EFFECTS OF DEPRENYL (SELEGILINE) ON COGNITION AND AFFECT IN PERSONS WITH IDIOPATHIC PARKINSON'S DISEASE

A thesis
submitted in partial fulfilment
of the requirements for the degree
of
Master of Science in Psychology

by

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University of Canterbury
February 1992

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Acknowledgements

Many people have made the clinical trial of deprenyl and this thesis possible.

I am grateful for the assistance of my supervisor Dr John Dalrymple-Alford for his guidance and the time he has given throughout the entire investigation. My heartfelt thanks also to Professor Ivan Donaldson, Consultant Neurologist Christchurch Hospital, for giving me the opportunity to conduct this study, for willingly referring his patients and for his support in designing the protocol. I have learned a great deal about Parkinsons Disease from him and his patients.

I would also like to acknowledge the following people;

Doctors Sean Riminton and Allison Ross who performed the motor assessments, wrote numerous prescriptions and were available at short notice for the patients who needed to be seen.

Michael Jamieson, for his assistance with the recruiting and testing of the controls, typing, assistance with the statistical analysis and for his on-going support and encouragement.

Jane Jeffries and Lorraine Moser from Reckitt and Colman Pharmaceuticals for arranging the supply and delivery of the medication through Farmos Group Limited, Finland and for the financial assistance with the costs incurred in the project.

Diana Jackson, Health Educator for the Parkinson's Support Group, Christchurch, New Zealand for her assistance in recruiting subjects.

Sue McKenzie from the Pharmacy Department at Christchurch Hospital for the randomising and dispensing the medication, often at short notice.

Michelle Scott from the medical records department, Christchurch Hospital.

Judith Sutherland, Judith Campbell and Chris Donaldson for their assistance with organising appointments and liaising with the subjects.

Dr Adriaan Hovestadt, for sending his thesis and clarification of the procedure for the Rod Orientation Test; and Selwyn Taylor for its construction.

Last, but not least, I would also like to thank all the subjects who generously gave their time to participate in the research. Those with Parkinson's and their families have taught me a great deal about living with a chronic disability and it has been privilege to work with them.

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ABSTRACT

Ten milligrams (mg) per day of deprenyl (selegiline), a relatively new selective monoamine oxidase inhibitor (MAOI) type B is believed to reduce the rate at which motor symptoms in idiopathic Parkinson's Disease (IPD) progress (Parkinson's study group, 1989). It has also been suggested to have a positive impact on cognitive deficits in persons with IPD. This claim was investigated in a double-blind placebo controlled trial with 23 dementia-free mild to moderate IPD subjects, eight of whom had established IPD requiring levodopa therapy. The remaining 15 subjects formed a second group of more recently diagnosed early IPD. Ten control subjects were used for comparative purposes on the baseline cognitive and affective measures. Subjects with IPD were significantly more depressed than controls, and demonstrated impairment on the Wisconsin Card Sorting Test, and a trend towards reduced immediate recall of prose. The results of this study indicated that eight weeks of deprenyl therapy did not result in improved motor, cognitive or affective functioning. The lack of improvement is consistent with Heitanen (1991), but conflicts with claims made by Lees (1991) and Portin & Rinnie (1983) who suggest that deprenyl improves cognitive functioning in IPD. Instead, deprenyl's effect may be to delay cognitive deterioration in early untreated IPD (Como, 1990).

1. INTRODUCTION

Primary or Idiopathic Parkinsons Disease (IPD) is a chronic neurodegenerative disorder, with an onset that typically occurs between ages 50 to 69. James Parkinson (1817) first described this disorder in his "Essay on the Shaking Palsy" which detailed the major motor signs in six cases, and suggested that intellect and emotions remained preserved (Hovestadt, 1990). In 1892, the French neurologist Charcot used the term "maladie de Parkinson" (Parkinsons Disease) because he believed its former titles "shaking palsy," and "Paralysis Agitans" did not describe the condition adequately (Heinonen, 1989). The cardinal signs and symptoms of IPD include resting tremor, rigidity, impaired righting and postural reflexes, slowness and delayed initiation of movement (bradykinesia). The range of symptoms associated with IPD which may manifest themselves during the course of the condition include shuffling gait, loss of finger dexterity, micrographia (small writing), facial masking, drooling, loss of volume and clarity in speech, loss of arm swing and autonomic nervous system (ANS) dysfunction. The motor deficits in IPD are known to result from a deficiency in striatal dopamine due to the reduction of "dopaminergic neuronal projections from the substantia nigra (pars compacta) to synapses in the caudate and putamen" (LeWitt & Galloway, 1990 p63). The major dopamine pathways effected by IPD are shown in Figure 1.0. The key pathological and histological features includes "..degeneration, gliosis and Lewy body formation in the substantia nigra" (Growdon, Corkin & Rosen, 1990. p371).

Although IPD is diagnosed by its clinical appearance the search continues for a neurochemical marker to aid in diagnosis. To this end, various substances throughout the central nervous system (CNS) are being evaluated in PD patients (relative to normal controls). These substances include Cerebro Spinal Fluid (CSF) levels of the Dopamine (DA) metabolite Homovanillic Acid (HVA), the Serotonin metabolite 5-HIAA , the norepinephrine metabolite MHPG, and several CSF neuropeptides, amino compounds, enzymes, proteins, antibodies and immunoglobulins (LeWitt & Galloway, 1990). Despite promising leads, major progress toward a biochemical marker is yet to

be made and the condition is generally distinguished from others within the Parkinsonian Syndrome by a detailed history and the absence of other secondary disorders which may mimic IPD, such as toxic poisoning. Diagnosis of IPD is one of exclusion (Jankovic et al, 1990).

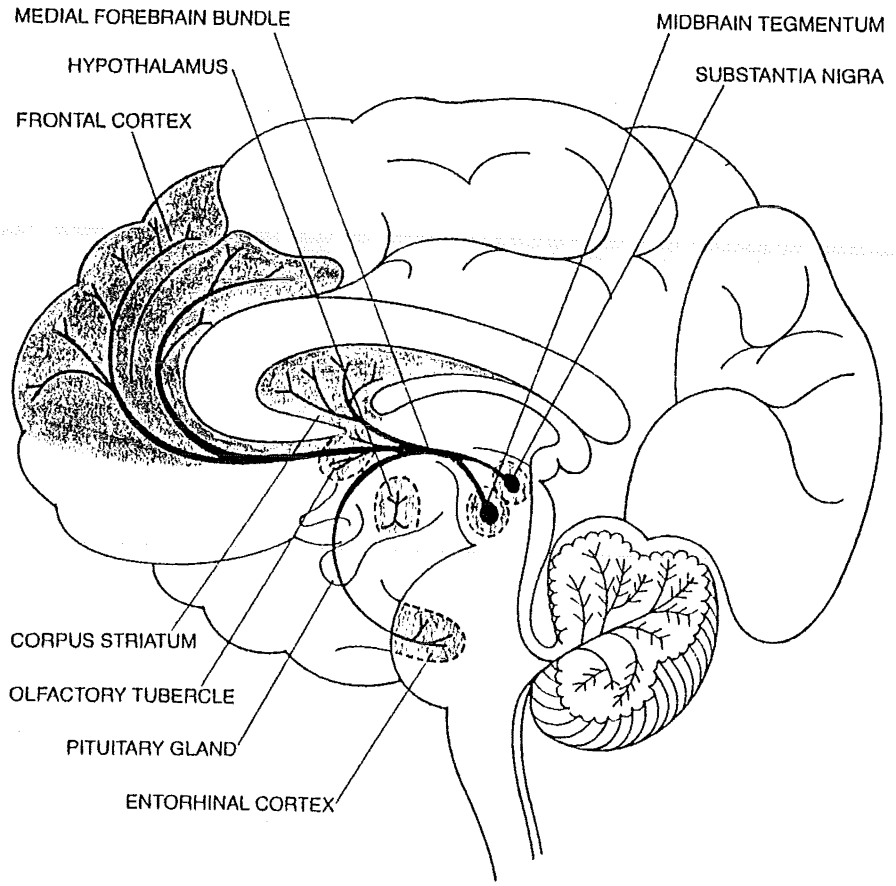


Figure1.0. Dopamine pathways in the human brain are shown schematically. The neurons that contain dopamine have their cell bodies clustered in two small regions of the midbrain: the substantia nigra and the tegmentum (Iversen, 1979 p125).

James Parkinson's essay indicated PD left the senses untouched but by the late 19the century this belief was challenged as evidence mounted of associated cognitive deficits (Hovestadt, 1990). It is now acknowledged that IPD may affect specific aspects of cognitive and affective functioning, and that these deficits may remain distinct from a generalised global dementia or senile dementia of the Alzheimer type (SDAT) (Mayeux,

1989). More specifically, there is growing recognition that a percentage of people with IPD may also experience depression, difficulty shifting set, visuospatial impairments and memory impairments (Brown & Marsden, 1988a).

Drug therapy remains the cornerstone of motor symptom management whereas the cognitive symptoms have not yet been specifically targeted by pharmacological preparations. In some cases the cognitive deficits may be equally as disabling as the more obvious motor deficits. The present thesis investigated whether a low dose (10 milligrams per day) of deprenyl, a relatively newly introduced drug for IPD patients, has a positive effect on cognition and affect in persons recently diagnosed as suffering from IPD and those with established IPD who are currently receiving levodopa medication.

1.1 Aetiology of Idiopathic Parkinson's Disease.

The cause of IPD has yet to be discovered but present evidence suggests that the dopamine depletion is due to the influence of toxic compounds present either in the external environment,or intracellularly (Poirier, Kogan & Gauthier, 1991). However numerous hypotheses exist as to the causation of IPD.

1. Random Process Hypothesis - (also referred to as accelerated ageing).

Advocates of this hypothesis suggest that IPD is the result of cumulative actions within life such as toxins, virus and brain injury (Poirier et al., 1991).

2. Neurotrophic Factor (NTF) Deficiency Hypothesis.

This theory suggests substantia nigra (SN) neurones are impaired by the inability of target striatal cells to provide sufficient dopaminergic neurotrophic factors. NTF's are believed to be particularly important for neurones with long axonal processes (Rossor, 1981).

3. Defective DNA Repair Mechanism Hypothesis.

This postulates that mutations in early embryogenesis lead to unrepaired DNA damage in the neurones (Poirier et al., 1991).

4. Genetic Factors.

This model suggests that people can inherit "susceptibility" to PD via genetic factors. However, studies of monozygotic twins have yielded low concordance rates (Marsden, 1987), but the discovery of a dysfunctional enzyme has added to the possible value of genetic models (Golbe, 1991).

5. Viral Aetiology.

Viral antibody titre studies suggest IPD may result from a rare complication of a systemic infection (Poirier et al., 1991).

6. Environmental Toxic Compounds.

This hypothesis proposes that IPD is triggered by the presence of environmental toxins, such as N-methyl-4-phenyl, 1,2,3,6-tetrahydropyridine (MPTP). Within the human body this compound is metabolised into a toxic substance, MPP^+ (Pyridinium-ion), which causes a Parkinsonian syndrome with many similarities to IPD, that can be managed with medication, but not reversed. This compelling hypothesis suggests that those exposed to industrial compounds or toxins similar to MPTP could be at greater risk of developing IPD. The MPTP findings inspired the line of research that lead to the use deprenyl in IPD sufferers (Heinonen, 1989).

7. Nutritional Factors

It has been suggested that diet may contribute to the cause of IPD and is therefore related to environmental factors. Evidence for this proposal is drawn from investigations in Guam, where existence of a parkinson-dementia-motor neuron disease complex has been linked to the consumption of cycad, which has cytotoxic effects and produces free radicals. Theoretically, diets lacking free radical scavengers (vitamin E, vitamin C,

selenium, methionine and beta carotene) may leave people vulnerable to developing PD (Nutt & Carter, 1990). Because of the delay between inadequate nutrition and the appearance of clinical symptoms, nutritionists suggest that preventative measures are probably useful.

8. Assault Theory.

Because the dopamine depletion is 80% below normal before the symptoms of IPD are evident, it is postulated that an assault leads to the loss of dopamine neurones and has caused the emergence of symptoms (Heinonen, 1989).

9. Psychological factors.

In the 1940's, psychological factors were suggested to be the cause of motor deficits in the IPD and it was felt that the abnormality of the posture represented a subconscious attitude of defence or hostility, and that Parkinsonism had developed in connection with the psychological condition of modern culture (Rogers, 1986). There is a small body of evidence suggesting that premorbid personality may predispose to IPD. One study of 30 young onset PD subjects noted that the PD group had significantly greater levels of personal injury and bereavement in childhood, were more cautious, conventional, rigid and unassuming than a matched group of subjects with Rheumatoid Arthritis and normals (Eatough, Kempster, Stern & Lees, 1990)

1.2 Epidemiology: Incidence and Prevalence

The incidence of IPD is estimated to be 1 in 1000 of the population under 60 years of age (Macleod, Edwards & Bouchier, 1987). For those over 60 incidence and prevalence rates rise sharply and in the 70 to 79 year old age range estimates of annual incidence vary from 53 to 299, and prevalence rates from 300 to 800 per 100,000 of the population. Young onset IPD (age 35-39) occurs at a rate of 0.15 per 100,000, which is a tenth of the incidence for the 60-64 age group (Golbe, 1991). IPD is found in every race but Africans and Asians have lower rates than Caucasians (Heinonen, 1989), but it does not appear to be more common in one gender than the other (Mayeux, 1990a).

Data from rural China indicate that fewer rural people develop IPD compared to urban centres. This is in contrast to rural Canada where rural subjects aged as young as 20 may have 18% reductions in substantia nigra neurons compared to their urban peers (detected in post mortems) (Thiessen, Rajput, Laverty, & Desai, 1990).

The incidence and prevalence of dementia in IPD is four times greater than in the general healthy population over 60 years of age, and five times greater for people over 70 years of age. Those with PD and dementia appear to have a later onset of motor deficits and develop a more malignant form of PD (Mayeux et al, 1988). The severity of the Parkinsonian condition and its prevalence attest to the pressing need to develop effective therapies and symptom management for sufferers.

1.3 Course and Prominent Physical Signs and Symptoms of IPD

Although IPD has a typical course it is by no means a homogeneous disorder. A recent study involving 800 subjects suggested that distinct subgroups may represent different pathologies (Jankovic et al, 1990).

1. Early vs. late onset: (early onset is classified prior to 40 years of age; late onset after 70 years of age). Early onset subjects have a slower progression, whereas late onset subjects deteriorate more rapidly.

2. Benign vs. malignant: Malignant PD appears to progress at a significantly faster rate whereas those with the benign form tend to be younger (mean age of 54 years). The malignant type tend to involve Postural Instability and Gait Deformity (PIGD) symptoms at onset.

3. Tremor vs. PIGD: These groups represent the initial predominant symptom. Those with PIGD tend to be more impaired in cognition, affect and activities of daily living (ADL) compared with those whose predominant initial symptom is tremor. However

such groups need to be regarded with caution as it may be age and the reduction of neuronal plasticity that influences the manner in which IPD manifests itself.

For those with tremor as their first symptom, the condition usually begins asymetrically, with a slight tremor in one hand or leg. For those with PIGD, the most obvious early symptom may be hypokinesia (slow movement) or muscular rigidity. The latter have diminution of movement, an immobile facial expression and general slowness with retardation of the spontaneous movements required for postural alignment. Although controlled by drugs, the condition continues to deteriorate and at its end point a person with IPD is identified by a rhythmic limb tremor, stiffness and slow movement, a stooped posture and masklike face. Although never totally paralysed, the fully developed IPD sufferer becomes weakened by the changes in muscle tone. Due to an inability to harness the appropriate postural reflex mechanisms there is a tendency to falls and a characteristic festinating gait. Despite greatly reduced mobility, those with even the most severe symptoms can temporarily move in an almost normal and efficient manner when they are placed in life threatening or fear inducing situations (Wilson et al. 1991a). Aside from the major motor and postural deficits, IPD can also lead to muscle pain and cramps, loss of finger dexterity, micrographia, loss of diction and volume in speech, general fatigue, drooling, loss of arm swing, dysphagia, paraesthesia and drowsiness (Hoehn & Yahr, 1967).

If the ANS is involved, the following may occur: seborrhea (a characteristic greasy skin); siolorrhea (excess saliva) leading to drooling, difficulties with micturition (frequency and urgency); changes in gastrointestinal functioning, especially constipation; food aspiration, secondary to disordered swallowing; and in extreme cases a pseudo-intestinal obstruction may occur. Cardiac arythmias are rare in PD and are generally iatrogenic. Orthostatic hypotension is seen commonly in PD but again is probably secondary to medication. Many of the ANS symptoms may be due to causes other than PD.

Young or early onset PD has been studied in an effort to detect differences between the varying age of onset. Young onset PD is usually considered to occur between 21 to 40 years of age. Juvenile Parkinsons is that which appears in those under the age of 21. Investigations in the 21-40 year old group indicate some difference from the older onset age group. Young onset PD subjects frequently have facial dystonias, (43% in one study compared to 4% in older onset subjects) as an early or initial symptom, tremor and PIGD tend to occur later (adults tend to have more tremor or PIGD) (Giovanni et al, 1991). Young onset PD progresses more slowly and as mentioned earlier, may be more benign. It has been suggested that dyskinesias (motor fluctuations and involuntary movements) are more prevalent at 3-5 years post diagnosis in the young onset PD group (possibly due to levodopa) than in matched pairs in the older age group (Cedarbaum, Gandy & McDowell, 1991). Pathological studies of Lewy bodies show no significant difference between the young onset PD and later onset. However, most researchers regard young onset PD as the same as it older-onset counterpart (Golbe, 1991; Gershanik & Nygaard, 1990; Quinn, Critchley & Marsden, 1987).

1.4 Psychological Effects

Cognitive defects inherent in PD are now acknowledged to affect up to 30% of IPD patients. A lowering of affect, either reactive or endogenous in nature, may also occur in a significant percentage of IPD patients. Controversy is currently focussed on the anatomical and neurochemical basis of these deficits (Rogers, 1986) and their incidence and prevalence (Mayeux, 1988).

Variously titled as bradyphrenia, psychic akinesia, and subcortical dementia (Rogers, 1986), a slowing of cognitive process in IPD has been claimed. The term subcortical dementia was proposed by Albert, Feldman & Willis, (1974) to describe a generalised slowing of thought processes in the absence of intellectual deterioration. Albert et al (1974) pointed out that changes in the subcortical matter in the frontal lobe regions lead to a different type of impairment than that caused by cortical pathology.

Cortical dementias tend to be characterised by aphasia, apraxia and agnosia, as in SDAT, whereas subcortical dementias are distinguished by slowing of intellectual functioning, depression and apathy (Brown & Marsden, 1988). The cortical/subcortical distinction is not universally accepted because there is evidence that the brain functions in a more integrated manner than these classifications would suggest (Brown & Marsden, 1988). Brown and Marsden's (1988) review of the existing neuropsychological evidence concluded that the labels cortical and subcortical dementia should only be used when individuals present with the classical features of these categories, until further evidence can conclusively support such a distinction. Whatever the outcome of this theoretical debate, a significant portion of IPD patients do develop dementia and/or distinctive cognitive deficits. From the evidence presented thus far there appears to be a continuum with dementia being the extreme end and specific, isolated cognitive deficits occurring at the other end. Gauging the specific percentage of these deficits is difficult because a variety of methodologies and definitions of dementia have made comparisons among studies almost impossible (Xuereb, Tomlinson, Irving, Perry, Blessed & Perry, 1990). Brown and Marsden (1984) suggested that the estimation of 30% dementia in PD patients is unjustified, and that toxic effects of drugs and depression, mania and vitamin deficiencies may all present as pseudo dementia, and proposed that after excluding artherosclerotic and akinetic types of PD the figure is probably 15-20%.

