.

In all studies, apomorphine was given to patients with advanced PD, present in most patients for at least 10 years, so that progression of the underlying neurodegenerative disorder may have been responsible for the development of psychotic symptoms. In this

regard, progression of PD is associated with Lewy body pathology in the cortex.¹⁰⁸ In fact, the occurrence of psychosis in PD independent of pharmacotherapy has long been recognized.¹²⁴ Of the 51 subjects taking apomorphine and experiencing psychotic symptoms, 1 had experienced nocturnal confusion before starting apomorphine, and in 5, the psychotic symptoms were associated with confusion (i.e., impaired level of consciousness), a symptom which may reflect underlying brain pathology. Further, in the study of Pietz et al¹¹⁴ the frequency of cognitive problems was higher in patients developing psychiatric side effects; 4 of the 11 patients who developed neuropsychiatric side effects had cognitive problems before starting apomorphine and 7 at the termination of the study. In contrast, in 14 patients who did not develop psychiatric side effects, 1 at the start of apomorphine treatment and 2 at the end of treatment had cognitive problems.

In 2 of 51 subjects, the psychotic symptoms with apomorphine administration lasted only 2 days^{90,91} and resolved spontaneously despite continuation of apomorphine. Also, in 1 subject, visual hallucinations and paranoia were present when apomorphine was started, and these symptoms decreased with apomorphine.⁷⁹ Accordingly, attribution of the psychotic symptoms to apomorphine in these 3 subjects is unlikely. Onset of the psychotic symptoms after the initiation of apomorphine treatment was unspecified in 32 cases, and in 1 case symptoms were already present when apomorphine was started. In the remaining 18 subjects, the onset was less than 1 week in 2 cases, 2 weeks in 1, 2–7 months in 7, 9–12 months in 5 and 32–48 months in 3 cases. The long interval in some of these cases makes a cause–effect relationship difficult to determine.

Suggestive of a psychotogenic effect of apomorphine is the resolution of psychotic symptoms in 5 patients on dose reduction and in 5 patients on apomorphine discontinuation (4 within 6 wk of withdrawal). These 10 subjects, however, were not rechallenged with apomorphine, so the relationship between apomorphine and psychotic symptoms is unclear. In 7 other cases, psychotic symptoms were controlled with temporary use of clozapine. It appears, although the presented data are unclear, that continuation of apomorphine after discontinuation of clozapine was not associated with relapse.

Several authors have stated that neuropsychiatric side effects with apomorphine are uncommon¹²⁰ or much less common than after other DA receptor

Table 1: Details of studies reporting neuropsychiatric side effects of apomorphine therapy in patients with Parkinson's disease

