operator gave an eight year history of attacks of unilateral headache with minimal nausea, lasting for up to two days. These occurred initially at intervals of two months but more recently every three days. At first the attacks were preceded by a typical 25 minute visual aura, in which he experienced a coloured rotating diamond and zig zag lines, usually in the right visual field, but since the age of 25 an increasing proportion of them have been preceded by a momentary feeling that his actual behaviour is unduly familiar, followed by a 20 minute sequence of unpleasant, almost morbid sensations that he felt he had come across before, as if in previous dreams, "in another world". This would be followed by some impairment of memory lasting for three days, and a rather milder, though sometimes more generalised headache with nausea that would last for one day. In addition some attacks were preceded by 15 seconds of quite intense giddiness and there have been rarer episodes of dysphasia. There have never been any lapses of concentration or impairment of consciousness, and he said he was able to carry on speaking and working while the aura was in progress. There is no family history of migraine. He derived some benefit from pizotifen which seemed to shorten his aura, but was not helped much by methysergide.

There were no physical abnormalities on examination. A CT scan was normal and two EEGs showed a generalised excess of slow wave activity.

Visual, sensory and motor symptoms, usually in that order of frequency, are the commonest seen in the aura phase of classical migraine.¹² Occasional patients become dysphasic and some symptoms (for example, ataxia, dysarthria and vertigo) have been attributed to disturbances in the vertebro-basilar circulation.³⁴ In one series of patients with transient global amnesia, 42% gave a past history of migraine, a figure considered significantly greater than the prevalence in the general population.⁵ It seems likely that some such cases, which are only rarely recurrent, are indeed manifestations of migraine while others are ischaemic in origin.⁶⁷ Raskin⁸ describes a young woman who experienced 15 episodes of transient global amnesia, each lasting up to six hours followed by headache, each after drinking a glass of red wine. While olfactory and auditory hallucinations have been described in the aura phase of classical migraine,⁹⁻¹¹ recurrent transient memory disturbances of the type experienced by this patient, which are reminiscent of déjà vu phenomena, do not appear to have been reported in detail, though Saul¹² and Sacks¹³ allude to similar cases.

There is much, admittedly circumstantial, evidence that the cortical disturbances of classical migraine are due to spreading depression moving across the cortical surface.^{14,15} Olesen and Jorgensen¹⁶ have speculated that transient global amnesia is due to a wave of spreading depression moving across the hippocampal surface. This patient's déjà vu phenomena, which have a frequency and duration typical of classical migraine, are probably mediated similarly, and it is speculated that this is due to spreading depression in the temporal lobe. Migraine therefore should be considered among the causes of déjà vu phenomenon, particularly if prolonged.

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Subcutaneous apomorphine for Parkinsonian patients with psychiatric side effects on oral treatment

Subcutaneous apomorphine has recently been shown to reduce off periods in patients with Parkinson's disease (PD) who are resistant to conventional management.¹² A previous study indicated that neuropsychiatric symptoms in patients on oral treatment did not recur when apomorphine was used, but the effects of apomorphine in those for whom these complications were the major dose limiting factor has not been investigated.¹ We describe three patients with PD whose optimal control was compromised by severe neuropsychiatric side effects and who responded to treatment with apomorphine.

The first case was a 46 year old woman who had had PD for eight years and was underdosing herself with oral levodopa because of side effects. Bromocriptine had produced psychosis, and levodopa/benserazide (madopar 62.5 mgs) in excess of seven times daily caused hallucinations, paranoid delusions and aggression predominantly in the on periods, which led to two hospital admissions.

Subcutaneous apomorphine infusion was started at 3 mg/hour for 12 hours daily and dramatically reduced her off periods from eight hours daily to one hour. Tremor was abolished and levodopa dosage could be reduced from 350 mg/day to 200 mg/day. She has now been maintained on this treatment for eight months without psychiatric side effects.

The second case was a 67 year old nun who had had PD for 10 years. Eight Madopar 62.5 mg tablets caused severe dyskinesias and visual hallucinations mainly in the on periods. Bromocriptine 2.5 mg four times daily caused visual hallucinations and confusion and was discontinued. She could tolerate seven madopar 62.5 mg tablets and had nine hours off periods daily. Apomorphine was given initially by a "Penject" system and subsequently by subcutaneous infusion at a dose of 40 mg/day. Off periods fell to one hour daily and levodopa could be reduced from 400 mg daily to 300 mg daily. She has now been maintained on apomorphine infusion for 14 months with mild involuntary movements but no psychiatric side effects.