Distinguishing where IPD patients fall on the postulated continuum is difficult because it has been suggested that the DSMIII-R criteria for dementia are inappropriate for IPD because they focus on factors that are dependent on intact motor functioning (Hovestadt, 1990). Many studies have used the criteria of Benson & Cummings (1983) as an alternative, but again they have been criticised for the reason cited above. One critical question is whether the dementia in IPD is the result of a co-existing SDAT, or is dissociable from SDAT on histological and neuropsychological grounds. SDAT is characterised by neurofibrillary tangles and neuritic plaques in the neocortex. Xuereb at al (1990) autopsied 38 subjects with IPD in an effort to determine if the two conditions

co-exist: 22 did not show histological changes consistent with SDAT, 13 had some evidence, but this was consistent with their age, three cases displayed both Lewy body and histological changes consistent with progressive dementia; one had evidence of PD and Picks disease; and two displayed evidence of SDAT and PD combined. Subcortical changes consistent with Alzheimer dementia have been detected by several groups of researchers, and include: loss of cholinergic neurons from the nucleus of Meynert in the basal forebrain, and reduced levels of choline acetytransferance in the neocortex. Findings of reduced neurotransmitter substances have been implicated in IPD but their relationship to cognitive deficits is yet to be established (Agid et al, 1990). Determining whether dementia is inherent in IPD, or coexists as a result of non-dopaminergic lesions remains to occur. Nevertheless, people with IPD do demonstrate various deficits in the cognitive and affective domain, including depression, difficulty shifting set, impaired visual perception and memorial functions. as discussed in sections 1.4.1 to 1.4.4.

1.4.1 Executive Functions

Executive functions is a term used to describe various higher order cognitive operations presumed to depend on the integrity of the frontal lobes (Cooper at al, 1991). These various cognitive operations include: set formation," "shifting set," "temporal ordering," "sequencing," and "planning ability," and are characterised by the cognitive demands they place on a person to find solutions to novel problems (Taylor, Saint-Cyr & Lang, 1990). Suggestions that executive functions are impaired as a result of IPD and not due to generalised dementia, are drawn from investigations such as Lees & Smith (1983) in which newly diagnosed IPD subjects performed relative to matched controls on the WAIS and the New Adult Reading IQ Tests, but were inferior to controls on tests of executive functions.

Executive functions are usually assessed by card sorting tests, such as the Wisconsin Card Sorting Test (WCST) and verbal fluency tasks. Taylor et al (1988) also

consider learning supraspan word lists, a test of executive functions, and Morris, Downes, Sahakian, Evenden, Heald & Robbins (1988) used the Tower of Hanoi Task to assess "planning." It appears that computer tasks are increasingly being employed to assess executive functions and the work of Tamaru & Yanagiswa (1990) is one example of the nature of computer assessments.

Verbal fluency assessments such as word and category generation tasks have been used by Matison, Mayeux, Rosen & Fahn, (1982) and Girotti, Carella, Grassi, Solveri, Marono & Caracenti (1986), with IPD subjects, and both groups of investigators reported deficits relative to controls. Lees & Smith (1983) used the letters D, B, M to assess verbal fluency in 30 mild IPD subjects and found that the IPD subjects generated fewer words, perseverated more frequently on the third letter, but performed in a similar way to controls on D and B. Gurd, Ward & Hodges (1990) used twelve different measures of verbal fluency and noted that IPD subjects were significantly impaired on single and alternating verbal fluency. However Miller (1985), and Taylor, Saint - Cyr, & Lang (1986a) found no impairment in IPD subjects using the letters F, A, S. Gotham, Brown & Marsden (1988) found IPD subjects were impaired on a verbal fluency task when "off" levodopa, but were able to complete it successfully when "on." These mixed findings suggest verbal fluency tasks do not provide conclusive evidence of an executive deficit in IPD subjects, possibly because of confounding variables such as age and depression.

A test sensitive to frontal lobe functions (Milner, 1963), the Wisconsin Card Sorting Test (WCST), is also frequently employed and seems to provide less equivocal results in IPD subjects. However, there are several different versions and methods of scoring the WCST, making it difficult to compare investigations. Nevertheless, the majority of studies using the WCST detect a deficit in IPD subjects relative to controls. Bowen, Kamienny, Burns & Yahr (1975) were one of the earliest investigations to use the WCST and they noted that some IPD subjects were unable to complete a single category, and many found it difficult to shift from one category to the next. Lees &

Smith (1983) reported mild IPD subjects made more perseverative errors and completed fewer categories compared to controls on Nelson's (1976) version of the WCST. Taylor et al (1986a) used the 128 card version of the WCST and reported IPD subjects achieved fewer categories and required more trials to achieve the first category. Additionally, IPD subjects tended to verbalise the correct strategy but failed to execute it when selecting where to place the card. Cooper et al (1991) also noted IPD subjects sort more cards before achieving the first category and suggest that IPD leads to difficulty forming "sets." However, Cools et al, (1984) propose that the deficit lies in "shifting set," and encompasses cognitive, motor, verbal and figural modalities. Levin, Llabre & Weiner (1989) reported their IPD subjects could "shift set," but made more perseverative errors than controls, whereas Litvan, Mohr, Williams, Gomez & Chase (1990) noted many subjects failed to achieve a single category. Failure on various measures of the WCST has been found in a majority of studies, except that of Mohr, Juncos, Cos, Lituan, Feilio & Chase, (1990), possibly because their IPD subjects were all highly educated and functioning well in conceptually demanding occupations.

There is thus clear evidence that executive functions, as measured by the WCST, are compromised in IPD all studies except that of Mohr et al. (1990). Having established the deficit exists, research is now directed towards explaining why IPD subjects are impaired on the WCST.

Brown & Marsden (1988b) have investigated what they have termed "the phenomenon of set" using a reaction time paradigm. Sixteen IPD subjects and controls were required to make left or right discriminations under two special perspectives on a computer and results indicated that the IPD subjects were not impaired relative to controls in that task, but continued to be impaired on the WCST. Brown & Marsden (1988b) postulated that failure in the WCST was the result of impaired "internal control" and the IPD subjects had succeeded on computer generated task because it provided external guidance. Taylor et al. (1986a) and Brown & Marsden (1988b) suggest that

tasks dependent on the efficient generation of self-directed task-specific strategies, such as WCST, are impaired in IPD.

In an effort to look at the link between impairment on the WCST and dopamine, Gotham, Brown & Marsden (1988) looked at performance on the WCST when subjects were in "on" and "off" states of motor functions, by withholding levodopa treatment. No significant difference was noted between "on" and "off states, and IPD subjects were impaired relative to controls in both states again supporting the suggestion that performance on the WCST may not be dependent on dopamine levels.

Taylor, Saint - Cyr, & Lang (1987) noted subjects with varying responses to Levodopa performed at the same level as subjects not receiving levodopa, and significantly worse than controls on the WCST, providing further evidence that executive functions may not be related to severity of motor symptoms. Furthermore, Blonder, Passafiume, Keefe, Rogers, Marrow & Kim, (1989) noted IPD subjects with left sided symptoms sorted fewer cards correctly on the WCST than subjects with right hemiparkinsonism, a finding consistent with investigations into other neurological conditions leading to right hemispheric lesions and cerebral blood flow studies (Robinson, Heaton, Lehman & Stilson, 1980).

Taylor et al. (1986a) have developed the "outflow model" to account for impairment in terms of compromised frontal lobe functions, and suggest that they are secondary to disturbed outflow from the basal ganglia. The model also accounts for the massive subcortical support the frontal lobes receive in processing "familiar structured, and rule - bound behaviour" and predicts the loss of "internally guided behaviour" a cardinal feature of the motor, cognitive and affective aspects of IPD (Taylor et al, 1986a p877).

1.4.2 Memory

Prior to the advent of specific investigations into memory functions in IPD patients there was anecdotal evidence of mild forgetfulness and a tendency to repetition (Lees & Smith, 1983). Attempts to clarify the exact nature of the presumed memory deficits have produced an increasing number of investigations, which are gradually being conducted on dementia-free homogeneous groups, some of whom have exceptional professional standing (Mohr et al, 1990). Common evaluations include the Wechsler Memory Scale (WMS), subtests of the Wechsler Adult Intelligence Scale (WAIS) and the Rey Auditory Verbal Learning Test.

Results from many studies suggest that the pattern of memory deficits is selective, and that IPD subjects do not fail on all memory tasks. For example, in tests of logical memory IPD subjects recall as much in delayed recall as they do at immediate recall (Heitanen & Teravainen, 1986). The impairment is related to reduced immediate registration or retrieval, not accelerated forgetting (Cooper at al, 1991). The investigations of Taylor et al. (1988), Sullivan & Sagar (1991) and Sullivan, Sagar, Gabrieli, Corkin & Growden, (1989) support this view.

However there are some inconsistent results in delayed memory investigations. Levin, Llabre & Weiner, (1989) for example found long-term recall to be impaired, although compared to controls the proportion of decline was similar. In tests of immediate recall such as the digit span, IPD subjects generally perform within normal limits (Hietanen & Teravainen, 1988). Lees & Smith (1983) used a Two-Choice Recognition Memory Test for Words and Unknown Faces with a 30 drug-free mild PD patients and 30 healthy matched controls. No significant differences were noted between the two groups on this measure. More recently Cooper et al, (1991) studied 60 untreated subjects and 37 controls and found deficits in immediate verbal recall and working memory assessed via the WMS, the Rey-Osterrieth Figure and Brown-Peterson Task. Results indicated IPD subjects do have inferior performance on logical memory, digit span (backwards), visual reproduction and associate learning subtests on the

WMS. The Brown-Peterson Task also indicated an inferior performance in IPD subjects. Mohr et al. (1990) also noted that those tasks that demand more effort, such as tests of logical memory, are generally impaired. Mortimer, Pirozzolo, Hansch & Webster, (1982) suggested that overlearned, impermeable long-standing cognitive operations remain preserved, and are not influenced by the IPD, whereas more "fluid" functions are compromised.

A deficit in "working memory" has been proposed more recently. The working memory model classifies memorial functions into the controller, called the central executive, and a series of sub-systems, including the articulatory loop, which is a system responsible for the retention of short term verbal information (Baddeley, 1986). Using the working memory model, Morris et al. (cited in Brown & Marsden, 1988) assessed short term memory using tasks that required spatial memory span. Although no deficits were noted in IPD subjects it was again suggested that more effort demanding tasks such as the Brown-Peterson Technique would reveal deficits in IPD subjects.

Other components of memory such as long-term recall, and long-term recognition, remote memory and procedural skill learning, have also been investigated in IPD subjects, frequently comparing PD with SDAT. At this stage, there are insufficient studies to be conclusive about the specific nature of such functions but evidence of dissociations between the two conditions is beginning to emerge (Brown & Marsden, 1988; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988).

The relationships between dopamine levels, motor disability and memory functions are far from clear. Suggestions that cognitive impairments are the result of non dopaminergic lesions (Dubois, Pillon, Lhermitte & Agid, 1990) has led to investigations examining relationships between motor symptoms and memory functions. Indeed, levodopa seems to have had little effect on memory in IPD subjects (Pillon et al, 1989b; Rafal, Posner, Walker & Friedrich, 1984). However, these findings contrast with

the work of Mohr et al. (1989) who found levodopa treatment provided selective and modest improvement in episodic memory function (defined as memory that requires cognitive capacity and sustained effort). Mohr et al. (1989) reported levodopa improved scores on delayed episodic memory, whereas tests of verbal immediate recall were the same on and off levodopa.

1.4.3 Visuospatial Functioning

Although controversy exists regarding the nature, prevalence and severity of a specific visuospatial deficit in IPD, (Levin, Llabre, Ansley, Weiner, & Sanchez-Ramos, 1990), investigations continue to demonstrate decrements in performance of IPD subjects relative to matched controls on a variety of tasks. One example is Hovestadt's (1990) investigation using the Rod Orientation Test (ROT), a simple device devised by De Renzi, Faglioni & Scotti, (1971), on 44 newly diagnosed drug naive, dementia-free IPD subjects. Forty three of the subjects were severely impaired on the test compared to the normative data (Meerwaldt & Van Harskamp, 1982), and they did not improve following levodopa (Hovestadt, De Jong, & Meerwaldt, 1988).

Levin et al (1991) studied 183 IPD subjects at varying degrees of disease duration and cognitive functions. Their findings indicated that both dementia and disease duration contribute to the decline in visuospatial abilities, but in a somewhat complex manner. Of the six visuospatial tests used facial recognition was able to indicate a decrement, even in relatively early PD subjects, which was not related to age. Danta & Hilton (1975) assessed 66 IPD subjects ability to judge visual vertical and horizontal perception, and noted that subjects varied considerably on the task, but that 19 of the subjects performed three standard deviations below the normal controls. Boller, Passafiume, Keefe, Rogers, Marrow & Kim, (1984) employed tasks minimising motor function in 30 IPD subjects at grades I to III on the Hoehn & Yahr Scale and they noted a deficit in angle perception that could not be related to intellectual decrements because on standardised intellectual tests, the subjects performed relative to matched

controls. Evidence also comes from the consistent discrepancy between verbal and performance scales on the WAIS (Brown & Marsden, 1986) in IPD subjects.

Findings of visuospatial deficits have sometimes led to suggestions that these deficits are due to other factors such as reduced ability to switch set (Brown & Marsden, 1986), a deficit in the visuospatial subsystem of working memory (Bradley, Welch & Dick, 1989), a slowness in executing movement (Stelmach, Phillips & Chau, 1989), reduced attention span (Morris et al, 1988) or reduced sequencing ability (Canavan, Passingham, Marsden, Quinn, Wyke, & Polkey, 1990; Girotti, Soliveri, Carella, Geminiani, Aiello & Caraceni, 1988).

Added to this are claims that the tasks used to assess visuospatial functioning in IPD subjects, such as route walking tests, (Bowen, Hoehn & Yahr, 1972), Tower of Hanoi task (Morris et al, 1988) and computer tasks (Sharpe, 1990) are all dependent on factors beyond the purely visuospatial. Tower of Hanoi and route walking require motor skills and some computer based tasks have included reaction times, thus biasing the IPD subjects who tend to be slower on such tasks. Computer tasks are generally two dimensional and this may not represent a true assessment of the visuospatial functioning required to manage the three dimensional world in which IPD subjects must cope. Many studies have treated IPD subjects as a homogeneous group and failed to control for the subjects age, duration of IPD subjects, and the presence or absence of dementia.

It has been suggested that controversy in visuospatial research is due to problems with interpretations and failure to define and specifically limit which visuospatial functions are actually being measured. Boller et al. (1984) and Bradley, Welch & Dick, (1989) point out that visuospatial research in IPD lacks an appropriate model and investigators have been assessing a range of functions that are encompassed by the broad category visuospatial. In an attempt to be more specific and precise, the classification system and definition of visuospatial deficit is defined by Boller

et al. (1984) as " ...difficulty in appreciating the relative position of stimulus-objects in space, difficulty in integrating those objects into a coherent spatial framework, and difficulty in performing mental operations involving spatial concepts..." (Boller et al, 1984 p485).

Task requirements seem to appear to confound results. Consequently Brown and Marsden (1986) advocate the use of simple tasks for studying visuospatial functioning in IPD subjects. Studies using more elementary tasks such as the ROT have claimed a deficit in visuospatial functioning Hovestadt (1990).

1.4.4 Affect

Depression is frequently encountered in IPD, (Huber, Freidenberg, Paulson, Shuttleworth, & Christy, 1990; Robins, 1976), and estimates of incidence and prevalence vary from 20% to 90% (Mayeux, 1989). Inappropriate selection criteria, heterogeneous populations and biased controls, have contributed to the varying estimates of depression in IPD. The cause of depression in IPD has yet to be clarified. Some groups suggest that depression is organic ie: endogenous, and occurs as the result of structural, and/or biochemical changes in IPD (Mayeux, Stern, Cote & Williams, 1984; Wolfe et al, 1990). Other groups propose it is a reaction to the diagnosis and occurs as an adjustment disorder (Taylor et al, 1986). However according to the DSM III - R criteria adjustment disorder is rarely diagnosed in IPD patients (Mayeux, 1990a). The reasons for this dichotomy relate to uncertainty about the natural history of depression in IPD (Mayeux, 1990a). Suggestions that it is secondary to the anti-PD medications have some support however counter evidence is also available (Mayeux, 1990a).

In some instances depressive features pre-date the emergence of motor symptoms and researchers have wondered if depression can pre-date the movement disorders, or if a combined affective and motor disorder is a subtype of IPD (Santamaria, Tolosa, & Valles, 1986). Some groups have attempted to find a

relationship between cognitive deficits and depression (Starkstein, Preziosi, Berthier, Bolduc, Mayberg & Robinson, 1989). or motor symptoms (Starkstein, Bolduc, Mayberg, Preziosi & Robinson, 1990a). Links between the severity of depression and duration of symptoms have been noted (Huber et al, 1990). Added to this, is a host of methodological difficulties. As yet, there is no generally accepted, consistent definition of depression or tool for its diagnosis in IPD. Although quick screening tests such as the Hamilton's Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) are frequently used to detect depression, they are not specifically diagnostic and IPD patients may be misclassified on the basis of their cut off scores (Taylor et al, 1986b) which do not indicate the qualitative (behavioural) impact of depression (Taylor et al, 1988). The tests have been criticised for their content, because changes in sleep and appetite are not specific to IPD. Indeed they can occur in many conditions or in the absence of depression (Levin et al, 1988; Mayeux, 1990b). Symptoms of endogenous depression, such as anergia and psychomotor retardation are also part of IPD, but may occur in the absence of a lowered affect. Although some researchers have excluded such questions from screening tests, Robins (1976) and Starkstein et al. (1990b) suggest that this procedure may invalidate the tests. However this has not been investigated. Starkstein, Preziosi, Torrerter & Robinson, (1990b) suggest the current situation would be resolved by a specific guide to diagnostic criteria.

Despite limited consensus, several perspectives on causation are provided by biochemical models. The serotonergic hypothesis postulates that depression in IPD is due to degeneration of the serotonergic pathways. Support for this is based on findings of up to 50% reductions of the transmitters metabolite 5 - HIAA in IPD patients and depressed and suicidal patients (Mayeux et al, 1984). Additionally, up to 50% reductions in decarboxylase activity in the raphe nuclei and associated ascending pathways have been noted in IPD patients, possibly as a result of the down regulation to compensate for the reduced nigrastriatal dopamine (Mayeux, 1990a). One of the drawbacks of this model is that non-depressed people may lack 5 - HIAA and the role of the serotonin in motor function is not clear, nor has it been related to age, sex, duration

or severity of PD or levodopa treatment (Taylor et al, 1988). Mayeux (1990b) suggests a serotonergic deficit may be one of a number of pre-requisites that predispose IPD patients to depression. Alternatively, Taylor et al. (1986a) suggest degeneration of mesocortical pathways may lead to "...transmitter related influences affecting the prefrontal region via the interaction of disturbed nigrostriatal output..." (Taylor et al, 1986a, p289). However this group prefers a non-organic explanation for mood disorders and to this end they attempted to demonstrate short term memory deficits in IPD subjects akin to those found in endogenous depression. They found that the IPD subjects could be positively influenced by the surroundings and unlike people with endogenous depression, depressed IPD subjects moods would lift in a conducive environment. Taylor et al, (1986a) found they could "test through" lowered affect, to reveal normal performances in tasks assessing short term memory, unlike those subjects with endogenous depression who continued to display pseudo-dementia, despite the surroundings.

Rogers, Lees, Smith, Trimble & Stern, (1987) suggest that the links between dopamine levels and depression are limited. Their experiment comparing 30 endogenously depressed and 30 Parkinsonian subjects on a computerised digit symbol test noted that anti-Parkinsonian and anti-depressant medications had different effects. The depressed subjects improved on the task following treatment whereas the Parkinsonian subjects did not improve following dopaminergic therapy.

Studies focussing on the anotomical relationship between affect in IPD and motor symptoms have provided more conclusive findings. Starkstein, Preziosi, Bolduc & Robinson, (1990c) found that people with right motor symptoms (left hemisphere pathology) are more prone to suffer from depression than those with left sided motor symptoms. This finding is consistent with other anotomical lesions that lead to depression eg: brain injury, and signify the presence of biochemical and/or structural changes in the left basal ganglia. Menza et al (1990) argue multiple aetiologies cause depression in IPD which lends weight to some current proposals regarding causation.