Reference	n	Mean age (range) Duration PD Duration L*	Treatment with apomorphine (dose range)	Duration (range)	Concomitant anti-PD medication†	Mental status before apomorphine	Neuropsychiatric effects of apomorphine‡
Pollak et al ⁹⁰	10	55.8 9.4 —	Continuous waking SC infusion 3.8 mg/h + 4 x 1.5 mg bolus/d (n = 4) or multiple SC injections 2.25 mg x 4 injections/d (n = 6)	Up to 6 mo	L (n = 10) BC (n = 8)	1 of 10 evening and nocturnal hallucinations	Resolved on apomorphine 1 on apomorphine infusion developed visual hallucinations for 2 d
Pollak et al ⁹¹	9	52 (34–67) 14.8 (7–24) 13 (7–22)	Continuous SC infusion 93 mg/d (52–145)	10 mo (2–18)	L (n = 9) BC (n = 7)	No dementia — 5 of 14 past episodes of transient delusions or visual hallucinations on BC	1 systematized delusions on BC 6 yrs previously developed visual hallucinations for 48 h which spontaneously resolved despite continuation of apomorphine
	5	57 (34–72) 9.6 (7–13) 7 (5–10)	Multiple SC injections 8.9 (SD 3.6) mg/d	11 mo (3–19)	L (n = 5) BC (n = 5)		
Pollak et al ⁹²	17	55 (34–73) 16 —	Continuous waking with or without nocturnal SC infusion and boluses 95 (SD 28) mg/d	12–55 mo	L (n = 17)	Not stated	2 of 17 Apo discontinued because of behavioural side effects
Poewe et al ⁹³	7	57 (44–68) 11 (2.5–15) —	Multiple SC injections 4.7 mg x 3–5 injections/d	Up to 6 mo	L (n = 7)	Not stated	No psychiatric side effects
Poewe et al ⁹⁴	17	58.5 (45–76) 9.9 (3–18) 9 (2–15)	Multiple SC injections 12.2 (5–32) mg/d	7.2 mo (3–15)	L (n = 17)	1 of 17 past acute paranoid hallucinatory syndrome on LIS plus L	No acute psychotic symptoms
	6	60.3 (45–69) 11.3 (6–26) 9.3 (4–18)	Continuous SC infusion 140 (22–264) mg/d	5.5 mo (1–13)	L (n = 6)	1 of 6 visual delusions 1 yr prior on L plus BC	Benign visual delusions which resolved when Apo infusion decreased from 10 to 9 mg/h
Durif et al ⁹⁵	12	57 (42–72) 12 (5–19) 10 (2–19)	Multiple SL doses 133 (60–270) mg/d	8 mo (2–12) (n = 11)	L (n = 12) BC (n = 8)	Not stated	None developed confusional episode
Poewe et al ⁹⁶	18	60.2 (49–72) 12.4 (4–24) 9.9 (2–18)	Continuous 24-h SC infusion 160 (84–300) mg/d	20.6 mo (8–35) (n = 14) < 6 mo (n = 4)	L (n = 18) BC (n = 4) LIS (n = 1) SEL (n = 1) BIP (n = 1)	Not stated	3 visual delusions controlled by dose reduction
Durif et al ⁹⁷	3	65 (61–72) 15.3 (12–40) —	Multiple SC injections 45–180 µg/kg x 3–7 injections/d	~ 1–1.3 yr	L (n = 3) BC (n = 1)	Not stated	1 with mild hallucinations on 85 µg/kg x 4/d – ? onset after 9–12 mo of treatment