Case 3 was a 74 year old man with severe Parkinsonian tremor and bradykinesia who could not tolerate optimal doses of levodopa, bromocriptine or benhexol. Madopar in excess of 62.5 mg four times daily caused nausea and psychosis, both during on and off phases. Bromocriptine 2.5 mg, three times daily caused visual hallucinations with confusion and the same problems occurred with benhexol 2 mg, twice daily. He tolerated subcutaneous apomorphine infusion at 3 mg/hr for 12 hours daily and his tremor grading (modified King's College scoring system) improved from 3 to 1 (3 = severe, 1 = mild) along with improvement in his bradykinesia. Single blind infusion of normal saline in place of apomorphine resulted in a return of the severe Parkinsonism. His levodopa dosage could be reduced from 200 mg to 150 mg daily and he has been maintained on apomorphine for 14 months without any neuropsychiatric problems except for occasional nocturnal confusion.

Over the past two years we have treated 12 non-demented PD patients with refractory on-off oscillations, using subcutaneous apomorphine. Nine have continued treatment resulting in reduction of their mean daily off periods and levodopa dosage by 85% and 39% respectively. Five of the nine patients had some form of neuropsychiatric complications on oral treatment, before apomorphine was started. Only one patient developed hallucinations for the first time with apomorphine. Thus we have shown that apomorphine will improve the quality of life of PD patients who develop severe neuropsychiatric side effects on optimal doses of oral treatment. Resistant off periods can be reduced without the development of these problems. Lisuride has also been used as parenteral treatment in PD, but neuropsychiatric complications were the major limiting factor in its use.³

It is unclear why apomorphine should be better tolerated than oral therapies. It contains a piperidine moiety which may itself be antipsychotic and it lacks the serotonergic effects of bromocriptine or the ergolides.¹³ Furthermore, its potent effect on both D₁ and D₂ receptors may differentiate it from other dopaminergic agents. For instance, unlike levodopa and amphetamine, small doses of apomorphine in schizophrenics do not exacerbate the psychosis.⁴ Likewise, although it induces stereotyped behaviour in laboratory animals, an emetic dose of apomorphine does not lead to behavioural changes in humans.⁵

To date our experience suggests that PD patients with neuropsychiatric problems with conventional treatment benefit from treatment with apomorphine. Further experience with large number of patients may confirm it

to be the treatment of choice in this subgroup of patients.

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Subcutaneous and sublingual levodopa methyl ester in Parkinson's disease

Subcutaneous continuous infusions or intermittent injections of the dopamine receptor agonist apomorphine have proved to be an effective treatment for motor fluctuations in patients with Parkinson's disease receiving long term levodopa treatment.^{1,2} Levodopa itself is impractical for chronic parenteral treatment because of its low solubility and high acidity. The highly soluble levodopa methyl ester (LDME), however, might be a more suitable candidate for parenteral application³ and its longer half-life compared with that of apomorphine could be of clinical advantage. We have therefore investigated the possibility of administering LDME both by the subcutaneous and, following a previous anecdotal report,⁴ by the sublingual route.

Five sublingual and five subcutaneous doses of LDME were given to seven patients with idiopathic Parkinson's disease and motor fluctuations. Their mean age was 59 years, mean duration of disease 12 (4-22) years, mean duration of levodopa therapy 9.5 (1.5-19) years and mean stage of Hoehn and Yahr 3.4 when "off" and 2.4 when "on". All patients were known to respond to their first morning dose of 100 or 200 mg of oral levodopa plus decarboxylase inhibitor within 15 to 30 minutes and the mean duration of effect was 135 (90-120) minutes. On test days the morning dose was replaced by 1 ml of LDME (equivalent to 200 mg levodopa) either injected subcutaneously or given sublingually. Patients were given 50 mg of oral benserazide one hour before the LDME challenge. Subcutaneous doses were injected in two boluses of 0.5 ml each into different sites of the abdominal wall. With sublingual applications patients were instructed to keep the liquid underneath their tongue as long as possible and spit it out as soon as they felt forced to swallow. Motor assessments were carried out using the modified Webster scale at baseline and at the time of maximum therapeutic effect as well as unilateral hand

tapping tests 10 minutes before and every 10 minutes after administration of LDME until drug effects had completely worn off or up to one and a half hours when there was no clinical effect.