2.0 PHARMACOLOGICAL TREATMENTS OF IPD

The early treatments for PD were somewhat barbaric by today's standards. James Parkinsons original essay suggested "....blood letting from the upper part of the neck followed by the induction of a purulent discharge from the wound...." (Comella and Tanner, 1990 p123). Plant extracts, including belladonna alkaloids (which contains atropine), hyposcyamine, stramonium and Jamestown weed have been used for their anticholinergic effect, but were plagued by side effects. Charcot proposed that belladonna alkaloids blocked parasympathetic overactivity. Gowers prescribed a combination of arsenic, Indian hemp (cannabis) and opium to control tremor. The cannabis has known anticholinergic and adrenergic properties. The beneficial effects of plants extracts led to the development of synthetic anticholinergics in 1946, which for many years was the major treatment of IPD (Comella and Tanner, 1990).

2.1 Anticholinergic Agents

Trade names: Artane (Tritexyphenidyl), Disipal (Orphenadrine), Cogentin (Benztropine Mecylate), Kemadrin and Artane (Procyclidine).

As the name suggests, this group of drugs alter the imbalance between striatal levels of dopamine and acetylcholine, by reducing cholinergic transmission (Heinonen, 1989). This leads to a reduction in tremor and rigidity, but is thought to have little effect on hypokinesia (Macleod et al, 1987). At a cellular level, they act by blocking muscarinic receptors and are generally prescribed early in the course of IPD for people who are younger, cognitively intact and present with tremor. Their limiting factor is side effects, including dry mouth, constipation, blurring of vision, dizziness, difficulty initiating micturition plus disruption of the body's temperature regulation system and their cognitive sequalae, memory impairment, confusion and dementia like features (Comella and Tanner, 1990). Consequently anticholinergics are not recommended for those with older onset IPD. Following the cholinergic hypothesis of memory impairment, their role has been re-assessed with respect to the treatment of IPD. The cognitive effects of anticholinergics were recently compared to those of amantadine in 52 dementia-free PD

subjects and contrary to earlier findings it was noted that both groups were comparable in a series of cognitive tests (Hovestadt, 1990). This suggests anticholinergics are relatively safe in dementia-free subjects and remain a useful option for treating the symptoms IPD; they are also an adjunct to levodopa and are proven to reduce foot dystonia (Wilson et al, 1991a).

2.2 Amantadine Hydrochloride (Symmetrel)

Amantadine (Symmetrel) was originally developed, are an anti-viral agent, and its benefit in IPD was accidentally discovered in 1969 (Heinonen, 1989). It is used as a second line drug and generally prescribed early in the course of IPD. Its mechanism of action is not entirely clear but it probably affects both pre- and post-synaptic structures. Pre-synaptically, it is thought to inhibit catecholamine release from dopaminergic terminals; post-synaptic actions include anticholinergic and dopamine receptor agonist effects, plus an arousing effect on the mechanisms in the reticular formation (Kulisevsky & Folosa, 1990). Amantadine is generally considered to have mild transient and reversible side effects including: constipation, anorexia, giddiness, light-headedness, livedo reticularis (skin discolouration), peripheral oedema, orthostatic hypotension, and at higher doses congestive heart failure and neuropsychiatric effects. As monotherapy, it tends to reduce akinesia and rigidity more predominantly than tremor, with little effect on cognitive function. Although useful as monotherapy in early IPD, as symptoms progress, it ceases to provide sufficient control, and thus other medications have to be added to gain control of motor deficits, especially tremor. Amantadine combines effectively with many anti-PD agents and potentiates the effect of dopaminergic preparations (Kulisevsky & Folosa, 1990). It is a useful precursor to levodopa and is used as monotherapy in approximately 1/2 to 2/3 of PD subjects until such time as motor symptoms are interfering with daily functions and greater control is required. Although a number of people use it as long-term monotherapy, its efficacy does diminish over time. Studies of the effect on cognitive functioning are not common and the few that exist indicate mental confusion and seizures as a rare side effect (Macleod et al, 1987).

2.3 Dopamine Receptor Agonists

Trade Name: lisuride (dopergin), bromocriptine (parlodel) and pergolide.

2.3.1 Bromocriptine

Bromocriptine is an ergot derivative first used in 1974 (Heinonen, 1989). (Ergot is dried sclerotium (Friel, 1977) the hard - thickwalled blackish mass formed by certain fungi such as rye). Dopamine receptor agonists stimulate the post-synaptic striatal dopamine receptor cells and are not dependent on pre-synaptic dopamine neurons. Two post synaptic dopamine receptors have been identified, D1 and D2, each with differential affinities for various substances (Pfeiffer and Murrin, 1990). Bromocriptine activates D2 receptors (Lieberman, 1990), and is used as monotherapy, and as an adjunct to levodopa. Early introduction of bromocriptine may reduce the likelihood of dystonias and dyskinesias later in IPD and extend levodopa's period of optimal benefit. Its advantage is to by-pass the erratic synthesis and storage of striatal dopamine (Lieberman, 1990). It is used in early PD, as monotherapy and improves symptoms in up to 65% of IPD patients but, like amantidine, its effect reduces over time, and levodopa needs to be added to regain symptomatic control. It is a frequent adjunct to levodopa for reducing dystonias, dykinesias, response fluctuations and long term levodopa related problems because of its synergistic action with levodopa. Effects on cognitive functioning are not well documented, but in subjects with advanced PD and dementia increased confusion has been noted (Lieberman, 1990). Side effects are the same as for levodopa and include: nausea, vomiting and orthostatic hypotension, but these are not common.

2.3.2 Lisuride

Lisuride (Revanit, Dopergin) like bromocriptine is also a dopamine agonist which may bind to D2 dopamine receptors, but there are qualitative differences between the two preparations and it is suggested that lisuride also binds to D1 agonists. Additionally it lowers proclactin levels and is used in conditions other than PD. As monotherapy, it is effective in treating rigidity and tremor, although less so than levodopa or a combination

of the two. Side effects include nausea and vomiting, sweating,bradycardia, drowsiness and orthostatic hypotension. There is a " tendency towards mental changes " (Horowski & Obeso, 1990) but in keeping with PD drugs, the cognitive effects are not well researched.

2.4 DOPAMINERGIC AGENTS - Levodopa (Madopar and Sinemet)

Ehringer and Hornykiewicz's (cited in Pletscher, 1990) discovery that striatal dopamine depletion caused many IPD symptoms led to attempts to replace endogenous dopamine. A year later researchers had developed ways of replacing the depleted dopamine and although this was a major breakthrough in controlling IPD symptoms, getting the synthetic dopamine across the blood brain barrier (BBB) in sufficient quantities, and minimising its effects outside the Central Nervous System (CNS) proved to be difficult. The addition of decarboxylase inhibitors assisted transport across the BBB and reduced peripheral effects. When introduced, levodopa was a breakthrough, and thought to be the cure for IPD (Pletscher, 1990), but within two or three years of levodopa treatment its effect and symptom control begin to wear off. Dosages were increased but at greater levels, side effects were prevalent including: cardiac arrythmias, othostatic hypotension, anorexia, nausea, vomiting, hallucinations, delirium and paranoia. Furthermore, higher dosages led to dykinesias and as the dosage wore off patients experienced sudden and unpredictable fluctuations (Kurlan and Shoulson, 1991). Levodopa preparations have been modified to avoid some of the dose related fluctuations and controlled release preparations are now available, to avoid such problems (Lees, 1990). Nevertheless, levodopa remains the most effective form of symptomatic therapy for improving rigidity, bradykinesia and postural disturbances, and, less so, tremor. The way in which it does this has yet to be fully explained. Its effects on the cognitive sequalae of IPD such as spatial disorientation are not well researched, but Hovestadt et al (1988) recently suggested that levodopa had no effect on subtle neuropsychological functions. Pillon et al, (1989b) noted similar findings with a visual

discrimination task. If levodopa has a positive effect on cognition in IPD it is probably only mild, and in the early stages.

2.5 ANTIOXIDANTS

Following the MPTP model of causation in IPD, scientists have attempted to inhibit the formation of free radicals. It is postulated that excessive, unstable free oxyradicals are produced by the oxidative deamination of dopamine, and these cause cellular damage. Vitamin E (tocopherol) is an antioxidant, which is known to protect cellular membranes from oxidation by free radicals. There is evidence, albeit limited, that supplementing diet with tocopheral may protect cell membranes from perioxidation (secondary to the presence of free radicals). In IPD, the use of vitamin E is thought to protect cell membranes from this destructive process, and thus reduce the rate at which the disease progresses (Factor, Sanchez-Ramos & Weiner, 1990). However a large multi-centre trial recently compared Vitamin E with deprenyl, a monoamine oxidase inhibitor, and found the latter a more protective agent in IPD subjects (Parkinson Study Group, 1989b).

3.0 SURGICAL TREATMENTS

3.1 Stereotactic Thalamotomy

Before levodopa, surgical correction of symptoms, especially tremor, was common. Surgeons had been lesioning IPD subjects in the globus pallidus region for some time, but in the 1950's lesions in the ventral lateral thalamus were shown to relieve tremor and rigidity without serious side effects (eg hemiplegia, memory deficits). Stereotactic thalamotomy aims at creating a lesion the pallidofugal pathways, which project into the ventral lateral thalamus and forms part of a circuit which extends from the cortex, to the striatum, to the pallidum ventral thalamic nuclear mass, and back to the cortex (See Figure 1.0 on page 2). The techniques for lesioning have been refined and surgeons now use low frequency electrical stimulation to locate structures responsible for tremor, prior to ablation. Although thalamotomy is still used in a small number of levodopa resistant patients, for whom unilateral tremor is the predominant symptom, generally such subjects are younger, and free from rigidity and bradykinesia. Results of this procedure fall along a continuum from poor to excellent. The procedure does not have a positive impact on cognition, gait disorders or speech disturbances and the effect is not likely be permanent nor does it alter the progression of IPD (Kelly, 1990).

3.2 Neural Transplantation

Neural transplantation is a relatively new treatment for IPD and much remains to be discovered. There are basically two types:

1) Autografts from the adrenal medulla cells.

2) Allografts from human fetal dopamine containing cells.

The procedure involves grafting chromaffin cells from the subjects own adrenal medulla, or developing ventral mesencephalon cells from a human fetus. The addition of nerve growth factor (NGF) to the cells aids the process of neuronal regeneration. Dopamine rich cells are placed adjacent to the striatum and if the transplant is

successful, axons grow and synapse with neurons in the striatal region. New neurones re-establish dopamine metabolism from between 7-50% more than prior to the procedure. Mixed and often only partially beneficial results have been found in humans, both with adrenal and fetal transplants (Bjorklund, 1991).

It is estimated that at least 25 clinical trials are now in progress, with varying designs and methods. None are randomised or controlled. It is early days for this method of treatment and conclusive findings are yet to be published. The benefits of these trials will be to refine and develop the techniques and reduce mortality and morbidity (Burns, Allen & Tulipan, 1990). Although they have been performed on animals (including mice, rats and monkeys), transferring the benefits to humans is less clear cut. Animals do not have IPD and their Parkinsonian-like lesions are usually the result of human interventions. Although animal models are an important aspect of developing neural transplantation, it is important that distinctions between people and humans be retained.

4. NON DRUG THERAPIES

In addition to pharmacological treatments, the day-to-day coping and management of IPD can be made easier by input from a multidisciplinary team. The goals of the allied health professionals are to assist the IPD sufferer and families to maintain quality of life and independence for as long as possible. Each discipline provides a different function to achieve this end.

Although not well researched, the importance of exercise in PD seems obvious, consequently physiotherapists teach IPD patients specific exercises that will increase range of movement, increase or maintain chest expansion, relaxation, assist with balance and prevent the development of contractures and phlebitis. The exercises aim to facilitate movement and involve rythmic, symmetrical movement. Therapists suggest they be done twice daily, when medication is at its optimal benefit. Physiotherapists may prescribe ambulatory aids if required (Melnick and Paulson, 1990).

Like physiotherapists, occupational therapists can offer advice, and provide specialist equipment to maintain independence and reduce risks (eg falling) in daily activities such as bathing and dressing. They are able to teach IPD patients alternative methods of doing daily activities and frequently visit patients in their homes to recommend appropriate environmental modifications to maintain safety and independence (Melnick and Paulson, 1990).

Because IPD patients lose clarity, dictation and volume in speaking, talking and being understood may become difficult. Speech therapists can assist PD patients to project their voices and overcome limited volume by teaching them abdominal breathing methods and ways to improve articulation by gaining more facial mobility. They teach the patient to compensate for the effects of the disease and advise on appropriate positions during eating and swallowing to avoid aspiration of food into the lung. In conjunction with dieticians, that may advise on appropriate semi-solid foods (Melnick and Paulson, 1990).

People with IPD often benefit from sharing their concerns with peers. Consequently voluntary groups have appeared world-wide to fulfil this need. Such organisations usually support the carer, or spouse, as well as the IPD patient, and often provide exercise groups, social activities and newsletters to keep their members abreast of latest trends in the treatment of IPD (Melnick and Paulson, 1990).

Dieticians may assist the IPD patient in two ways. They can advise on the composition of diets to ensure adequate intake, and reduce the likelihood of constipation, a frequent side effect of many PD medications. They also have a role in enhancing the effect of levodopa absorption by manipulation of dietary protein and educating patients and their caregivers in appropriate diets (Nutt & Carter, 1990).

Despite all the above mentioned medications and strategies the treatment of IPD has remained solely at the level of symptom management. None of these techniques or preparations alters the natural history of IPD. Scientists continue their attempts to develop a treatment that will extend beyond symptomatic control and perhaps cure, rather than control the condition. The panacea for IPD is some way off, but the development of deprenyl (Selegiline Hydrochloride: marketed as Eldepryl in New Zealand) has provided fresh hope that a cure is not impossible.

5.0 DEPRENYL: A New Pharmacological Preparation

In comparison to levodopa, deprenyl (a Monoamine Oxidase Inhibitor - B) is a relatively new agent used to treat IPD. Although Knoll (1983) and colleagues developed the drug in 1964, originally as an anti-depressant, it was not until 1975 that the first human clinical trial by Birkmayer was commenced with IPD subjects (Birkmayer, Knoll, Riederer, Youdium, Hars & Marton, 1985). The MPTP model of IPD has also been responsible for the renewed interest in monoamine oxidase inhibition as a treatment strategy for IPD (Heinonen, 1989). The following section reviews:

The therapeutic rationale for using deprenyl.

The action of deprenyl.

Deprenyl's effect on affective functioning.

The motor effects in IPD, including possible protective and symptomatic effects.

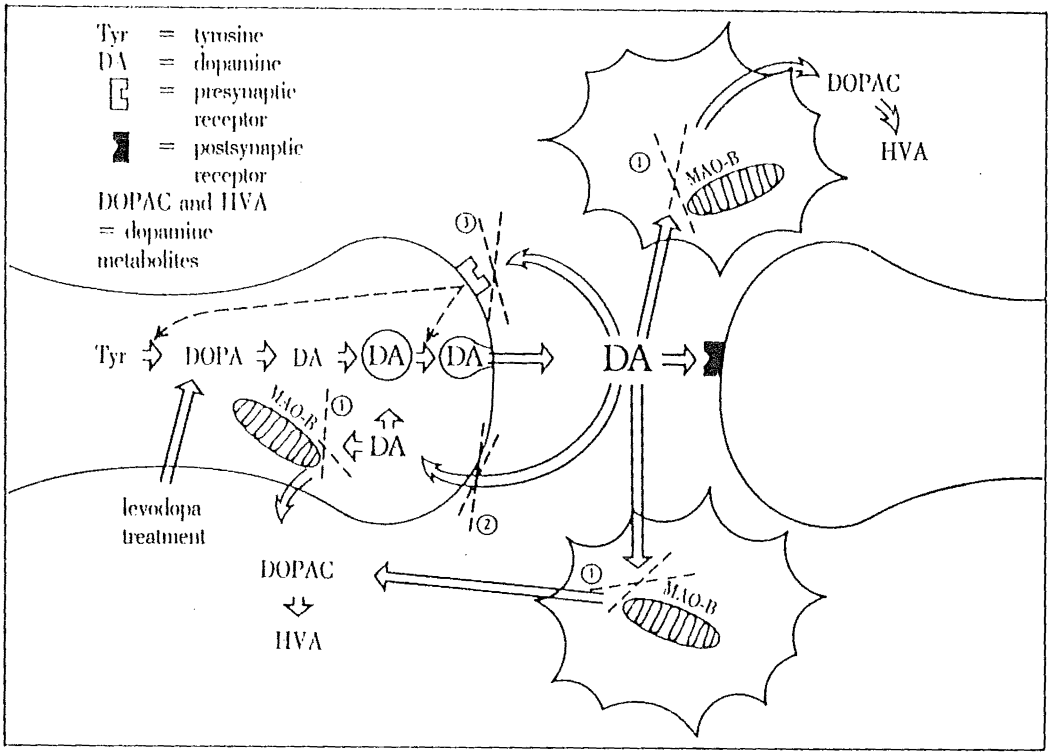
Deprenyl's effect on cognition in SDAT and IPD

5.1 Therapeutic Rationale for Deprenyl

Monoamine oxidase (MAO) is an enzyme which protects the body by deaminating concentrations of substances that might otherwise cause cell damage. Prior to the mid 1960's MAO was thought to be a single substance, but Johnson's discovery that there were two distinct forms A, and B, led to the development of drugs that could selectively inhibit these compounds. Blocking oxidation seemed logical on theoretical grounds, and had been tried in IPD patients on levodopa prior to Johnson's discovery but failed because of the "cheese effect". Deprenyl was a significant development because it could selectively inhibit MAO-Bs. Large quantities of MAO-B are found in the dopamine rich striatum and unlike MAO-A , are important in dopamine catabolism. Deprenyl is therefore a rational choice for IPD because by inhibiting dopamine catabolism, it potentiates the availability of any remaining endogenous dopamine (Heinonen, 1989).

5.2 Mode of Action

According to Heinonen (1989), deprenyl has three presumed modes of action: These are shown in Figure 5.0; firstly, at low but therapeutic doses (below 20 mg) MAO-B inhibition occurs selectively (ie MAO-A is unaffected) and irreversibly; microsomal catabolism of dopamine is also blocked; secondly, deprenyl reduces the rate of amine re-uptake (ie pre-synaptic re-absorbtion). These two effects, plus the ability to stimulate the release of dopamine allows the IPD patient with a dopamine deficiency increased activity of endogenous dopamine. Unlike other MAOIs, deprenyl is safe because it prevents a simultaneous increase in noradrenaline (Heinonen, 1989).



Site of effects

1 MAO-B inhibition
2 Inhibition of dopamine re-uptake
3 Inhibition of the dopamine auto receptor and the resultant release of dopamine and increase of synthesis.

Figure 5.0 The pharmacological mode of action of deprenyl (Heinonen, 1989 p10).

Deprenyl's metabolites are also postulated to have specific actions. One of these, an amphetamine (dextroamphetamine) is thought to have a mood-elevating

effect and may be responsible for the awakening effect reported by some subjects (Heinonen, 1989). Although researchers can be sure of some of the actions of deprenyl, a full understanding is not yet available.

5.3 The Influence of Deprenyl on Affect

Table 5.3 summarises the early clinical trials of deprenyl which was originally developed as an anti-depressant. Early trials by Knoll (1983) and Mann & Gershon (1980) claimed positive results with endogenously depressed patients at dosages of 20 mg per day. However these results were not always consistently replicated (Mendis, Pare, Sandler, Glover & Stern, 1981). In those investigations which reported positive results (Tringer, Haits & Varga, (1971, cited in Lees, 1987); Mendlewicz & Youdim, 1983), there were mixed groups - some subjects with unipolar affective disorders, others bipolar. Dosages and durations have also varied, making it difficult to compare studies.

A more efficacious anti-depressant effect appears to be found in studies using 30 mg or more per day (Prasad & Stern (1977, cited in Lees, 1987); Mann et al , 1989). Quitkin et al (1984) found that subjects with atypical depressions may also benefit from this dosage. Studies of subjects with SDAT investigating affective and cognitive functioning detected modest changes in the Hamilton's Depression Rating Scale (HDRS) but an increase in irritability at 40 mg per day. However these subjects did not demonstrate mood disorders on the HDRS at baseline (Tariot et al, 1987).