Table 1: Continued

Reference	n	Mean age (range) Duration PD Duration L*	Treatment with apomorphine (dose range)	Duration (range)	Concomitant anti-PD medication†	Mental status before apomorphine	Neuropsychiatric effects of apomorphine‡
Deffond et al ⁹⁸	7	60 (SD 7) 13.5 (SD 4.5) 12.4 (SD 5.4)	Multiple SC injections 4.1 mg x 3.2 injections/d (cross-over design) Multiple SL doses 42.8 mg x 2.6 doses/d	7.7 mo (4–15) 6.8 mo (2–12)	L (n = 7) BC (n = 5)	No neuropsychiatric disorder	No adverse psychiatric symptoms described
Esteban Munoz et al ⁹⁹	11 9	57.6 (42–67) 13.5 (10–19) 12 (9–19) 61.2 (51–69) 13.3 (8–23) 11 (7–17)	Multiple SC injections 3 mg/dose (2–4) x 3 doses (1–5) Intranasal nebulization 3 mg/dose (2–4) x 2.5 doses (1–4)	23 mo (4–40) 12.3 mo (2–21)	L (n = 11) BC (n = 3) PER (n = 8) SEL (n = 5) L (n = 9) P (n = 8) SEL (n = 2)	 Subjects with psychiatric disorder or dementia excluded	No neuropsychiatric side effects 1 transient feeling of confusion
Muhiddin et al ¹⁰⁰	13	69 (53–80) 15 (6–28) —	Continuous SC infusion 12–24 h 74.2 (4–140) mg/d	22–28 mo (n = 3) Others? Others?	L (n = 13) Others not stated	Not stated	1 psychotic side effect 1 confusion 1 hallucinations and delusions
Montastruc et al ¹⁰¹	8	66 (51–71) 11 (6–16) 10 (4–16)	Sublingual 87.4 (27–120) mg/d	4 mo (1–6)	L (n = 8) BC (n = 8)	Not stated	None described
Hughes et al ¹⁰²	5	51 (42–59) 11 (7–16) 10 (5–16)	Sublingual (n = 3) 133 (57–228) mg/d Unspecified dose (n = 2)	4.7 mo (3–8) 3 wk	Anti-PD meds unchanged	Not stated	1 mild confusion – withdrawn at 3 wk
Ray-Chaudhuri et al ⁷⁷	9	59 (52–64) 17 (12–20) —	Continuous diurnal SC infusion (n = 7) or multiple SC injections (n = 2) 29.7 (15–55) mg/d	Up to 11 mo	L (n = 9)	3 hallucinations 1 confusion	No psychiatric side effects Hallucinations resolved
Ray-Chaudhuri et al ⁷⁸	3 12	62.3 (46–74) — — — — —	Continuous diurnal SC infusion 36–40 mg/d SC Dose not specified	8–14 mo Up to 2 yr	L (n = 3) Not stated	1 past psychosis on BC, hallucinations and paranoid delusions on L 1 visual hallucinations and confusion on L 1 psychoses on L and visual hallucinations and confusion on BC or BEN Non-demented 5 of 9 some form of neuro- psychiatric complications	No psychiatric side effects No psychiatric side effects Occasional nocturnal confusion 1 hallucinations for the first time

Table 1: Continued

Reference	n	Mean age (range) Duration PD Duration L*	Treatment with apomorphine (dose range)	Duration (range)	Concomitant anti-PD medication†	Mental status before apomorphine	Neuropsychiatric effects of apomorphine‡
Broussolle et al ¹⁰³	4	46–78 7–18 —	Continuous SC infusion 3–7 mg/h	4–15 d	L (n = 4)	Confusion postop (n = 2)	No neuropsychiatric symptoms reported
Ellis et al ⁷⁹	12	59 (39–78) 11 (3–23) —	Continuous SC infusion 60 (30–114) mg/d (n = 8) or multiple SC injections 30 (10–60) mg/d (n = 4)	28 mo (8–72)	L (n = 12) PER (n = 5) BC (n = 4) SEL (n = 4) AM (n = 4) BE (n = 2)	All non-demented 5 visual hallucinations 1 visual hallucination and paranoid delusions 1 visual hallucination and psychosis 1 “on-off” paranoia and nightmares 1 visual hallucination and “on-off” paranoia 3 confusion	No new neuropsychiatric symptoms observed 4 resolved; 1 initial confusion resolved when L reduced Resolved Occasional nocturnal confusion Resolved Decrease visual hallucinations No recurrence
Ruggieri et al ²⁷	6	52–63 4–14 3–12	Continuous SC infusion 1.5–3.5 mg/h x 12 h	2.6 mo (0.5–7)	L = (n = 6)	No prior psychiatric complications with L 5 intolerant of LIS: 1 confusion and delusion 1 acoustic hallucinations 1 confusion and hallucinations 1 no psychiatric side effects 1 nocturnal confusion 1 acoustic hallucinations, confusion and vivid dreams	Confusion and visual hallucinations at 7 mo No psychiatric complications Confusion and visual hallucinations at 2 wk Visual hallucinations and confusion in the third month Acute psychosis at 2 mo No psychiatric complications
Gancher et al ¹⁰⁴	6	60 (36–73) 18 (6–36) 12.5 (3–20)	Continuous waking SC infusion 25–200 µg/kg/h	3 mo	L (n = 6) BC (n = 4) PER (n = 2) TRI (n = 1) ETH (n = 3)	Not stated	1 confusion and emotional lability 1 euphoria Both improved with decrease Apo and d/c oral dopamine agonists