Two patients switched "on" with subcutaneous LDME with the same quality and duration of therapeutic effect seen after their oral levodopa doses. The time from injection to full switch "on" was 60 minutes in both patients. Two patients had no effect over the entire observation period of 90 minutes and another one experienced onset-of-dose dyskinesias continuing for 110 minutes without ever switching fully "on". One of the responders then received a second injection which after a latency of 80 minutes produced some clinical effects with an inferior "on"-quality lasting for only 15 minutes. All patients had burning sensations at the injection site with rapidly developing nodules which slowly disappeared over two to four days.

Sublingual LDME was ineffective in all patients who managed to keep the liquid underneath their tongues for an average of 13 (5-20) minutes. No local side effects were observed.

The cause for the unpredictable response to subcutaneous LDME is unclear. The rate of de-esterification of LDME and resulting absorption of levodopa is influenced by pH, temperature and distribution and activity of esterases.⁵ Different individual conditions at the subcutaneous injection site may therefore be responsible for the varying clinical effects observed. As the local toxic reaction to subcutaneous LDME was seen in both responders and non-responders it is unlikely to be a

major reason for poor absorption.

The failure of sublingual LDME to produce clinical effects provides no evidence for absorption through the oral mucosa.

Although the number of patients in this trial was small we conclude that due to the variability and unreliability of clinical response subcutaneous LDME is unlikely to become a practical treatment for fluctuating Parkinson's disease.

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Cortical nicotinic receptors in Alzheimer's disease and Parkinson's disease

Cognitive impairment and central cholinergic dysfunction are common features of Alzheimer's disease (AD) and Parkinson's disease (PD). Degeneration of subcortico-cortical cholinergic systems and reductions in cortical pre-synaptic cholinergic markers, such as choline acetyltransferase (CAT) activity, have been consistently demonstrated in AD and PD.^{1,2} Most investigations of muscarinic cholinergic receptors in the neocortex indicate that receptor binding is unchanged in AD and increased in PD.^{3,4} The status of nicotinic cholinergic receptors is less clear. We have examined nicotinic receptor binding and CAT activity in the cortex in AD and PD.

Brain tissue was obtained at necropsy from ten patients with AD and from ten matched control subjects with no evidence of

neurological or psychiatric diseases, and from ten patients with PD, five of whom were clinically demented according to DSM III criteria, and ten matched controls. AD and PD were confirmed neuropathologically. The Parkinsonian patients had been treated with levodopa up to the time of death. Patients with AD and controls had not received any medication that is known to affect the central nervous system. Using washed membrane homogenates we performed saturation analysis for nicotinic receptors with (-)-[³H]-nicotine (concentrations 0.5-64 nM) in the frontal cortex (Brodmann area 8) and temporal cortex (Brodmann area 38). Non-specific binding was defined by unlabelled nicotine. Protein concentrations and enzyme activities were measured by standard techniques.

CAT activity was reduced in the frontal and temporal cortex of patients with AD and demented and non-demented patients with PD (table). Cortical maximal densities of

Table Mean (SEM) maximal nicotinic receptor binding in the cortex

	Control (n = 10)	AD (n = 10)	Control (n = 10)	PD (n = 10)
Age (year)	79.8 (2.4)	82.7 (2.3)	73.1 (5.5)	73.7 (2.5)
Death to brain removal (h)	40.5 (6.0)	42.6 (6.2)	19.6 (2.4)	18.1 (2.7)
CAT activity				
in frontal cortex	4.0 (0.7)	1.8 (0.4)*	4.2 (0.4)	2.3 (0.4)*
in temporal cortex	4.4 (0.3)	1.4 (0.3)*	4.5 (0.2)	2.5 (0.3)*
(-)-[³ H]-nicotine binding				
in frontal cortex	21.7 (1.3)	11.0 (1.4)*	23.1 (1.1)	12.2 (1.3)*
in temporal cortex	26.9 (1.1)	11.5 (1.2)*	25.0 (1.1)	13.3 (0.9)*

Wilcoxon's rank-sum test: *p < 0.05.

CAT activity in nmol/h/mg protein; nicotine binding as B_{max} in fmol/mg protein.