The anti-depressant efficacy of deprenyl has also been investigated in patients with IPD, many of whom, as noted earlier, exhibit depressive symptomology. These studies have typically investigated the benefits of 10 mg/day and as in subjects with endogenous depression, results have been mixed. Lees et al (1977), Przuntek & Kuhn (1987), Portin & Rinnie (1983) and Nappi et al (1991) report no significant benefit over placebo, whereas Como (Parkinsons Study Group, 1990) noted a less rapid decline on the HDRS in the subjects treated with deprenyl over a 12 month period.

The one consistent finding in IPD subjects receiving 10 mg per day of deprenyl is an awakening effect. Lees, Frankel, Eatough & Stern, (1989) report no change in mood, but an increase in "mental aclarity" (not defined by authors) and energy. Portin & Rinnie (1983) reported an increase in arousal that led to disturbances in cognition and emotion in subjects with concurrent dementia

The investigations thus far indicate that dosages below 30 mg per day are probably not likely to lead to significant improvements in mood in subjects with IPD or endogenous depression. Heinonen & Rinnie (1989) propose that at low levels deprenyl only inhibits MAO-B where above 30-40 mg inhibition of MAO-A also occurs, and it is this that leads to the anti-depressant effect. However the risk of the "cheese effect" is also greater at higher dosages. Clearly more research into the antidepressant efficacy of deprenyl is required. Consequently the present study addresses this concern, in addition to others in the cognitive realm.

Table 5.3: Studies on the effect of Deprenyl on Affect

Authors	Year	Nature of subjects and sample size.	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Lees et al.	1977	15 IPD with depression (moderate or severe), on levodopa.	56-79	Zung Scale.	DBPC Crossover.	10 mg /day on alternate days for 6 months.	No change in mood but greater mental aclarity. Increased speed of thinking.
Lees et al.	1989	9 untreated newly diagnosed IPD.	Mean 46 yrs.	HDRS.	DBPC (on-going)	10 mg/day for 1 week.	Mild trend for lower scores in deprenyl group.
Mann et al.	1989	44 out patients with clinical depression. 7 atypical.	29-68 yrs. Mean 45.2 yrs.	HDRS Clinical Impression Scale. BDI.	Single blind.	10 mg for 3 weeks then 30 mg for 3 weeks. Up to a maximum of 50 mg.	Active drug group: 11 of 22 improved on HDRS and Clinical global set. 3 of 22 improved on placebo.
Mann & Gershon.	1980	12 - endogenously depressed. (6 unipolar) (6 bipolar)	Mean 42 yrs.	HDRS	DBPC	Two weeks single blind for drug washouts. Week 1: 5 mg. Week 2: 10 mg. Week 3: 15 mg for 4 weeks.	1 subject responded to placebo then remitted 1 month later. Main clinical improvements occurred at weeks 1 and 3. 7 out of 10 reduced HDRS scores by 50%. 2 dropped out due to negative effects.
Mendis et al.	1981	31 with mild to moderate primary depression.	Mean age 42 years.	Visual analogue scale. HDRS - 17 item version.	Limited DBPC	1 week placebo then up to 15 mg/day for 3-5 weeks.	No benefit of Selegiline over placebo in 22 who completed trial.
Mendlewicz & Youdin.	1983	14 active: - 2 bipolar. - 12 unipolar. 13 placebo - 3 bipolar. - 10 unipolar.	26 - 64 yrs Mean 43 years.	HDRS	DBPC.	20 mg/day. 6 weeks.	Deprenyl superior to placebo in improving depression.

* **HDRS:** Hamilton's Depression Rating scale; **DBPC:** Double Blind Placebo Control; **BDI:** Beck Depression Inventory.

TABLE 5.3: Studies on the effect of Deprenyl on Affect . Continued on next page....

TABLE 5.3: Studies on the effect of Deprenyl on Affect.....Continued.

Authors	Year	Nature of subjects and sample size.	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Nappi et al.	1991	20 IPD de novo.	33 - 71	HDRS. Hamilton Rating Scale for Anxiety. BDI.	DBPC.	10 mg. 3 months blind. 3 months open.	No change detected in mood scores. I
Parkinsons Study Group. DATATOP.	1989	800 subjects. PD less than 5 years.	Mean 61 yr	HDRS.	DBPC.	10 mg/day up to two years.	No anti depressant effect detected but subjects not depressed at baseline.
Portin & Rinnie.	1983	7 IPD long-term (8-9 years). 3 dementia free. 4 with dementia. 2 with transient clinical depression.	59 - 70 yrs. Mean 64.3 yrs.	MMPI. D Scale.	Open.	5 or 10 mg/day. 4 weeks.	2 subjects - mild elevation in mood. 2 subjects no change. Dementia subjects developed behavioural disturbances.
Prasad & Stern (cited in Lees (1987).	1987	40 Primary depressive.	Not stated.	Montgomery -Asberg depression scale.	Randomised (8 Groups) - Selegeline: 30-60 mg/day. - Phenelzine: 30 mg/day. Tranycypromin e: 20 mg/day.	6 months.	Phenetzine more effective for anxiety. deprenyl for depression.
Przuntek & Kuhn	1987	30 IPD (De novo).	Mean 68 years.	Zung Scale.	DBPC Crossover.	Levodopa with 10 mg/day of deprenyl.	No changes.
Quitkin et al.	1984	17 with atypical depression.	18 - 55 yrs.	HDRS Symptom check-list - 90.	Open pilot study.	1 week drug free then 10 days single blind of placebo, 5 subjects who did not improve then went into 6 week open trial. Max 30 mg/day.	10- responded to deprenyl at dosages above 20 mg.

* **HDRS:** Hamilton's Depression Rating scale; **DBPC:** Double Blind Placebo Control; **BDI:** Beck Depression Inventory.

TABLE 5.3: Studies on the effect of Deprenyl on Affect. Continued.on next page....

TABLE 5.3: Studies on the effect of Deprenyl on Affect.....Continued.

Authors	Year	Nature of subjects and sample size.	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Tariot et al.	1987	17 Primary degenerative dementia.	42-72 yrs. Mean 59.3 yrs.	HDRS.	DBPC. Serial design. 10 mg/day then 40 mg/day.	10 mg for 28 days. 40 mg for 35 days. Placebo for 14 days.	Increased energy & social interaction. Reduced anxiety & tension at 10mg. Modest changes in HDRS scores.
Tringer et al.	1980	30 subjects. Endogenous depression.	Mean 52 years.	HDRS		20 mg/day. 14 days.	9 recovered. 12 improved. 9 not greatly helped.

* **HDRS:** Hamilton's Depression Rating scale; **DBPC:** Double Blind Placebo Control; **BDI:** Beck Depression Inventory.

5.4 Effect of Deprenyl on Motor Function

Investigations into the effects of deprenyl on motor function fall into two categories, those using deprenyl as monotherapy and those using it in combination with other anti-PD preparations, usually levodopa. Studies of each category will be discussed separately

5.4.1 Deprenyl as an adjuvant to Levodopa

Aside from its anti-depressant properties, the selective inhibition of MAO-B also allowed the potentiation of endogenous dopamine and on theoretical grounds seemed a logical choice in the treatment of IPD. Non-selective MAO inhibitors had been tried in the early 1960's, but had failed because of the side effects of excessive levels of levodopa (Knoll, 1983). Birkmayer et al (1985) were the first group to attempt using the newly developed deprenyl in combination with levodopa in IPD patients. Their results indicated that this combination was of significant benefit: in particular the incidence of end-of-dose fluctuations and "on-off" periods were greatly reduced, in addition to this levodopa dosages were reduced by up to 30% in some patients, giving many a new lease of life and reducing the undesirable side effects of high levels of levodopa (Rinnie, 1987). This nine year study, however, was retrospective, open and

uncontrolled. Attempts to replicate it produced some mixed outcomes, a summary of the major trials is presented in Table 5.4.1. Yahr et al (1989) gave 200 long term levodopa patients deprenyl and followed their progress for 8-10 years. Their reports indicated that amelioration of the end-of-dose problems was significant, but not sustained beyond two years. As double-blind placebo controlled trials were reported, it became established that deprenyl was a safe effective adjuvant to levodopa (Lees, 1987). Short-term trials however indicate it does not appear to alter peak clinical responses in patients on optimal levodopa and dopamine agonist treatments (Teychenne & Parker, 1989). The synergistic role of the two preparations indicated both were essential in achieving symptomatic control of end-of-dose and akinesia difficulties.

Table 5.4.1: Studies on the effect of Deprenyl as an adjuvant to Levodopa on motor function in IPD.

Authors	Year	Nature of subjects and sample size.*	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Birkmayer et al.	1985	Group I - madopar: n = 377 Group II - madopar and deprenyl: n = 564. All established IPD.	38 - 78 years.		Retrospective analysis: open and uncontrolled	5-10 mg/day 9 years.	Deprenyl group lied 15.3 months longer than Group 1.
Csanda & Tarczy.	1987	Group 1. Levodopa: 10 subjects. Group 2. Selegeline and levodopa: 10 subjects.		Webster Scale. H & Y Scale. Motor performance scale.	Parallel.	10 mg/day for 1 year.	No difference between two groups at one year.
		18 subjects with "wearing off" effect. Step 3 on H & Y Scale.		North Western University Disability Scales.	Open.		12 of 18 improved and sustained 3-4 years.
Elizan et al.	1991	38 IPD for a mean of 6 years.	41 - 75 years. Mean 56 years.	H & Y Scale.. Mt Sinai Centre. Functional Stage (1-5). Motor disability (0-4).	Open. (Selegeline prior to levodopa).	10 mg/day initially as monotherapy Combined levodopa for 26 months.	Levodopa reversed disability in 75% of subjects. Selegiline alone did not control symptoms.
Fornadi & Ulm	1990	Group 1. n = 133. Levodopa for 2 years (average). Group 2. n = 113. Levodopa and selegiline for 2 years (average). Group 3. n = 33. Levodopa and bromocriptine or lisuride for 2 years (average).	Group 1. Mean 64.8 years. Group 2. Mean 64.1 years. Group 3. Mean 66.8 years.	Columbia University Rating Scale. Webster Scale.	Retrospective analysis.	4 years. Dose not stated.	Group 1 deterioration was significantly faster than Group 2.
Golbe.	1989	39 subjects IPD. Mean duration of PD, 2 - 4 on H & Y Scale.	Mean 62.4 years.	H & Y Scale. Patient subjective recordings. Modified Columbia University Disability Scale.	DBPC then Open	10 mg/day for 6 weeks DBPC, then into an open trial for 3 years.	17 of 39 subjects discontinued deprenyl within 3 months. Of the remaining 22 subjects, average duration of subjective benefit was 8.2 months.

TABLE 5.4.1: Studies on the effect of Deprenyl as an adjuvant to Levodopa on motor function in IPD. Continued on next page....

* **DBPC:** Double Blind Placebo Control; **H & Y:** Hoehn and Yahr Scale.

TABLE 5.4.1: Studies on the effect of Deprenyl as an adjuvant to Levodopa on motor function in IPD.....Continued.

Authors	Year	Nature of subjects and sample size.*	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Golbe & Duvolsin	1987	43 IPD. On sinemet with (on off).	35 - 75 years.	Modified Columbia Rating Scale. Patient self Assessment. "On-Off" H & Y Scale.	DBPC	10 mg/day. 6 weeks.	Placebo: 4 improved. Active: Improved facial expression, resting tremor "on-off". 12 of 17 moderate to marked improvement.
Lees et al.	1977	41 IPD. Max tolerated levodopa.		7 point scale. Self Scoring Diary.	DBPC Crossover .	10 mg daily or alternative days	Deprenyl effective in mild on-off and end of dose akinesia. No improvement in diurnal akinesia
Lieberman et al.	1987	33 IPD.	Deprenyl 42 - 69 years.	Modified Columbia University Rating Scale. Hourly patient diary. H & Y Scale.	DBPC	10 mg/day. 8 weeks.	Active drug: 22% decreased in disability. 12 of 17 improved. Placebo: 2 of 16 improved.
Poewe et al.	1987	28 Long-term levodopa treatment.	39 - 71 years. Mean 54.8 years.	H & Y Scale. Columbia University Rating Scale. North Western University Disability Scales: - dyskinesias (0-3). - on-off (0-3).	Retrospective	10 mg/day. 3 - 37 months.	18 of 28 had positive outcome.
Prztuntek & Kuhn.	1987	30 IPD.	Mean 50 years.	Columbia University Rating Scale. Schoppe Motor Performance Series.	DBPC Crossover.	10 mg/day with levodopa. 5 phases.	Improved when on active drug. Deteriorated on placebo. Improved akinesia·

TABLE 5.4.1: Studies on the effect of Deprenyl as an adjuvant to Levodopa on motor function in IPD. Continued on next page.....

* **DBPC:** Double Blind Placebo Control; **H & Y:** Hoehn and Yahr Scale.

TABLE 5.4.1: Studies on the effect of Deprenyl as an adjuvant to Levodopa on motor function in IPD.....Continued.

Authors	Year	Nature of subjects and sample size.*	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Rascol et al.	1988	16 IPD subjects with wearing off problems.	Mean 64.3. ± 2.3 yrs.	Unified Rating Scale for Parkinson's Disease. (Version 1).	DBPC Crossover.	2 weeks on active.	No statistical difference between deprenyl and placebo on global scores.
Rinnie et al.	1978	47 IPD. Long-term levodopa.	62 - 70 years.	PD Rating Scale, including on-off 5 point scale.	Open	5 or 10 mg. 1 - 3 months.	Improved "on-off"tremor. End of dose fluctuations. Nocturnal akinesia. Worse dyskinesia at peak dose.
Stern et al.	1983	44 4 groups levodopa but static. 2 - slowly deteriorating. 3 - weakening off at end of dose.	Mean 59.8 years.	North Western University Disability Scales. Self Rating. 4-on-off.	Single Blind Crossover.	10 mg/day for 6 weeks then placebo, then 1 year active then placebo again.	13 - true positive responses. 31 - not a positive response.
Teychenne & Parker	1989	10 levodopa subjects with wearing off problems. IPD for approx 5 years. (Also 90% on bromocriptine).		Unified PD Rating Scale	Randomised. DBPC. Crossover	16 weeks on active drug. 12.5 mg/day maximum.	Active drug improved wearing off problems and extended levodopa dosages by 2-3 hours. Placebo group: Significant deterioration noted over the trial period compared to those subjects on active drug.
Yahr et al.	1989	Two groups. 1. 21 IPD started selegeline first. 2. 200 IPD long-term levodopa.	Not stated.	H & Y Scale.	Open.	10 mg/day.	1. 19 subjects improved. 2 continued to worsen. No evidence of fluctuating to levodopa. 2. End of dose problems improved but not sustained long-term.

* **DBPC:** Double Blind Placebo Control; **H & Y:** Hoehn and Yahr Scale.

5.4.2 Motor Monotherapy.

Despite many investigations into deprenyl as an adjuvant to levodopa researchers were still unclear of the most suitable time to commence deprenyl, and the duration of its benefit. It was suggested that it had a narrow therapeutic window (Parkes, 1983) and researchers began to search for the appropriate time to commence deprenyl (Lees, 1987). Birkmayer et al (1985) had suggested that aside from reducing dose related difficulties such as wearing off, deprenyl retarded cell loss from the dopaminergic neurones in the striatum, and promised to be the first anti-PD drug to extend beyond symptomatic control. Knoll's (1989) earlier work with animal models seemed to suggest a protective effect. He demonstrated that continuous low doses of deprenyl significantly prolonged the life-span of aged rats and also increased their sexual vigour (a function dependent on adequate striatal dopamine levels). These findings led to the notion that deprenyl might enhance the turnover rate of dopaminergic neurones in the striatum and the possibility of a protective effect in IPD.

The simultaneous discovery that the toxic substance MPTP (converted to MPP+) produced dopaminergic neurone damage and a syndrome almost identical to IPD in a group of young drug addicts (Stern & Langston, 1985) led to a new line of research and a useful animal model of IPD (Heinonen, 1989). Because the Parkinsonian Syndrome displayed by the young addicts was successfully controlled with deprenyl (Tetrud & Langston, 1987), further evidence of its value as monotherapy and possible protective effect in IPD was also implied. Tetrud & Langston, (1987) went on to demonstrate that primates and older animals were extremely sensitive to MPTP and that this toxic substance converts to MPP+, and probably enters the dopaminergic neurones via the dopamine uptake system. Of particular relevance, deprenyl inhibited the conversion of the toxin MPTP to MPP+ (Heinonen, 1989). These findings led to the first North American pilot study of deprenyl as monotherapy in IPD.

Clearly the issue of whether deprenyl actually alters the natural history of PD remains controversial. From the investigations reviewed in Table 5.4.2, it appears that

the drug is of value in early untreated IPD, but that it does not achieve symptom control as effectively as levodopa, amantadine, anticholinergics or dopamine receptor agonists beyond an average period of 12 months. This begs the question, " Are these studies evidence for protective effect ? " Tetrud and Langston (1989) acknowledge that establishing the existence of a protective effect is difficult , " ....it would be necessary to show that death of nigral neurones is being prevented, and as yet there is no way to determine this in living humans.... " (Tetrud and Langston, 1989 p521). Meanwhile they suggest that there is a compelling case for pursuing preventative strategies because it may become possible to predict IPD prior to the development of symptoms. Any prevention would be used at the pre-clinical stage (Tetrud & Langston, 1989).

If a protective effect was to occur, it followed that deprenyl should be commenced as soon as possible. To this end, investigators began to research its effect as monotherapy in early IPD. The findings on these studies are summarised in Table 5.4.2. Most of the early studies on deprenyl as monotherapy (Csanda & Tarczy, 1987; Teravainen, 1990; Myllyla, Sotapiemi, Tuominen, Heinonen, 1989) used moderate sample sizes (20 - 56) and generally indicated that deprenyl had a slight symptomatic effect that was seldom sustained beyond 10 - 18 months (Elizan, Yahr, Moros, Mindoza, Pand & Bodian, 1989). Some studies allowed subjects to take anticholinergics in addition to the deprenyl (Teravainen, 1990) which creates a difficulty in determining whether the drug has a symptomatic benefit.

In the first North American pilot project using a double-blind placebo controlled design, results indicated that if deprenyl was given in early untreated IPD the necessity for levodopa treatment would be significantly delayed (Tetrud & Langston, 1989). This led to the largest study thus far, with 800 subjects code named DATATOP (Deprenyl and Tocopheral Antioxidative Therapy in Parkinsonism) which confirmed that deprenyl treatment extended the time before IPD patients required levodopa, compared to placebo and tocopherol (Vitamin E) alone (Parkinson Study Group, 1989). However this

finding has to be regarded with caution as the study has been criticised for determining the time when levodopa is required using subjective criteria (Landau, 1990).

TABLE 5.4.2: Studies on the effect of deprenyl as monotherapy on motor function in IPD.

Authors	Year	Nature of subjects and sample size.	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Csanda & Tarczy.	1987	30 Early IPD.	38 - 56 yrs. Mean 55.2 yrs.	Webster Rating Scale. H & Y Scale.. Motor Scale Performance.	Open.	10 mg/day. 6 months.	10 patients improved. 20 needed other drugs at six months.
Elizan et al.	1989	22 IPD newly diagnosed.	44 - 75 yrs. Mean 58 yrs.	Rated Disability Scale. H & Y Scale.	Open.	10 mg/day. 7 - 84 months.	Symptoms progressed in 20 of 22 within two years. Two subjects improved. Symptom control not great.
Myllyla et al.	1989	56 IPD.	Active: Mean 61 yrs. Placebo: 60.8 yrs.	Columbia University Rating Scale. North Western Disability Scale. Webster Rating Scale.	Randomised.DBPC.	10 mg/day. Analysed at 12 months. On-going.	Disability scores less in active drug group at 12 months. levodopa needed by 46% in deprenyl group and 56% of placebo.
Nappi et al.	1991	20 de novos - early IPD. Lisuride commenced first over 3-4 weeks. I - III on H & Y Scale.	33-70 yrs.	Webster Rating Scale. North Western Disability Scale. Columbia University Rating Scale.	DBPC with lisuride.	10 mg/day. 3 months blind, 3 months open.	Active drug group had lower levels of lisuride to achieve symptom control.
Parkinson Study Group (DATATOP)	1989	800 subjects. IPD less than 5 years. All drug free.	Mean 61 yrs.	H & Y Scale.	DBPC. 4 groups: 1. deprenyl & tocopherol placebo. 2. deprenyl placebo and tocopherol. 3. deprenyl & tocopherol. 4. deprenyl placebo and tocopherol placebo.	10 mg/day for 2 years.	Deprenyl group remained off levodopa for almost one year compared to the placebo and tocopherol groups. Short term slight symptomatic alleviation was noted.
Teravainen.	1990	20 IPD. Some on dopamine agonists, anticholinergics or betablocker. None on levodopa.	43 - 70 yrs. Mean 67.9 yrs.	H & Y Scale. Unified Rating Scale for Parkinsonian Disease. Patients subjective opinion.	DBPC. Crossover.	30 mg/day. 8 weeks active. 4 weeks placebo.	No significant clinical benefit or subjective benefit.