Table 1: Continued

Reference	n	Mean age (range) Duration PD Duration L*	Treatment with apomorphine (dose range)	Duration (range)	Concomitant anti-PD medication†	Mental status before apomorphine	Neuropsychiatric effects of apomorphine‡
Frankel et al ¹⁰⁵	25	58.8 (40–74) 17.8 (7–24) 15.6 (3–20)	Continuous SC infusion and boluses (7 on 24-h infusions) 89 (24–207) mg/d	22 mo (5–32) (n = 21) < 5 mo (n = 4)	L (n = 25) AC (n = 6) BC (n = 3) AM (n = 2) SEL (n = 1)	No current dementia or neuropsychiatric disturbance	1 withdrawn because of hallucinations 1 visual hallucinations at 6 mo, resolved on dose reduction 1 visual pseudo-hallucinations (history of hallucinations on L)
	32	59 (40–73) 14.5 (5–23) 12.8 (3–20)	Multiple SC injections 10.2 (0.8–27.5) mg/d	13.5 mo (5–26) (n = 30) < 5 mo (n = 2)	L (n = 32) SEL (n = 12) BC, AM or AC (n = 15)	3 of 57 history of psychosis on other anti-PD meds (no recurrence on Apo)	1 visual hallucinations and paranoid ideas, resolved on apomorphine withdrawal 1 paranoid mute, withdrawn at 6 mo; persisted after Apo and L withdrawn No neuropsychiatric side effects
Ostergaard et al ¹⁰⁶	22	59.3 (44–76) 9.8 (34–19.2) 8 (3–19)	Multiple SC injections 3.4 (0.8–6) mg/dose x 5.8 injections (1–12.7)	8 wk (n = 14) 2 wk (n = 2)	L (n = 22) BC (n = 12) SEL (n = 9) BEN (n = 1) AM (n = 1)	No psychiatric disease but 8 on amitriptyline 2 on imipramine 1 on clozapine	None reported
Stibe et al ¹⁰⁷	6	53 (36–70) 14.3 (9–20) 13 (9–16)	Continuous SC infusion 0.04–0.06 mg/kg/h	Up to 5 mo	L (n = 6)	3 severe psychiatric reactions after oral dopaminergic meds 1 nightmares, depressed and withdrawn	Metallic distortion of taste in 2
Hughes et al ¹⁰⁸	22	60.6 (43–75) 19.2 (9–28) 16.6 (6–24)	Continuous mainly waking SC infusion and boluses 70–93.2 (28–180) mg/d	36.5 mo (12–61)	L (n = 22)	4 similar psychiatric side effects before and after Apo	2 occasional nightmares, 3 mild benign visual hallucinations 2 described mild confusion only when dose increased
	49	62.6 (42–78) 15.2 (5–26) 13 (4–21)	Multiple SC injections 11.7–18.6 (0.4–75) mg/d	27 mo (12–54)	L (n = 49) Other anti-PD meds (unspecified)	Not stated	Hyperlibidinous and paranoid after 32 mo and after L d/c, recovered with clozapine; no recurrence on d/c clozapine and continuation of Apo
	37	— — —	Continuous SC infusion (n = 9) Multiple SC injections (n = 28)	< 1 yr	L (n = 37)	Not stated	3 nightmares and 2 benign visual hallucinations for the first time after 1 yr of treatment None reported