TABLE 3: Studies on the effect of deprenyl as monotherapy on motor function in IPD Continued on next page....

* **UPDRS:** Unified PD Rating Scale; **DBPC:** Double Blind Placebo Control; **H & Y:** Hoehn and Yahr Scale; **ADL:** Activities of Daily Living

TABLE 5.4.2: Studies on the effect of deprenyl as monotherapy on motor function in IPD....Continued.

Authors	Year	Nature of subjects and sample size.	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Tetrud & Langston.	1989	57 subjects, IPD less than five years.	30 - 80 years old.	UPDRS, H & Y Stages. Webster Step-Second Test. Schwab and England ADL Scale.	Randomised. DBPC.	10 mg/day. Followed for 3 years.	Deprenyl group significantly delayed start of levodopa compared to placebo.

* **UPDRS:** Unified PD Rating Scale; **DBPC:** Double Blind Placebo Control; **H & Y:** Hoehn and Yahr Scale; **ADL:** Activities of Daily Living

5.5 Cognitive Effects of Deprenyl

In addition to the studies on affect and motor functions there have been a limited number of studies into deprenyl's effect on cognition. (See Table 5.5). Investigations thus far have ben conducted with animals, people with SDAT and those with IPD. Each is briefly summarised in Table 5.5. Knoll's (1983) early work with animals examined learning capacity in two matched groups of low performing rats using the shuttle box task. Following baseline assessments the rats were given deprenyl or saline. At 36 weeks reassessment it was found that the deprenyl group significantly out-performed the saline group, suggesting they had improved their learning ability.

Enhancement of learning seemed to be an appealing prospect and led to the use of deprenyl in conditions such as SDAT, where learning is severely compromised, and also in the 'normal' elderly (Knoll, 1983, 1989). A search of recent literature indicated there have been at least six investigations into the benefits of deprenyl with SDAT patients. Although SDAT is generally associated with reduced acetylcholine, additional impairments in the dopaminergic and noradrenergic systems have been found in patients with the condition. This has led to the use of deprenyl in SDAT (Finali, Piccirilli, Oliani & Piccinin, 1991).

The first reported double-blind, placebo controlled trials with SDAT subjects were conducted by Tariot et al. (1987a) and Tariot, Sunderland, Weigartner, Murphy, Thompson & Cohen, (1987b) on subjects with mild to moderate symptoms, but who

were still sufficiently cognitively intact to complete psychometric testing. Tariot et al. (1987a, 1987b) used a serial treatment design to compare 10 mg/day (for 28 days) and 40 mg/day (for 35 days) with placebo (14 days). Statistically significant improvement on tasks of learning and episodic memory occurred at 10 mg/day, but not at 40 mg/day in the SDAT subjects. Social interaction and activity levels, (rated on Blessed's Dementia Scale) also improved at 10 mg/day.

Monteverde et al. (1990) also reported improvements in SDAT subjects treated with 10 mg/day of deprenyl compared to matched subjects treated with phosphatidylserine, a cholinergic agonist (ie. enhances cholinergic function). Subjects treated with phosphatidylserine also demonstrated significant improvement relative to baseline on the information, memory and concentration subscale of Blessed's Dementia Scale. Improvements tended to occur two and three months after commencing phosphatidylserine, whereas the deprenyl group showed significant improvement as early as one month after commencing treatment. Furthermore, 10 mg/day was more effective than 40 mg/day for improving the cognitive test results. The improvements in memory seemed to be related to enhanced retrieval, which led to more efficacious immediate, short term memory and delayed recall. A similar single-blind study by Falsaperla, Preiti & Oliani, (1990) compared deprenyl and oxicracetam in a group of mild-moderate Alzheimer's type dementia sufferers. The same psychometric tests used by Monteverde et al (1990) were employed by Falsaperla et al. (1990). The results indicated improved autonomy in daily activities and improved concentration span, leading to significantly better performance in effortfull memory tasks and visuospatial abilities as measured by the Gibson Spiral Maze.

The notion that deprenyl enhances attention span was suggested by Piccinin, Finali & Piccirilli, (1990) who investigated the effects of 10 mg/day of deprenyl compared to placebo in 20 SDAT subjects with slight to moderate cognitive impairment. Subjects took placebo or deprenyl for three months and then without washout, crossed over to receive the alternative preparation. Psychometric tests were administered at baseline,

three and six months and the results indicated deprenyl therapy led to superior performances relative to placebo in all measures (verbal and visuospatial memory attention, constructional apraxia and visuospatial abilities) except the Token Test, where placebo treated subjects also improved slightly, but this did not reach significance. Subjects with early disturbances who received deprenyl improved substantially on memory functions as a result of increased attention span and the reported anti-depressant effect of deprenyl.

A recent investigation in Alzheimer's subjects by Finali et al. (1991), also employing a double-blind placebo controlled crossover design used with the Rey Auditory Verbal Learning Test, to assess changes at three and six months. The results indicated deprenyl was more effective than placebo in improving total recall, delayed recall, verbal learning and middle position of the serial position curve, which suggests that deprenyl enhances the acquisition and consolidation of memory and makes amnesic patients less prone to the effects of interference, possibly due to increased attention span.

Deprenyl's effect on cognitive functioning in persons with IPD is not well established, primarily because most investigations have concentrated on the more obvious motor deficits associated with IPD. Although some of those motor function studies have included brief general measures of cognitive functioning (eg Nappi et al, 1991) such as the Mini Mental State Test (Folstein, Folstein & McHugh, 1975) , tests of this nature appear to lack the sensitivity to detect changes in cognitive functioning. More detailed tests are needed to detect the subtle cognitive deficits that are likely to occur, especially in early IPD (Lees & Smith, 1983). To date, the four published investigations, specifically looking at deprenyl's effect on cognitive functioning in IPD, provide preliminary, but encouraging evidence that deprenyl has a positive effect. The first of these studies was an open trial conducted by Portin and Rinnie (1983) on a mixed group of subjects, all of whom were on long-term levodopa. Following baseline assessments the subjects took 5 or 10 mg of deprenyl per day for four weeks.

Reassessments showed that subjects with dementia who were given 5 mg/day did not improve, whereas those without dementia who took 10 mg/day, improved scores in motor speed and naming in the Modified Kim Test of Memory. Further scrutiny of Portin & Rinnie (1983) indicates there was no main effect for trial (deprenyl vs. non deprenyl) and no interaction (group x trial), but rather means improved in non-demented group, and reduced in the demented group on a test of immediate and delayed recall of 30 word pairs. This shows that deprenyl therapy did not lead to the improved memory scores, because when compared to normal controls, increments were equal in the three non-demented subjects and the controls. As the sample size was small (n = 7), Portin & Rinnie's (1983) limited results could only be considered an indication that further studies were warranted. In another small study (n = 5), 10 mg/day of deprenyl has been reported to improve simple reaction times, but not choice reaction times (Lees et al, 1989; Eatough et al, 1990).

The most extensive double blind study with a large sample size (n = 800) has provided the most promising results in IPD subjects thus far. Although the DATATOP study (Como, 1990; Parkinsons Study Group, 1989a; Parkinsons Study Group, 1989b) examined only a broad range of general neuropsychological functions and the final results are yet to be reported a preliminary analysis provides support for the notion that deprenyl is of value in arresting, rather than improving deterioration in IPD. Performance on the Digit Symbol Test deteriorated within six months in subjects treated with placebo, compared to the deprenyl (n = 344) at six months. By 12 months further impairment on long-term storage and recall was noted in the placebo group. The DATATOP results suggested deprenyl arrested cognitive deterioration in early untreated IPD, but no improvements over baseline were noted. Because the DATATOP study detected a significant treatment effect (on motor function) at approximately 12 months ($\pm$5 months) all subjects receiving placebos were changed to deprenyl and this aspect of the double blind portion of the study was abandoned. The Vitamin E part remains double-blind (LeWitt, 1991).

Although abandoning the placebo vs. deprenyl aspect of DATATOP was important for ethical reasons (ie withholding deprenyl would disadvantage IPD subjects with respect to motor function), it leaves the question of deprenyl's effect on cognitive function only partially answered. The psychometric tests used in DATATOP were of a more general nature, especially subtests from the WAIS. As stated above, it is possible for IPD subjects to score as well as controls on the WAIS yet display deficits on more sensitive tests (Lees & Smith, 1983). Furthermore, the investigation of Heitanen (1991), published after commencement of the present study, found only one measure; paired associate learning for easy words, improved with deprenyl therapy. No statistically significant changes occurred in any other measure on a battery of tests which included simple and choice reaction time, visuospatial tests and memory tests.

These preliminary studies, with IPD subjects, some of which have had heterogeneous and inadequate sample sizes, indicate that more research is needed to conclusively establish if deprenyl does have an effect on cognitive functioning in mild-moderate dementia-free IPD subjects. It is important that future investigations use tests that are sufficiently sensitive to probe the established cognitive deficits and more complex functions than reaction times. The duration of studies may also be a critical factor because investigations into motor function must be at least three weeks long to detect a therapeutic response (Teychenne & Parker, 1989); a longer duration may be required to detect changes in cognitive functioning. In view of the mixed findings with IPD and seemingly clearer benefits with SDAT, the present study seeks to determine deprenyl's effect on cognitive functioning in a homogeneous group of mild to moderate dementia-free IPD subjects.

TABLE 5.5: Studies on the effect of Deprenyl on Cognitive functioning.

Authors	Year	No. of Subjects	Age	Evaluation Tools	Type of Study	Dosage & Duration	Outcomes
a. Como b. Parkinsons Study Group	1990 1989	800 IPD. Less than 5 years.	Mean 61 yrs.	Long-term recall, delayed recall, selective reminding, symbol digit, visual memory.	DBPC.	10 mg/day for up to 2 years.	Results suggest that deprenyl may delay cognitive decline in early unrelated IPD.
Falsaperla et al.	1990	40 mild to moderate senile and presinile dementia (Alzheimer type).	38 - 89 yrs.	Blessed's Dementia Scale. Randt Memory Test-: - five item test: - digit span forward. - short story subtest. - Gibson spiral maze. - word fluency test.	Randomised, single blind parallel. Selegiline vs.. oxiracetam.	10 mg/day for three months.	Selegiline group improved on Blessed Scale but more efficacy on selegiline than oxiracetam where 13 of 20 improved on Blessed Scale.
Finali et al	1991	19 early onset SDAT with mild - moderate cognitive impairment.	55 - 70 yrs. Mean 62.5 yrs.	Rey Auditory Verbal Learning Test. Mini Mental Status Test. Immediate and Delayed recall of verbal material.	DBPC Crossover.	3 months in each arm. 10 mg/day.	Significantly better improvement in deprenyl group than placebo in delayed recall.
Heitanen.	1991	18 subjects. None on levodopa. Some on amantadine, anticholinergics, bromochriptine, beta blockers and imiprimine	44 - 70 yrs. Mean 56.9 yrs.	Similarities and block design from WAIS. WMS-digit span, logical memory, associate learning, visual reproduction. Mannequin test. Reaction and movement times. Purdue pegboard. Writing speed. Trial making test. Stroop colour test.	DBPC	Max dose 30 mg/day. Placebo 4 weeks. deprenyl 8 weeks.	No statistically significant changes in any of the neurological tests.
Knoll.	1989	Low performing rats. 3 - 8 months.	53 - 80 yrs.	Learning in shuttle box.		0.25 mg/kg 3 times per week for several months.	Deprenyl induced enhancement in learning on shuttle box.
Lees et al.	1989	9 IPD untreated. Newly diagnosed.	Mean 46 yrs.	Computer based Reaction Time tasks 1 - 3 choices.	DBPC.	10 mg/day. 7 days before testing.	Reaction time improved in deprenyl group.

TABLE 5.5: Studies on the effect of Deprenyl on Cognitive functioning. Continued on next page.....

TABLE 5.5: Studies on the effect of Deprenyl on Cognitive functioning....Continued.

Authors	Year	Nature of subjects and sample size.*	Age	Evaluation Tools *	Type of Study *	Dosage & Duration	Outcomes
Monteverde et al.	1990	40 SDAT and primary degenerative dementia (mild to moderate).	38 - 79 yrs.	Blessed's Dementia Scale. Randt Memory Test-: - five item test: - digit span forward. - short story subtest. - Gibson spiral maze. - word fluency test.	Randomised, single blind parallel. Selegiline vs.. phosphatidyl-serine.	10 mg/day for three months.	Selegiline - significant improvement of Blessed Dementia Scale, short story test, digit span, word fluency and Gibson spiral maze compared to phosphatidylserine group.
Nappi et al.	1991	20 IPD de novo with 3-4 weeks lisuride.		Mini mental status.	DBPC.		No change detected in scores throughout the study.
Piccin et al.	1990	20 Primary degenerative dementia Alzheimer type. Slight to moderate cognitive impairment.	Mean 64.6 yrs.	Verbal comprehension, verbal fluency, verbal memory, attention and visuospatial abilities and constructional apraxia.	DBPC. Crossover.	10 mg/day. 3 months.	Deprenyl group improved more than placebo. Placebo in some instances declined from baseline.
Portin & Rinnie.	1983	7 IPD long-term levodopa (8-9 years). 4 with dementia, 3 dementia free.	59 - 70 yrs. Mean 64.3 yrs.	Modified Kim test, associative memory test (immediate and delayed). Digit span and digit symbol from WAIS, visuographic speed test, Bourdon - Wiersma vigilance test.	Open.	5 or 10 mg/day. 4 weeks.	Two response patterns. Dementia-free subjects improved in naming memory and motor speed.
Tariot et al.	1987 (a)	17 primary degenerative dementia - probable Alzheimers type.	42 - 72 yrs. Mean 59.3 yrs.	Psychiatric Rating Scale (0 - 5 Scale). Selective reminding.	DBPC. Serial Design.	28 days 10 mg then 40 mg/day for 35 days.	Active drug group: Improved scores on Psychiatric Rating Scale. Selective reminding improved. Placebo - no change.
Tariot et al.	1987 (b)	17 primary degenerative dementia - probable Alzheimers type.	42 - 72 yrs. Mean 59.3 yrs.	Global Deterioration Scale. Selective Reminding Task. Category Retrieval. Continuous Performance Task. Reaction Time Tests.	DBPC. Serial Design.	28 days 10 mg then 40 mg/day for 35 days.	Drug related improvements in delayed recall at 10 mg/day .

6.0 THE PRESENT STUDY

The possibility that deprenyl might improve neuropsychological functioning in persons with IPD is raised by the above mentioned investigations, and has promoted the present study. There is clearly a pressing need to examine deprenyl's effect in a homogeneous group of dementia-free, mild to moderate idiopathic Parkinsonian subjects. Furthermore, assessments that detect the established non dementia linked cognitive disorders in Parkinson's disease must be used to measure any benefits that may occur from deprenyl therapy. These deficits, as discussed in Section 1.4 were investigated prior to treatment and following treatment with deprenyl. This investigation differs from others in the cognitive realm because rather than administering general neuropsychological tests (eg. WAIS, WMS), the battery of tests and measures in the present study were selected because they assess deficits that are most likely to exist in persons with IPD.

It was hypothesised that 10 milligrams per day of deprenyl would have a positive effect in dementia-free persons with mild to moderate IPD (Grades I - III on the Hoehn & Yahr Scale) by improving various relevant measures relative to normal controls and IPD subjects treated with a placebo.

The tests used to evaluate the effectiveness of deprenyl and the rationale for their selection is outlined below. Comparisons were made on:

1. Early vs. established IPD subjects at baseline (early being those subjects not taking preparations containing levodopa).
2. IPD subjects vs. controls who were matched on age and education.
3. The baseline performance on all measures of placebo vs. deprenyl in IPD subjects.
4. Deprenyl vs. placebo following eight weeks of treatment.

6.1 Rod Orientation Test (ROT)

Following Brown & Marsden's (1986) suggestion that simple tests are most likely to detect visuospatial deficits, the ROT was selected for this investigation because it limits dependence on conceptual abilities such as problem solving, attention, intelligence and is reported to be sensitive to visuospatial disorientation in IPD (Hovestadt, 1990). Norms for the test were published by Meerwaldt and Van Harskamp (1982) and Hovestadt's (1990) recent investigations suggests that IPD subjects are severely impaired on the ROT relative to subjects without neurological dysfunction. According to the taxonomy of Boller et al. (1984) (see Section 1.4 on Visuospatial Functioning) it was postulated that the ROT assess the ability to judge stimulus-objects in space. It was originally designed by De Renzi et al. (1967) to assesses visuospatial perception at an elementary level.

6.2 Wisconsin Card Sorting Test (WCST)

Section 1.4.1 Executive Functions discussed the tendency for IPD subjects to have difficulty on the WCST, a measure known to be a reliable and sensitive measure of frontal lobe disturbances. The present study has selected the full 128 card version of the WCST and used Heaton's (1981) guidelines for administration because the Nelson (1976) modification appears to be less sensitive in high functioning subjects, and many early IPD subjects continue to function well in their occupations despite IPD motor symptoms (Mohr et al,1990). Therefore a detailed scoring method is required to detect possible executive deficits.

6.3 Beck Depression Inventory (BDI)

There are at least four measures of affect currently being used in IPD research, including the BDI, HDRS, Zungs Scale and the Montgomery-Asberg Depression Scale. The 21 item form of the BDI has been selected for this investigation because it is known to be a valid and reliable measure of depression in IPD (Beck & Steer, 1987; Levin et al. 1988). Despite the fact seven items focus on the somatic symptoms that may occur in

IPD, it has been shown to differentiate varying components of depressive symptomology (Huber et al, 1990) and four sub scales: (mood, self reproach, vegetative and somatic symptoms) can be measured in addition to the total cutoff scores (Huber et al, 1990).

6.4 Rivermead Behavioural Memory Test (RBMT)

This measure has been selected for the present study because it provides measures of general memory performance, yet was developed to monitor change following treatment and to assess everyday memory impairment (Wilson et al, 1991b). This test attempts to bridge the gap between assessments obtained by questionnaire and observations and the more traditional laboratory based measures. The four parallel forms have alternate form reliability, thus reducing the practice effects that may occur with repeated testing. Measures of immediate and delayed recall of visual and auditory stimuli, and remembering a route are included. The scoring system gives a standardised profile and various subtests such as recollection of 5-6 lines of logical prose can be scored separately.

6.5 Advanced Progressive Matrices (APM)

This test assesses a person's ability to solve problems, see relationships and develop a systematic method of reasoning, and is generally considered to assess visual perception (Raven et al, 1983). The standard version is known as the Raven's Progressive Matrices (Raven, Court & Raven, 1988) and has been used in several recent investigations and results indicated that subjects with IPD consistently score one standard deviation lower than expected for their education levels. In this investigation the advanced version has been selected because it is free from a ceiling effect and may thus be more sensitive in the detection of any possible drug-related improvements. The APM test is motor free and was not timed so that IPD subjects were not disadvantaged by time limits. The test has two parts, Set I: a 12 item training set intended to introduce subjects to the method and thinking required to complete Set II. Set II has 36 problems that get increasingly more difficult.

In summary, the five tests used in this study were selected because, taken together, they provide a wide yet focussed range of evaluations of the putative psychological benefits of 10 mg/day of standard deprenyl therapy in subjects with mild - moderate IPD.

7.0 METHODS

7.1 Subjects

Ethical approval for this investigation was granted by the ethics committees of the Canterbury Area Health Board, Christchurch and the Psychology Department, University of Canterbury. All subjects gave written informed consent following an explanation of the testing and double-blind procedures. Family doctors of all the subjects in the IPD group were contacted by telephone and letter to obtain permission for participation in the study prior to the commencement of the study. All IPD subjects lived in Urban Christchurch, Banks Peninsula or North Canterbury. All but one subject continued to live independently in the community for the duration of the trial, (8-16 weeks) although many reported minor difficulties with activities of daily living.

Three groups were recruited for this study: subjects with mild-moderate IPD who were not receiving levodopa; subjects with more established IPD on optimum levodopa therapy but free from dose-related complications such as fluctuations and wearing off problems; and control subjects matched as closely as possible on age, sex, years of education and ethnic origin. The two IPD groups were combined for comparisons with controls (See Table 7.1). The majority of IPD subjects were referred by a consultant neurologist following requests made at initial or follow up appointments. Most of the remainder volunteered following a request for subjects through the Parkinson's Support Group, Canterbury, New Zealand. All subjects had been diagnosed as having IPD by a consultant neurologist. All fulfilled the inclusion and exclusion criteria, (see Section 7.1.1), which were adhered to in all but one instance where a subject revealed, after commencing the trial, that he was taking a low dose of anti-depressant (25 mg of Nortriptyline to aid sleeping).

Table 7.1

Subject characteristics

IPD Group[a] (N = 23)		Controls (N = 10)	
Age (Years)		Age (Years)	
Mean	63.9	Mean	60.7
Median	66.4	Median	62.1
SD	10.2	SD	12.2
Range	36.1 - 78.4	Range	36.7 - 73.1
Education (Years)		Education (Years)	
Mean	10.9	Mean	11.6
Median	12.5	Median	11.0
SD	2.6	SD	2.0
Range	8 - 17	Range	8 - 14
Number of Subjects		Number of Subjects	
Male	13	Male	5
Female	10	Female	5
Total	23	Total	10

Note. [a] Early and established groups combined.

7.1.1 Inclusion / Exclusion Criteria.

Inclusions.

1. Subjects with idiopathic PD, at stages I, II or III on the Hoehn and Yahr Scale.
2. Ages 35 to 80.
3. a PD subjects who had not taken levodopa, including those who had undergone a one month pre trial washout of anticholinergics or anti-depressants.

3. b PD subjects on levodopa (sinemet, madopar) who were not experiencing end-of-dose dyskinesias or fluctuations.

3. c PD subjects taking amantadine, bromocriptine or lisuride

Exclusions.

1. Subjects suffering from other serious psychiatric or medical disorders including cardiac, gastric, renal, hepatic, neurological (Multiple Sclerosis, Cerebral Vascular Accident, history of head injury, dementia), depression (related to factors other than PD).

2. Subjects with idiopathic PD who are at grades IV or V on the Hoehn and Yahr Scale.

3. Subjects with PD who are currently on anti-depressent, or anticholinergic medications.

4. Subjects with Shy-Drager Syndrome and any other atypical Parkinsonian variants (progressive supranuclear palsy, striatalonigral degeneration, olivopontocerebellar atrophy).

Control Exclusions

1. Subjects free from PD and drug regimes including anti-depressant, neuroleptics and anticholinergics, and with no history of neurological or psychiatric illness.

7.1.2 Subject Characteristics

The IPD and Control Groups were analysed by two tailed t - tests to ensure they were matched with respect to age and education . The baseline motor function scores characteristics of the IPD Group are presented in Table 7.1.3.2 and Appendix A details medications taken prior to the trial. Duration of IPD is calculated at the time of diagnosis, but it is acknowledged that symptoms may be present for several years before medical attention is sought.

7.1.3 Motor Function

7.1.3.1 Deprenyl Study: Patient Information Form

The deprenyl study patient information form (Appendix B) was designed to check that all IPD subjects fulfilled the inclusion criteria for the investigation, including the motor rating on the Hoehn and Yahr Scale (Hoehn & Yahr, 1967) (see Appendix B). It sought information on the following dependent measures: age, years of education, current medication, dosages and time taken, relevant medical and psychiatric history and medications, visual acuity, hand dominance, duration of IPD signs and symptoms and the presence or absence of various cardinal features of IPD. It was completed by the investigator and/or a neurological registrar in a semi-structured interview.

7.1.3.2 Unified Parkinson's Disease Rating Scale (Version 3)

This scale rates Mentation, Behaviour and Mood, Activities of Daily Living and Motor Function on a 0-4 scale (Lang, 1990) (See Appendix C). A low score indicates minimal disability. The motor portion was completed by a neurological registrar following neurological assessment.

The results of the Baseline Motor and Activities of Daily Living scales of the UPDRS are presented in Table 7.1.3.2. In some instances those with more established IPD may have lower scores because their symptoms are optimally controlled with medications relative to the early IPD group who seem more disabled because they may have "washed out" of anticholinergics, or may have delayed seeking medical attention because of a reluctance to take medication.

Table 7.1.3.2

Baseline Motor Functioning - Unified PD Rating Scale (UPDRS)

	Early IPD (N = 15)			Established IPD (N = 8)	
	Motor [a]	ADL[b]		Motor [a]	ADL[b]
Mean	12.1	10.9	Mean	17.8	13.8
Median	13.0	11.0	Median	16.0	13.0
S D	3.82	3.94	S D	11.5	4.77
Range	6 - 20	4 - 18	Range	2 - 38	8 - 19

[a] Maximum 70 (indicates severe disability)

[b] Maximum 60 (indicates severe disability)

7.2 TRIAL DESIGN and PROCEDURE

This investigation was a double blind study in which the short term (8 week) effects of deprenyl were compared with placebo and pre-drug baseline data. the subjects formed five groups:

Group I Deprenyl as monotherapy.

Group II Placebo as monotherapy.

Group III Deprenyl as an adjuvant to levodopa.

Group IV Placebo as an adjuvant to levodopa.

Group V Matched controls free from neurological or psychiatric illness.

Subsequent to initial analyses, groups I and III were combined and groups II and IV were combined (See Section 8.1).

7.2.1 IPD Group

The neurological assessments and motor portion of the Unified PD Rating Scale were conducted by a neurological registrar in the clinic area of the Neurosciences Unit, Christchurch Hospital. Neuropsychological testing took place in the subject's own home (except in one instance when the subject's work-place was used) usually during the day, at a time convenient to the subjects. The majority of subjects completed the test battery in one session, but five subjects required the testing to be conducted over two sessions.

Every effort was made to ensure subjects were not fatigued, with frequent breaks being taken between tests.

7.2.2 Control Group

Subjects were tested in their own homes at a time convenient to them the tests were completed in one session in nine of the ten subjects.

7.2.3 Testing

The tests were conducted in the following order: The Deprenyl Study Patient Information Sheet was completed, followed by the Mood, Mentation, Behavioural and Activities of Daily Living sections of the Unified PD Rating Scale via a semi-structured interview. The Rod Orientation Test (ROT) was the first test administered, then the WCST, BDI, RBMT and finally the Advanced Progressive Matrices (APM) sets I and II. A more extended break was taken after the WCST, with shorter breaks between other tests.

In keeping with the protocol of Hovestadt (1990) the test apparatus for the ROT consisted of a 55cm board with two pairs of rods set 38cm apart. Figure 3 illustrates the Rod Orientation Test (ROT) and its construction. The ROT consists of a "vertical rod which rotates about a 360^{o} axis and a second rod which is added to the vertical rod by a hinged joint, the second rod may be moved up or down in a sagittal plane" (Hovestatdt,1990 p26).

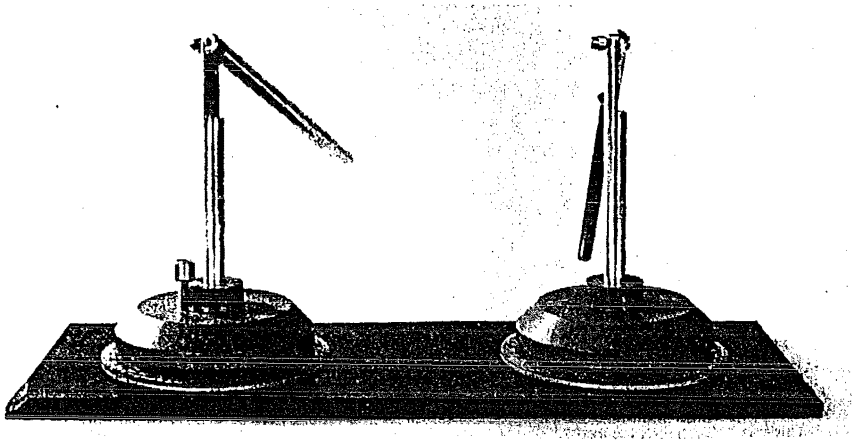


Figure 7.0 Rod Orientation Test (Hovestadt, 1990 p26).

Two variants of the ROT were administered:

1. **Visual Inspection**: Subjects were asked to set one pair of the rods in the same manner in which the other model was set, without touching the model rods.

2. **Tactile palpation:** Subjects were asked to put on a blindfold and following palpation of the model, estimate the angle, then set the other pair of rods to match.

The following angles in Table 7.2.3 were used for both variants (visual and tactile).

Table 7.2.3 Settings for the ROT.

Vertical Angles	Horizontal Angles
90^{o}	180^{o}
45^{o}	90^{o}
130^{o}	320^{o}
60^{o}	160^{o}
150^{o}	230^{o}

The subject was seated in front of the apparatus and permitted to move the head and eyes but not the trunk. The subjects were also informed that they could use a preferred hand to adjust the apparatus, but not both. For the visual part of the test, the

subject was not permitted to touch the model. The dependent measures included the mean error scores for visual vertical, visual horizontal, tactile vertical and tactile horizontal angles which were measured with a 360^{o} International Standard Goniometer.

The full 128 card version of the WCST was administered, and scored according to the manual (Heaton, 1981) but an additional measure, number of trials to reach the first category was also included because this measure indicates a subject's ability to form a set, rather than shift a set (Taylor et al, 1986b). All subtests of the RBMT were administered according to the manual except Item 3 "hiding a belonging". Instead placing the belonging in a cupboard in the subject's home, the item was placed in the investigator's briefcase in the first test and in a pocket in the second.

The BDI was conducted according to the standard guidelines (Beck & Steer, 1987). The APM was administered last to keep testing to a limit, and because of good split-half reliability, the odd numbers only were administered at baseline testing, and the even at 8 weeks. The entire battery took approximately 90 to 120 minutes to administer although some IPD subjects required more time than this.

Within one week of testing, subjects commenced on 10mg/day of deprenyl or placebo for 8 weeks. At the end of that period ($\pm$ 5 days) the neurological and neuropsychological tests were repeated; in addition a check list of standard side effects was completed. The medication was supplied free of charge to subjects by Reckett and Colman Pharmaceuticals.

Groups I - IV

Week 1: Baseline neurological and neuropsychological testing was completed. On the basis of these baseline assessments IPD subjects were assigned to groups I - IV (depending on their previous history of medications) on a matched pairs basis. Where possible IPD subjects were matched on the basis of age, education severity of motor symptoms, performance on the ROT and immediate recall of prose on the RBMT.

Because subjects commenced the trial at different times between July 1991 and January 1992 it was not always possible to match subjects. The consultant neurologist, neurological registrar and principal investigator were blind as to which group subjects were assigned. For safety reasons, the neurological registrar had access to the code.

Week 2: Subjects commenced taking either deprenyl or a matching placebo. Subjects took one tablet (5mg) per day at either breakfast or lunch, for the first week, then two tablets (10 mg) per day, one at breakfast and the second at lunch for the next seven weeks. All IPD subjects were asked to keep a diary for the eight weeks and to note any changes, (positive or negative) or side effects.

Week 10: Subjects in Groups I to IV were re-tested on the neurological and neuropsychological measures. Those on the placebo were then given deprenyl and those on deprenyl continued the drug regime as before.

The controls subjects were given one baseline assessment in the neuropsychological measures to enable comparisons between these subjects and those with IPD to be made.

8.0 RESULTS

The baseline motor, affective and cognitive measures were analysed by two-tailed t-tests to make possible comparisons between the early and established IPD groups, and between the IPD groups and controls. Subsequent to these analyses, the influence of eight weeks administration of deprenyl compared to placebo were analysed by two way analyses of variance (2 x 2 ANOVA) with a repeated measure on the second factor.

8.1 Early vs. Established IPD

The early and established IPD groups were comparable on all measures except the Hoehn & Yahr Scale ($t = 2.528$, $df = 21$, $p < 0.05$), which is to be expected because the established group have more severe motor deficits. (See Tables 8.1.1 to 8.1.7 for summaries of all baseline motor, cognitive and affective tests). The more sensitive measure of motor function, the UPDRS, motor scale did not reach statistical significance ($t = -1.75$, $df = 21$, $p = 0.095$), possibly because of the effects of medication in the established group. The only other measure on which the two IPD groups differed significantly was the mood subscale of the BDI ($t = 2.172$, $df = 21$, $p < 0.05$). This subscale focuses on items 1, 2, 4, 10, 11, 12 in the inventory and seeks measures on feelings of sorrow, discouragement, irritability, tearfulness, interest in others, boredom, and dissatisfaction. In the memory test immediate recall of prose on the was close to significance ($p = 0.064$). Because the two IPD groups were comparable on baseline measures, and because of to the small sample size of the established IPD group ($n = 8$), the two groups were combined for all subsequent analyses.

Table 8.1.1

Early vs. Established IPD at Baseline Hoehn & Yahr Mean Scores

	Early (N = 15)	Established (N = 8)	p
Mean	1.8	2.5	0.05 *
SD	0.67	0.53	
Median	2.0	2.5	
Range	1 - 3	2 - 3	

Note: Higher scores indicate increased severity of symptoms.

* $p < 0.05$

Table 8.1.2

Early vs. Established IPD at Baseline UPDRS Mean Scores

	Early (N = 15)	Established (N = 8)	p
Mood, Mentation and Behaviour			NS
Mean	4.8	3.6	
SD	1.4	2.1	
Median	3.0	3.5	
Range	0 - 5	0 - 7	
Activities of Daily Living			NS
Mean	10.9	13.7	
SD	1.4	2.1	
Median	11.0	13.0	
Range	1 - 15	8 - 19	
Motor			0.095
Mean	12.1	17.7	
SD	3.8	11.4	
Median	13.0	17.0	
Range	6 - 20	2 - 27	

Note: NS = Not Significant

Table 8.1.3

Early vs. Established IPD at Baseline Beck Depression Inventory Mean Scores

	Early (N = 15)	Established (N = 8)	p
Mood Subscale			0.041 *
Mean	1.8	4	
SD	1.3	3.4	
Median	2.0	3.5	
Range	0 - 4	0 - 10	
Self Reproach Subscale			0.105
Mean	1.2	2.8	
SD	1.3	3.4	
Median	1.0	2.0	
Range	0 - 4	0 - 10	
Vegetative Symptoms Subscale			NS
Mean	3.3	3.1	
SD	1.8	1.95	
Median	3.0	2.5	
Range	0 - 9	0 - 10	
Somatic Subscale			NS
Mean	3.3	3.1	
SD	1.8	1.95	
Median	5.0	3.5	
Range	0 - 8	0 - 5	
Total Score			NS
Mean	9.4	12.2	
SD	3.9	8.3	
Median	10.0	12.0	
Range	0 - 16	0 - 29	

Note: NS = Not Significant

* $p < 0.05$

Total Score Mood Scores

0 - 9 = normal / asymptomatic.
10 -18 = mild to moderate depression.
19 - 29 = moderate to severe depression.
30 - 63 = extremely severe depression.

Table 8.1.4

Early vs. Established IPD at Baseline Rod Orientation Test Mean Errors

	Early (N = 15)	Established (N = 8)	p
Visual Vertical			NS
Mean	4.1	5.1	
SD	1.35	1.86	
Median	4.2	5.4	
Range	1.0 - 6.0	2.2 - 7.6	
Visual Horizontal			NS
Mean	6.8	6.7	
SD	6.46	4.66	
Median	4.9	5.2	
Range	1.9 - 28.3	3.6 - 17.7	
Tactile Vertical			NS
Mean	10.2	7.9	
SD	4.99	3.84	
Median	9.8	7.8	
Range	4 - 22.6	4.8 - 10.2	
Tactile Horizontal			NS
Mean	8.0	8.0	
SD	4.87	3.37	
Median	6.7	7.5	
Range	2.4 - 22.1	2.6 - 12.2	

Note: NS = Not Significant

Table 8.1.5

Early vs. Established IPD at Baseline Advanced Progressive Matrices Mean Scores

	Early (N = 15)	Established (N = 8)	p
Total Correct (Set I)			NS
Mean	3.86	4.12	
SD	1.18	1.24	
Median	4.0	4.0	
Range	2 - 6	2 - 6	
Total Correct (Set II)			NS
Mean	5.3	3.8	
SD	2.55	2.47	
Median	6.0	3.5	
Range	1 - 10	1 - 8	

Note: Set I maximum score = 7
Set II maximum score = 18
NS = Not Significant

Table 8.1.6

Early vs. Established IPD at Baseline Wisconsin Card Sorting Test Mean Scores

	Early (N = 15)	Established (N = 8)	p
Total Correct Score			NS
Mean	68.1	62.4	
SD	15.45	19.8	
Median	702	654	
Range	33 - 93	33 - 88	
Total Error Score			NS
Mean	51.1	53.5	
SD	24.21	32.21	
Median	52	54	
Range	10 - 95	11 - 95	
Perseverative Responses			NS
Mean	33.7	41.87	
SD	21.36	38.44	
Median	30	35.5	
Range	6 - 85	6 - 127	
Non Perseverative Errors			NS
Mean	23.3	21.8	
SD	14.47	18.48	
Median	22.8	15.5	
Range	4 - 47	1 - 46	
Perseverative Errors			NS
Mean	28.27	31.8	
SD	15.47	28.13	
Median	29	22.5	
Range	6 - 63	6 - 94	
Categories [(a)]			NS
Mean	3.7	3.5	
SD	2.16	2.53	
Median	3.7	3.7	
Range	0.4 - 6	0.3 - 6	
Categories to complete first trial.			NS
Mean	38.1	45	
SD	41.88	52.41	
Median	18	13	
Range	11 - 128	11 - 128	

Note: NS = Not Significant

[(a)] Maximum number of categories = 6

Table 8.1.7

Early vs. Established IPD at Baseline Rivermead Behavioural Memory Test Mean Scores

	Early (N = 15)	Established (N = 8)	p
Standardised Profile			NS
Mean	19.2	18.6	
SD	2.8	2.6	
Median	19.0	20.0	
Range	14 - 24	14 - 21	
Screening Score			NS
Mean	8.0	7.7	
SD	2.47	2.12	
Median	8.0	8.5	
Range	4 - 12	5 - 10	
Immediate Recall			0.064
Mean	7.06	5.12	
SD	2.43	1.88	
Median	7.0	4.8	
Range	5 - 10.5	4 - 8.5	
Delayed Recall			NS
Mean	4.9	3.43	
SD	3.07	2.02	
Median	4.5	3.8	
Range	0 - 11	0 - 6.5	

Note: NS = Not Significant

Standardised Profile Score
22 - 24 = normal.
17 - 21 = poor memory.
10 - 16 = moderately impaired.
0 - 9 = severely impaired.

Screening Score
10 - 12 = normal.
7 - 9 = poor memory.
3 - 6 = moderately impaired.
0 - 2 = severely impaired.

Immediate and Delayed Recall Maximum Score = 21

8.2 Combined IPD Groups vs. Matched Controls

Baseline scores of the combined IPD groups and controls across various measures are presented in Table 8.2.1 to 8.2.5

Beck Depression Inventory (BDI)

As indicated in Table 8.2.1 statistically significant differences emerged between the IPD subjects and controls on three measures on the BDI. The total score, which is the combination of the four subscales, indicated IPD subjects were significantly more depressed than controls ($t = 3.271$, $df = 31$, $p < 0.005$). With respect to the specific subscales, scores on three of the subscales indicated the nature of the depressive features. The somatic subscale, which measures items 14,15, 17 and 20, relating to physical appearance, fatigue, ability to work and health concerns was significantly different from controls ($t = 4.736$, $df = 31$, $p < 0.001$). The vegetative subscale, which measures items 16, 18, 19, 21, libido, weight loss, sleep and appetite also differed ($t = 2.438$, $df = 31$, $p < 0.05$). The mood and self reproach subscales showed no difference from controls.