Table 1: Concluded

Reference	n	Mean age (range) Duration PD Duration L*	Treatment with apomorphine (dose range)	Duration (range)	Concomitant anti-PD medication†	Mental status before apomorphine	Neuropsychiatric effects of apomorphine‡
Stibe et al ¹⁰⁹	11	56 (32–70) 14.4 (9–20) 13.5 (9–17)	Continuous diurnal SC infusion with or without boluses 77 (30–150) mg/d	8 mo (1–15)	L (n = 6)	Non-demented 10 of 19 had prior visual hallucinations (3 psychotic reactions on L)	1 visual hallucination after 1 yr; 20 yr prior had febrile visual hallucinations
	8	57 (49–73) 14 (10–17) 12 (10–14)	Multiple SC injections Unspecified dose	Duration ?	L (n = 8)	2 of 19 prior confusion (1 paranoid on LIS)	
Scarzella et al ¹¹⁰	25	59.7 (42–73) 13.9 (4–27) 12.3 (3–23)	Continuous SC infusion 25 mg/d over 4.2 h	14 d	No anti-PD medication	Not stated	No hallucinatory phenomena
Steiger et al ²⁸	22	54 (38–75) 13.7 (6–25) —	Multiple SC injections 2.6 (1–4) mg/dose x ? number of doses	Median 5 mo (3–9) (n = 10) Up to 19 mo (n = 10) < 1 wk (n = 2)	L (n = 22)	Demented excluded Prior neuropsychiatric disturbance on dopamine agonists (n = 4) (1 delusions on BC)	5 of 22 psychiatric side effects (2 < 1 wk; 1 at 4, 6 and 12 mo): 1 visual illusions, 1 auditory hallucinations, 2 feelings of persecution (all 4 resolved within 6 wk of Apo d/c), 1 visual illusions, formication and morbid jealousy requiring suliride x 2 mo to resolve (3 of these had similar symptoms on other treatments; 2 de novo); 1 “on” period confusion
Kempster et al ¹¹¹	8	59.9 (41–68) 16.1 (10–21) —	Multiple SC injections 11.6 (4–25) mg/d	6.5 mo (n = 6) < 6.5 mo (n = 2)	L (n = 8) BC (n = 4) AC (n = 2)	2 cognitive impairment with prior episodic confusion	No neuropsychiatric toxicity
Colzi et al ¹¹²	19	58.5 (47–74) 17.4 (9–31) 15.6 (8–31)	Continuous waking SC infusion 77.6 (30–300) mg/d	2.7 yr and over	L (n = 9)	Not stated	After 3–4 yr: 2 paranoid psychosis (with mild confusion and visual hallucinations); resolved on temporary clozapine or sulpiride; Apo continued 1 mild confusion and visual hallucination
Wenning et al ¹¹³	16	— 11 9	Continuous 24-h SC infusion 162 (36–340) mg/d	57 mo (8–103)	L (10) Others ?	Not stated	5 visual delusions controlled with transient clozapine use Frank psychosis not seen
Pietz et al ¹¹⁴	25	64.7 (6.8 SD) 16 (6–27) 14 (5–23)	Continuous 24 h infusion 112.5 (57–174) mg/d	> 2 mo (median 44 mo)	L (16) Others ?	4 of 11 who developed neuropsychiatric symptoms had cognitive problems before Apo	5 psychotic, 3 visual hallucinations 1 intermittent illusions 1 confusion, 1 occasional nightmares
	24	58.9 (9.7 SD) 11.5 (3–25) 10.0 (3–23)	Intermittent injections 9.7 (2–26) mg/d	> 2 mo (median 22 mo)	L (20) Others ?	Not stated	2 visual hallucinations 1 confusion

Note: AC = anticholinergic antiparkinsonian agents; AM = amantadine; Apo = apomorphine; BC = bromocriptine; BEN = benzhexol; BIP = biperidine; d = day(s); d/c = discontinued; L = levodopa; LIS = lisuride; PER = pergolide; PD = Parkinson's disease; SC = subcutaneous; SD = standard deviation. SEL = selegiline; SL = sublingual.