Table 8.2.1

PD vs. Controls at Baseline Beck Depression Inventory Mean Scores

	PD (N = 23)	Controls (N = 10)	p
Mood Subscale			NS
Mean	2.6	1.5	
SD	2.4	2.2	
Median	2.0	0	
Range	0 - 10	0 - 6	
Self Reproach Subscale			NS
Mean	1.7	1.0	
SD	1.3	3.4	
Median	1.0	1.0	
Range	0 - 10	0 - 3	
Vegetative Symptoms Subscale			0.021 *
Mean	2.7	0.90	
SD	2.3	1.1	
Median	3.0	0.5	
Range	0 - 9	0 - 3	
Somatic Subscale			0.000 *
Mean	3.2	0.40	
SD	1.8	0.69	
Median	3.0	0	
Range	0 - 8	0 - 2	
Total Score			0.003 *
Mean	10.3	3.8	
SD	5.8	3.8	
Median	9.0	1.5	
Range	0 - 37	0 - 11	

Note: NS = Not Significant

* $p < 0.05$

Total Score Mood Score

0 - 9 = normal / asymptomatic.
10 -18 = mild to moderate depression.
19 - 29 = moderate to severe depression.
30 - 63 = extremely severe depression.

Wisconsin Card Sorting Test (WCST)

Results of this test of executive functions shown in Table 8.2.2, indicate significant differences between the IPD and the control group on the total number of incorrectly sorted cards (Total Error Scores) ($t = 2.204$, $df = 31$, $p < 0.05$) and the number of perseverations (Perseverative Error Scores) ($t = 2.045$, $df = 31$, $p < 0.05$). These results indicate that IPD subjects had difficulty shifting set and made more errors than controls.

Further differences between the control group and IPD subjects on the WCST are indicated by the scores in number of categories achieved, number of trials to complete the first category and number of correctly sorted cards, all of which came close to statistical significance.

Table 8.2.2

PD vs. Controls at Baseline Wisconsin Card Sorting Test Mean Scores

	PD (N = 23)	Controls (N = 10)	p
Total Correct Score			0.056
Mean	66.08	78.4	
SD	16.86	15.21	
Median	66.0	76.0	
Range	33 - 93	61 - 112	
Total Error Score			0.053
Mean	51.91	30.6	
SD	26.54	22.85	
Median	52.0	18.0	
Range	10 - 95	7 - 67	
Perseverative Responses			0.094
Mean	36.56	19.5	
SD	27.85	20.99	
Median	30.0	9.0	
Range	6 - 127	3 - 63	
Non Perseverative Errors			NS
Mean	22.43	16.0	
SD	15.56	14.94	
Median	20.0	11.5	
Range	1 - 47	3 - 55	
Perseverative Errors			0.049 *
Mean	29.47	14.6	
SD	20.17	16.47	
Median	26.0	8.0	
Range	6 - 94	3 - 52	
Categories [(a)]			0.055
Mean	3.59	5.1	
SD	2.2	2.8	
Median	3.7	6.0	
Range	0 - 6	3.9 - 6	
Categories to complete first trial.			0.073
Mean	41.0	14.4	
SD	44.54	8.92	
Median	16	12.0	
Range	11 -128	11 - 37	

Note: S = Not Significant

[(a)] Maximum number of categories = 6

* $p < 0.05$

Rivermead Behavioural Memory Test (RBMT)

As presented in Table 8.2.3, the differences between IPD subjects and controls on immediate recall of five to six lines of prose almost reached an acceptable level of significance ($t = -2.027$, $df = 31$, $p = 0.051$). Similarly the delayed recall of prose just failed to reach significance ($t = -1.935$, $df = 31$, $p = 0.062$), strongly suggesting impairment in the IPD groups relative to controls.

Table 8.2.3

PD vs. Controls at Baseline Rivermead Behavioural Memory Test Mean Scores

	PD (N = 23)	Controls (N = 10)	p
Standardised Profile			NS
Mean	19.0	19.6	
SD	2.7	3.5	
Median	20	19.5	
Range	14 - 24	13 - 24	
Screening Score			NS
Mean	7.91	9.2	
SD	2.37	2.09	
Median	8.0	9.5	
Range	4 - 12	5 - 12	
Immediate Recall			0.051
Mean	6.3	8.2	
SD	2.4	2.2	
Median	5.5	8.0	
Range	2.5 - 13	4.5 - 12	
Delayed Recall			0.062
Mean	4.3	6.4	
SD	2.7	2.6	
Median	4.0	6.8	
Range	0 - 11	3 - 12	

Note: NS = Not Significant

Standardised Profile Score
22 - 24 = normal.
17 - 21 = poor memory.
10 - 16 = moderately impaired.
0 - 9 = severely impaired.

Screening Score
10 - 12 = normal.
7 - 9 = poor memory.
3 - 6 = moderately impaired.
0 - 2 = severely impaired.

Immediate and Delayed Recall Maximum Score = 21

Rod Orientation Test (ROT) and Advanced Progressive Matrices (APM)

Comparisons of IPD subjects and controls on both the ROT and APM (See Table 8.2.4) showed no statistically significant differences between the groups on these two measures of visuospatial functions.

Table 8.2.4

PD vs. Controls at Baseline Rod Orientation Test Mean Errors

	PD (N = 23)	Controls (N = 10)	p
Visual Vertical			NS
Mean	4.41	4.48	
SD	1.5	0.9	
Median	4.7	4.3	
Range	1 - 7.6	3 - 5.8	
Visual Horizontal			NS
Mean	6.7	4.3	
SD	5.7	1.3	
Median	5.1	4.6	
Range	1.9 - 28.3	1.4 - 6	
Tactile Vertical			NS
Mean	9.3	7.9	
SD	4.6	3.6	
Median	8.6	7.4	
Range	2.8 - 22.6	2.6 - 17.8	
Tactile Horizontal			NS
Mean	8.0	6.9	
SD	4.3	3.2	
Median	6.7	7.1	
Range	2.4 - 22.1	2.6 - 12.5	

Note: NS = Not Significant

Table 8.2.5

PD vs. Controls at Baseline Advanced Progressive Matrices Mean Scores

	PD (N = 23)	Controls (N = 10)	p
Total Correct (Set I)			NS
Mean	3.9	4.2	
SD	1.1	1.4	
Median	4.0	5.0	
Range	2 - 6	2 - 7	
Total Correct (Set II)			NS
Mean	4.8	6.7	
SD	2.5	3.8	
Median	5.0	8.0	
Range	1 - 10	2 - 11	

Note: Set I maximum score = 7
Set II maximum score = 18

In summary, the t - tests used to analyse baseline measures of early vs. established IPD subjects and the combined IPD group vs. controls revealed:

1. A statistically significant difference between early and established IPD on the mood subscale of the BDI.
2. Statistically significant differences between the combined IPD subjects and controls on total error score and number of categories on the WCST; the total score on the BDI; and BDI Subscale scores of Vegetative Symptoms and Somatic Symptom.

8.3 Relationships between Idiopathic Parkinson's Disease and Motor, Cognitive and Affective Measures.

In order to determine if performance on the baseline cognitive and affective measures was related to age, severity, or duration of IPD, and if these variables could have influenced performance on the standard tests, Pearson Product Moment Correlation analyses were conducted. Because multiple analyses were being undertaken, the level of significance was set at $p < 0.02$.

8.3.1 Relationship between severity and duration of IPD and Affect.

Predictably, the severity of motor symptoms, indicated by the motor scale of the UPDRS, was related to duration of IPD ($r = 0.591$, $p < 0.005$) and reduced independence in daily living (measured on UPDRS Activities of Daily Living Scale) ($r = 0.678$, $p < 0.001$). Reduced independence and disease severity are also related to depressive features in IPD, (See Table 8.3.1). The mean BDI score of ten indicated that the IPD subjects were at the lower end of the cut-off score for mild to moderate depression, and the relationship with severity of symptoms was highly significant ($r = 0.607$, $p = 0.002$). Analysis of the four subscales shows that mood ($r = 0.63$, $p = 0.001$) and self reproach ($r = 0.688$, $p = 0.001$) were related to motor disability, whereas vegetative and somatic symptoms were not. The duration of IPD was also related to a lower mood score on the BDI subscale ($r = 0.493$, $p < 0.02$). Interestingly, in this group of subjects, age was not related to severity of motor symptoms ($r = 0.227$, $p > 0.1$).

Table 8.3.1

Pearson Product Moment Correlation Coefficients (r) between IPD duration, severity and affect.[a]

Measure	UPDRS (Motor) (r)	(p)	UPDRS (ADL) (r)	(p)	PD Duration (r)	(p)
Beck Depression Inventory						
Total Score	0.607	0.002 *	0.503	0.014 *	0.320	0.137
Mood	0.63	0.001 *	0.289	0.181	0.493	0.017 *
Somatic	0.127	0.563	0.366	0.086	- 0.185	0.399
Self Reproach	0.688	0.000 *	0.415	0.049	0.439	0.036
Vegetative	0.045	0.840	0.223	0.306	- 0.030	0.892

Note. [a] n = 23

* $p < 0.02$

8.3.2 Relationship between Affect and Cognition in IPD subjects.

A tendency towards depression in IPD subjects might also result in decrements in some aspects of memory, visuospatial and executive functions. This is indicated by some statistically significant correlations between measures of these variables.

8.3.3 Executive Functions.

The total number of errors made on the WCST is related to total score on the BDI ($r = 0.539$, $p < 0.02$), however, there was no significant relationship between the reportedly more sensitive measures of perseverative errors ($r = 0.434$, $p > 0.10$) and perseverative responses ($r = 0.407$, $p > 0.05$), or total scores on the BDI. The statistically significant relationship between age and total errors on the WCST ($r = 0.557$, $p < 0.02$) suggests that age, depression and disease severity have to be considered when examining decrements in performance on the WCST. A significant relationship between number of categories sorted on the WCST and Standardised Profile Score of the RBMT also emerged ($r = 0.481$, $p < 0.02$).

8.3.4 Memory, Visuospatial Functions and IPD

Contrary to evidence cited in Section 1.4 on visuospatial function, the present study found no significant relationship between the two measures of visuospatial function and IPD duration or severity.

The relationship between IPD severity duration and memory failed to reach significance, which gives some weight to the view that cognitive deficits in IPD are not the result of dopaminergic lesions. In summary, the multiple correlations revealed that although relationships exist between a number of motor and affective variables, very few cognitive functions have a statistically significant relationship with motor function.

8.4 The Influence of Eight Weeks of Deprenyl Therapy

The motor, cognitive and affective tests were repeated following eight weeks of 10 mg/day of deprenyl or placebo and the results are presented in Table 8.4.1.1 to Table 8.4.6.3. The two way analysis of variance Group (placebo vs. deprenyl) x Time (0 vs. 8 weeks), repeated over the second factor, were used to compare the effect of deprenyl with that of placebo.

8.4.1 Rod Orientation Test

The mean values for the placebo and deprenyl IPD groups at baseline and eight weeks on the four versions of the ROT are shown in Table 8.4.1.2 with corresponding graphs in Figure 8.4.1 to 8.4.4. There was no change in performance over time across both groups. (Main effects for time, $p > 0.1$ on all measures of the ROT). On the Tactile Vertical dimension, the deprenyl group improved slightly from baseline to eight weeks, while the placebo group's score deteriorated over this period, but these changes were not significant, Group (placebo vs. deprenyl) x Time (0 vs. 8 weeks) interaction ($F = 2.80865$, $df = 1.21$, $p > 0.1$). All other group x time interactions were not significant.

Table 8.4.1.1

Summary of ANOVA Results for Rod Orientation Test - placebo vs. deprenyl group subjects at baseline and at eight weeks.

Measure	Source	df	F	p
Rod Orientation Test				
Visual Vertical	P v D	1, 21	2.0817	0.1608
	0 v 8	1, 21	0.9279	0.3486
	P/D x 0/8	1, 21	0.4299	0.5257
Visual Horizontal	P v D	1, 21	0.1023	0.7470
	0 v 8	1, 21	2.0158	0.1674
	P/D x 0/8	1, 21	0.3698	0.5561
Tactile Vertical	P v D	1, 21	2.2599	0.1444
	0 v 8	1, 21	0.4032	0.5389
	P/D x 0/8	1, 21	2.8067	0.1052
Tactile Horizontal	P v D	1, 21	0.1764	0.6808
	0 v 8	1, 21	0.2102	0.6551
	P/D x 0/8	1, 21	0.4988	0.4943

Table 8.4.1.2

Placebo vs. Deprenyl at Baseline and at eight weeks. Rod Orientation Test

	Placebo (N = 11)		Deprenyl (N =12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
Visual Vertical					NS
Mean	4.6	5.3	4.2	4.3	
SD	1.6	0.79	1.5	2.11	
Median	4.7	5.2	4.6	4.1	
Range	2.2 - 7.6	4.2 - 6.8	1.0 - 6.4	1.3 - 8.4	
Visual Horizontal					NS
Mean	6.7	4.7	6.6	5.8	
SD	7.4	2.11	4.0	2.75	
Median	4.8	4.5	5.7	5.7	
Range	1.9 - 28.3	1.6 - 8.2	2.9 - 17.7	1.5 - 12.6	
Tactile Vertical					NS
Mean	9.8	12.52	8.9	7.75	
SD	5.5	7.81	3.8	2.98	
Median	9.8	9.5	8.0	6.9	
Range	4 - 22.6	5.2 -26.6	2.8 - 15	3.8 - 13	
Tactile Horizontal					NS
Mean	7.9	8.2	8.0	6.75	
SD	5.4	6.39	3.1	2.39	
Median	6.7	6.4	7.7	6.4	
Range	2.4 - 22.1	3.1 - 25.1	2.6 - 13.7	2.5 - 10.4	

Note: NS = Not Significant

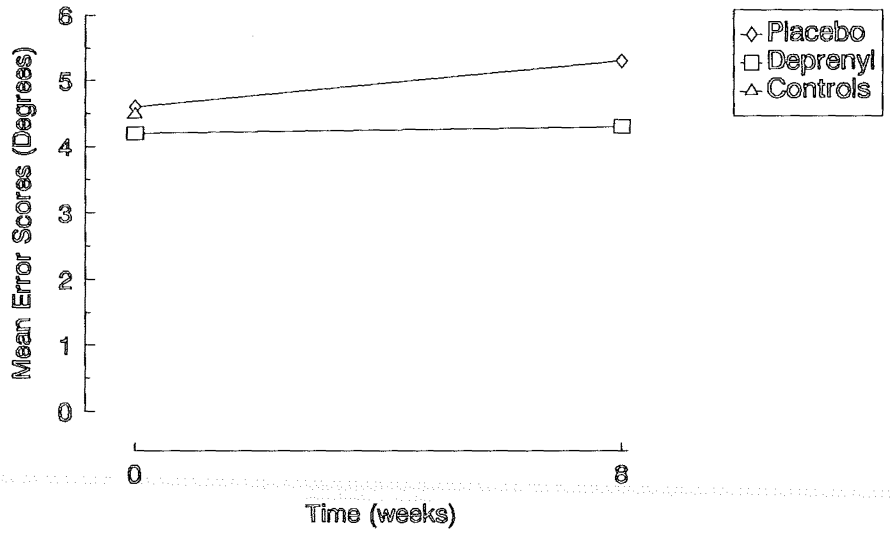


Figure 8.4.1.1: Mean error scores on the ROT (Visual Vertical) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

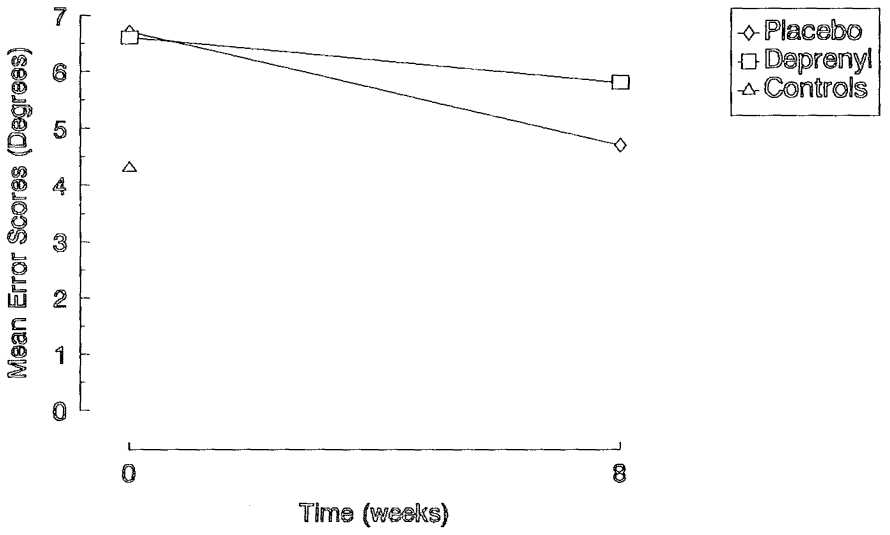


Figure 8.4.1.2: Mean error scores on the ROT (Visual Horizontal) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

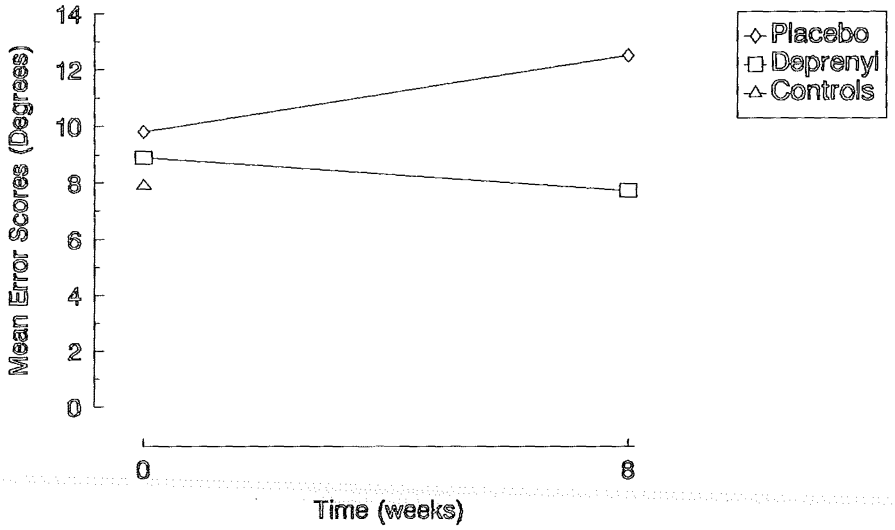


Figure 8.4.1.3: Mean error scores on the ROT (Tactile Vertical) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

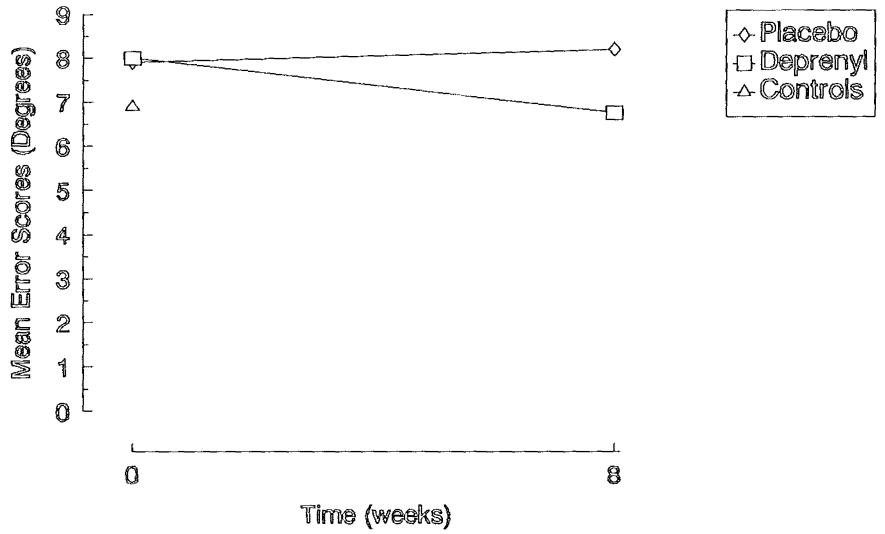


Figure 8.4.1.4: Mean scores on the ROT (Tactile Horizontal) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

8.4.2 Wisconsin Card Sorting Test

Table 8.4.2.2 shows the mean values for the placebo and deprenyl IPD group at baseline and at eight weeks on all seven measures of the WCST. Figure 8.4.2.1 to 8.4.2.7 presents these data in graphic form. Although IPD subjects are impaired on the specific measures of the WCST relative to controls, after eight weeks neither of the two groups, deprenyl or placebo, improved on any measure. (See Table 8.4.2.1). There were no main or interaction effects for Time (0 vs. 8 weeks) or Group (placebo vs. deprenyl) even for the non-perseverative error mean score which reduced from 20.5 to 16.3 in the deprenyl group and increased from 24.4 to 28.0 in the placebo group.