*Column data (and range) in years; †Subjects on L-dopa were also on a peripheral dopa decarboxylase inhibitor; several subjects were also on domperidone. ‡Terminology as used by the authors.

agonists.^{125,126} This low incidence has been considered an advantage in the treatment of PD.¹²⁷ Further, some authors have described an antipsychotic effect of apomorphine in patients with PD and have recommended its use in patients who develop psychotic symptoms on other anti-PD medication.⁷⁷⁻⁷⁹ However, the ability to reduce L-dopa requirements as a result of improvement of the motor symptoms with apomorphine may account for the improvement in the psychotic symptoms. Of the 560, 47 (8.4%) patients had either experienced psychotic symptoms before starting apomorphine ($n = 34$) or were experiencing such symptoms when apomorphine was started ($n = 13$). This is similar to the number experiencing psychotic symptoms during apomorphine therapy (i.e., adding apomorphine did not increase the prevalence of psychotic symptoms). Of the 13 patients experiencing psychotic symptoms when apomorphine was started, 12 resolved while taking apomorphine and in 1, the psychotic symptoms decreased. In 7 of the 47 patients, there was a recurrence of psychotic symptoms (including in 1 patient who had experienced febrile visual hallucinations in the past). However, in 2 of these cases, the symptoms only lasted 2 days and did not recur with continuation of apomorphine therapy. In the remaining 27 patients, there was no recurrence of psychotic symptoms on exposure to apomorphine.

Discussion

Aside from observations in patients with PD, there is little or no evidence that apomorphine, in doses that stimulate postsynaptic DA receptors, induces psychosis. Also, unlike amphetamine or methylphenidate, apomorphine does not cause relapse or exacerbation of psychosis in patients with schizophrenia. The short half-life of apomorphine, insufficient dosages or possible tolerance of DA receptor response to repeated or continuous apomorphine administration may account for the absence of a psychotogenic effect of apomorphine. In normal subjects, a subcutaneous dose of 0.5 mg apomorphine HCl is sufficient to stimulate postsynaptic DA receptors,⁷³ and doses of 0.5 mg apomorphine are sufficient to improve PD.⁷⁶ Accordingly, the studies cited have used apomorphine in doses sufficient to stimulate postsynaptic DA receptors. Evaluation of the effect of apomorphine on psychopathology in schizophrenia has usually involved only a single injection of apomorphine, so the duration of DA receptor

stimulation may have been insufficient to provoke an exacerbation of psychosis. However, in nonpsychotic subjects exposed to aversive therapy in which apomorphine was administered every 2 hours for several days,³⁶ psychotic symptoms were not reported. Also, repeated doses of apomorphine at hourly intervals over an 8-h period in patients with psychosis was not associated with an aggravation of psychosis.⁵¹

Most studies in patients with PD show that the antiparkinsonian effect of apomorphine continues with repeated or continuous administration of apomorphine, although a few studies show that while the antiparkinsonian effect continues, it is diminished. Hughes et al⁸⁴ administered repeated subcutaneous injections of apomorphine over a 10-h period to 7 patients with PD; each dose was given when the beneficial motor effects induced by the previous dose had worn off; no tolerance was observed. In a further study, 15 patients received 7 sequential subcutaneous injections of apomorphine, and no tolerance to the antiparkinsonian effects occurred.¹²⁸ Also, in 14 patients with PD who improved taking apomorphine and who had never received L-dopa, the magnitude of improvement was maintained after 4 repeated subcutaneous injections of apomorphine.¹²⁹ Grandas et al,¹³⁰ however, reported that if apomorphine doses were given at 2-h intervals, the duration of antiparkinsonian effects was reduced by 40% but was of equal duration when given at 4-h intervals. In contrast to repeated doses, Gancher et al⁸¹ showed that the antiparkinsonian effect of a challenge dose of apomorphine after continuous intravenous infusion of apomorphine over 6 hours was reduced by 35% and after 22-31 hours, by 68%. However, the same authors found that in patients receiving continuous subcutaneously infusion of apomorphine during the waking hours over a 3-month period, no tolerance to the antiparkinsonian effects of apomorphine occurred.¹⁰⁴ In fact, chronic administration of apomorphine, whether given intermittently or by continuous infusion, remained effective in improving PD symptoms without clinically significant tolerance or loss of therapeutic effect for up to 4-5 years of treatment.¹⁰⁸ This would indicate that, at least in the striatum, DA receptor responsiveness to apomorphine does not show tolerance.

Difficulties interpreting much of the data from studies in patients with PD derive from insufficient information on the mental status of subjects before apomorphine administration, advanced state of the neurodegenerative disorder, concomitant administra-

tion of drugs known to induce psychosis and paucity of information on rechallenge with apomorphine in suspected cases of apomorphine-induced psychotic symptoms. Prospective studies in PD patients showing resolution of psychotic symptoms with apomorphine^{77,79} (possibly because L-dopa doses could be reduced) raise questions concerning the psychotogenic properties of apomorphine. Unfortunately, there have been no studies in which subjects have been selected as suitable candidates for apomorphine treatment and then those given apomorphine compared with patients who declined to take it. Information to date suggests that apomorphine in high doses may induce psychotic symptoms in some patients with PD, but it is a relatively weak psychotomimetic agent.

Amphetamine and methylphenidate increase synaptic DA concentrations,^{131,132} whereas apomorphine enhances DA neurotransmission by a direct effect on D₁-like (D_{1A}, D_{1B}, D₃) and D₂-like (D₂, D₃, D₄) DA receptors.¹³³ Apomorphine shows a differential binding to DA receptor subtypes that differs from that of the endogenous ligand, DA. Apomorphine and DA have a similar affinity for the D₁ receptor; however, apomorphine has a greater affinity for the D₂ and D₄ receptors, whereas DA has a 7-fold greater affinity at the D₃ receptor than apomorphine.¹³³ This raises the possibility that apomorphine shows little psychotogenic potential compared with indirectly acting DA agonists because of its relatively weak effect at D₃ receptor sites. In this regard, D₃ receptors are localized to limbic areas of brain,¹³⁴ areas implicated in the pathophysiology of schizophrenia.¹³⁵ Further, the DA receptor agonists bromocriptine and pergolide, which induce psychosis,^{117,119} also have a comparable binding affinity at the D₃ receptor to DA.¹³³

Apomorphine and amphetamine induce compulsive sniffing, licking and biting in the rat. This behavioural response, which is inhibited by neuroleptics, is used to screen for antischizophrenic agents.¹³⁶ Whereas the stereotyped response induced by amphetamine and related compounds may be interrupted by episodes of reverse locomotion,¹³⁷ this is not seen after apomorphine administration.¹³⁸ This behavioural difference suggests central neurochemical differences in the action of these agents. In addition to the amphetamines, backward walking (reverse locomotion) is also seen after a variety of hallucinogens^{139,140} and is believed to be mediated by the simultaneous release of DA and serotonin.¹⁴¹ In addition to increasing DA turnover,

amphetamine increases the turnover of both noradrenaline¹³¹ and serotonin.¹⁴² In this regard, abnormalities in noradrenergic^{143,144} and serotonergic function¹⁴⁵ have been implicated in the pathophysiology of schizophrenia. In contrast, apomorphine is more selective in its effect on neurotransmitter systems; apomorphine stimulates DA function at doses that have no effect on noradrenaline¹⁴⁶ or serotonin turnover.¹⁴⁷ This difference may have relevance to the limited psychotogenicity of apomorphine.

In the context of the DA hypothesis of schizophrenia, the weak or questionable psychotogenic effect of apomorphine may suggest that whereas hyperdopaminergia is a necessary factor, at least in the genesis of positive symptoms of schizophrenia, by itself it is insufficient. This conclusion with respect to apomorphine further supports the view that other neurotransmitter derangements are relevant to the pathophysiology of schizophrenia.¹⁴⁸⁻¹⁵⁰

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