Table 8.4.2.1

Summary of ANOVA for Wisconsin Card Sorting Test - placebo vs. deprenyl groups subjects at baseline and at eight weeks.

Measure	Source	df	F	p
WCST				
Correct (Total)	P v D	1, 21	0.0285	0.8428
	0 v 8	1, 21	0.1443	0.7075
	P/D x 0/8	1, 21	1.1591	0.2941
Errors (Total)	P v D	1, 21	0.5120	0.4886
	0 v 8	1, 21	0.0415	0.8212
	P/D x 0/8	1, 21	0.8142	0.3806
Perseverative Responses	P v D	1, 21	0.1604	0.9450
	0 v 8	1, 21	0.2732	0.6128
	P/D x 0/8	1, 21	1.4379	0.2425
Non Perseverative Errors	P v D	1, 21	1.7508	0.1976
	0 v 8	1, 21	0.0192	0.8610
	P/D x 0/8	1, 21	2.3557	0.1364
Perseverative Errors	P v D	1, 21	0.0237	0.8518
	0 v 8	1, 21	0.4070	0.5369
	P/D x 0/8	1, 21	1.0758	0.3123
Categories	P v D	1, 21	0.0722	0.7801
	0 v 8	1, 21	0.9228	0.3500
	P/D x 0/8	1, 21	1.3840	0.2515
Trials to reach first category	P v D	1, 21	0.2304	0.6407
	0 v 8	1, 21	0.0965	0.7530
	P/D x 0/8	1, 21	0.1787	0.6790

Table 8.4.2.2

Placebo vs. Deprenyl at Baseline and at eight weeks. Wisconsin Card Sorting Test

	Placebo (N = 11)		Deprenyl (N = 12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
Total Correct Score					NS
Mean	65.0	69.2	67.0	65.0	
SD	13.1	21.1	20.2	16.7	
Median	64.0	76.0	71.0	72.0	
Range	46 - 84	22 - 100	33 - 93	34 - 84	
Total Error Score					NS
Mean	54.7	56.7	49.3	46.1	
SD	23.7	23.2	29.6	31.8	
Median	64.0	52.0	43.5	45.5	
Range	10 - 82	27 - 106	11 - 95	8 - 94	
Perseverative Responses					NS
Mean	39.3	31.7	34.0	37.0	
SD	22.0	19.3	33.1	37.3	
Median	43	23	25	29.5	
Range	6 - 85	11 - 76	6 - 127	4 - 126	
Non Perseverative Errors					NS
Mean	24.4	28	20.5	16.3	
SD	15.7	16.5	15.8	13.1	
Median	20.0	29.0	19.0	16.5	
Range	4 - 47	10 - 72	1 - 47	1 - 44	
Perseverative Errors					NS
Mean	30.2	25.7	28.7	29.8	
SD	16.0	13.1	24.0	27.1	
Median	31.0	21.0	22.5	27.0	
Range	6 - 63	11 - 56	6 - 94	4 - 93	
Categories					NS
Mean	3.1	4.2	4.0	3.9	
SD	1.9	4.2	2.5	2.5	
Median	2.5	2.7	5.6	5.4	
Range	0.6 - 6.0	0.4 - 6.0	0 - 6.0	0.3 - 6.0	
Categories to complete first trial.					NS
Mean	34.5	43.2	46.9	45.5	
SD	39.0	44.5	50.0	44.5	
Median	14.0	16.0	22.5	17.0	
Range	11 - 128	11 - 128	11 - 128	11 - 128	

Note: NS = Not Significant

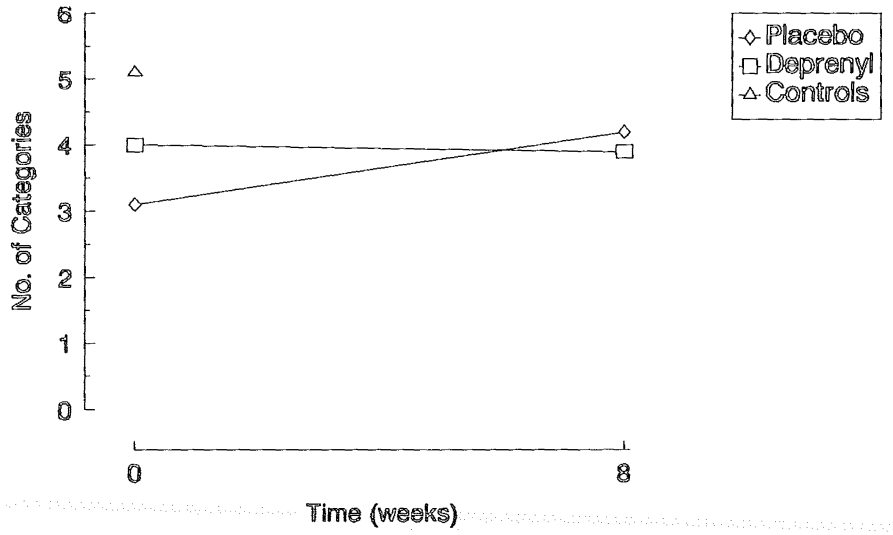


Figure 8.4.2.1: Mean scores on the Wisconsin Card Sorting Test (No. of Categories Sorted) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

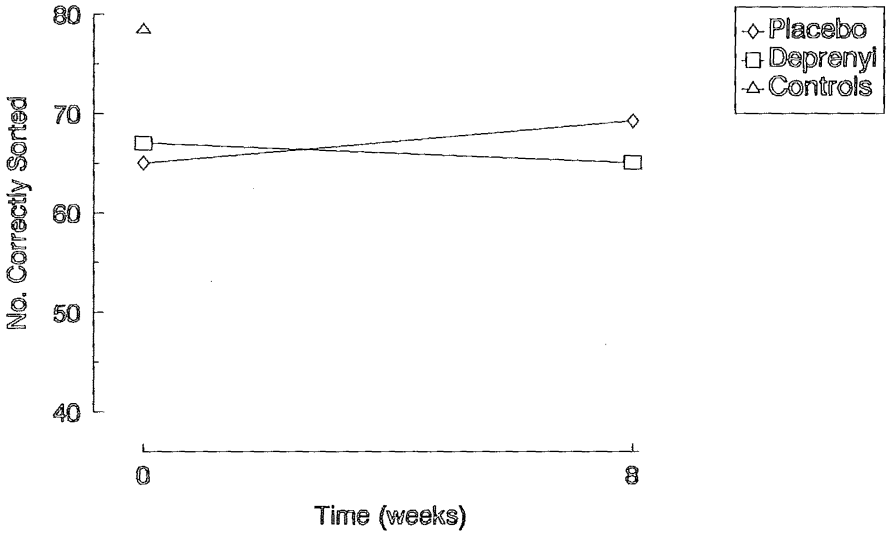


Figure 8.4.2.2: Mean scores on the Wisconsin Card Sorting Test (Total number of cards correctly sorted) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

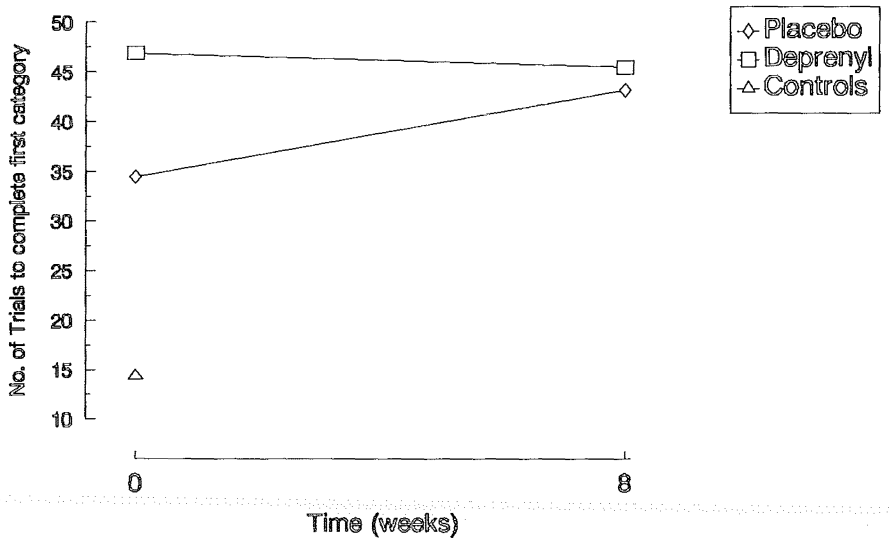


Figure 8.4.2.3: Mean scores on the Wisconsin Card Sorting Test (Number of trials to complete the first category) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

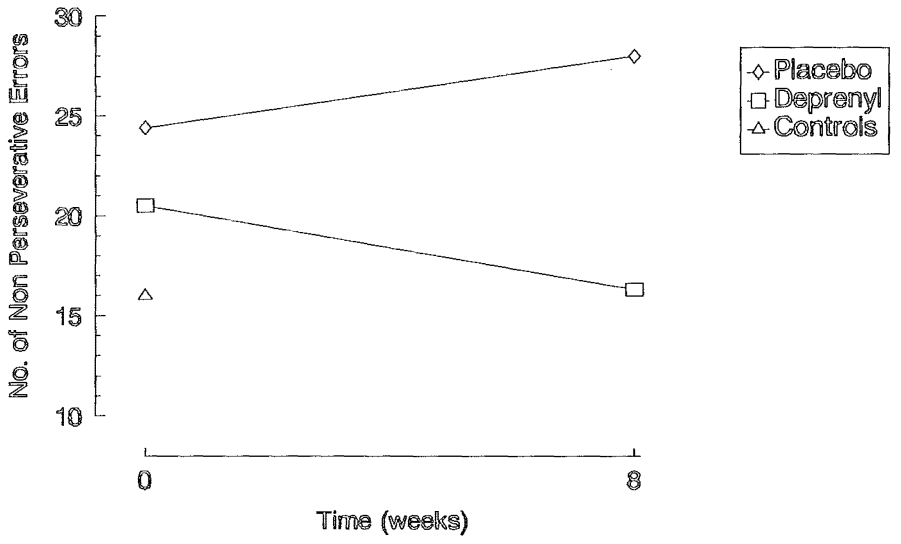


Figure 8.4.2.4: Mean scores on the Wisconsin Card Sorting Test (Number of Non-Perseverative Errors Scored) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

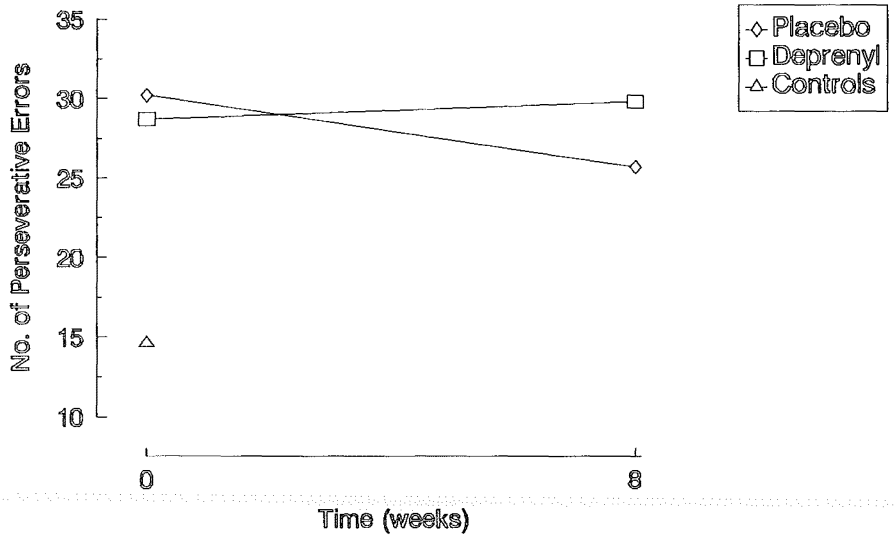


Figure 8.4.2.5: Mean scores on the Wisconsin Card Sorting Test (Number of Perseverative Errors Scored) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

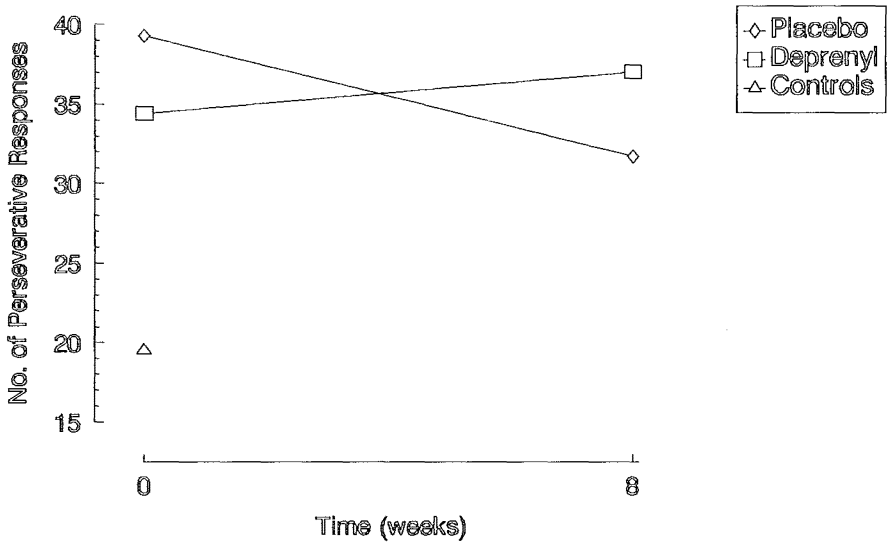


Figure 8.4.2.6: Mean scores on the Wisconsin Card Sorting Test (Perseverative Responses Scored) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

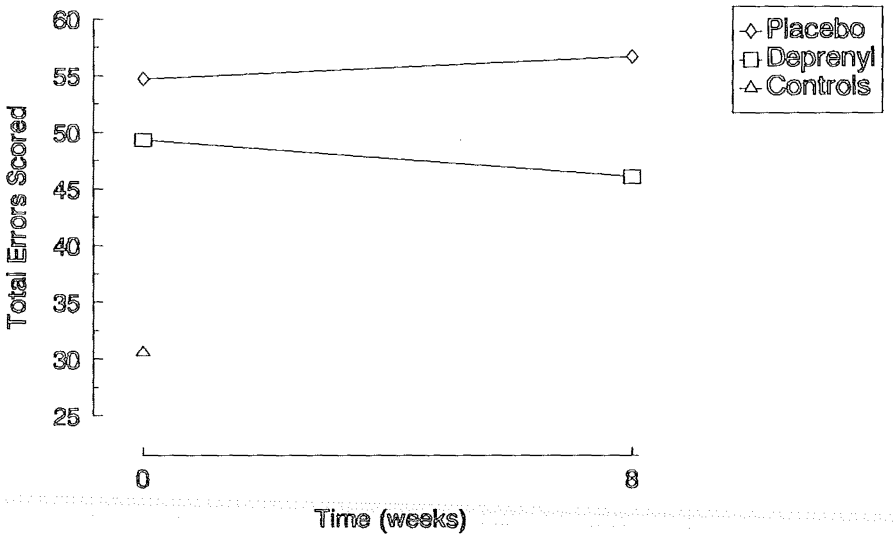


Figure 8.4.2.7: Mean scores on the Wisconsin Card Sorting Test (Total Errors Scored) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

8.4.3 Beck Depression Inventory

The BDI measures of affect showed that IPD subjects are depressed when compared to controls. The analysis of variance, Group (placebo vs. deprenyl) x Time (0 vs. 8 weeks) repeated over the second factor, performed on five measures of the BDI are summarised in Table 4.3.1. A main effect for time ($F = 7.5327$, $df = 1,21$, $p < 0.05$) was revealed, coupled with a significant interaction between Group and Time, ($F= 10.6905$, $df = 1,21$, $p < 0.02$), on the vegetative symptoms sub-scale. This interaction arose because the placebo groups reported that sleeping, appetite and libido improved between baseline and eight weeks, whereas the deprenyl group remained almost static. These changes in means are shown in Table 8.4.3.2 and Figures 8.4.3.1 to 8.4.3.4. The total score on the BDI also demonstrated a main effect for time, between baseline and eight weeks ($F = 6.09568$, $df = 1,21$, $p < 0.05$). An interaction emerged between Group (placebo vs. deprenyl) x Time (0 vs. 8) on the Total BDI scores, due to a significant decline in scores in the placebo group between baseline and eight weeks, however scores in the deprenyl group remained stable.

Table 8.4.3.1

Summary of ANOVA for the Beck Depression Inventory - placebo vs. deprenyl group subjects at baseline and at eight weeks.

Measure	Source	df	F	p
Beck Depression Inventory				
Mood	P v D	1, 21	0.4148	0.5331
	0 v 8	1, 21	0.1986	0.6637
	P/D x 0/8	1, 21	0.4169	0.5320
Self Reproach	P v D	1, 21	0.0003	0.9346
	0 v 8	1, 21	0.5567	0.4701
	P/D x 0/8	1, 21	0.5567	0.4701
Vegetative Symptoms	P v D	1, 21	0.2814	0.6071
	0 v 8	1, 21	7.5327	0.0117 *
	P/D x 0/8	1, 21	10.691	0.0039 *
Somatic Score	P v D	1, 21	0.0047	0.9026
	0 v 8	1, 21	3.1750	0.0860
	P/D x 0/8	1, 21	1.6199	0.2149
Total Score	P v D	1, 21	0.1760	0.6811
	0 v 8	1, 21	5.5743	0.0265 *
	P/D x 0/8	1, 21	6.0957	0.0211 *

Note. * $p < 0.05$

Table 8.4.3.2

Placebo vs. Deprenyl at Baseline and at eight weeks. Beck Depression Inventory

	Placebo (N = 11)		Deprenyl (N = 12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
Mood Subscale					NS
Mean	3.0	2.6	2.1	2.2	
SD	2.2	3.4	1.3	2.0	
Median	2.0	3.0	2.0	1.5	
Range	0 - 10	1 - 12	0 - 8	0 - 5	
Self Reproach Subscale					NS
Mean	1.9	1.4	1.6	1.6	.
SD	2.8	4.6	1.8	2.3	
Median	1.0	1.0	1.0	1.0	
Range	0 - 10	0 - 6	0 - 5	0 - 8	
Vegetative Symptoms Subscale					NS
Mean	3.5	1.6	2.0	2.2	
SD	1.6	0.92	2.6	2.4	
Median	3.0	2.0	1.0	1.5	
Range	2 - 8	0 - 3	0 - 9	0 - 8	
Somatic Subscale					NS
Mean	3.4	2.4	3.0	2.9	
SD	1.0	1.2	2.3	1.97	
Median	3.0	3.0	3.5	3.0	
Range	2 - 5	0 - 4	0 - 8	0 - 6	
Total Score					NS
Mean	11.9	8.1	9.0	9.0	
SD	5.9	6.3	5.5	6.3	
Median	10.0	8.0	9.0	8.0	
Range	7 - 29	1 - 24	0 - 16	0 - 20	

Note: NS = Not Significant

* $p < 0.05$

Total Score Mood Score

0 - 9 = normal / asymptomatic.
10 -18 = mild to moderate depression.
19 - 29 = moderate to severe depression.
30 - 63 = extremely severe depression.

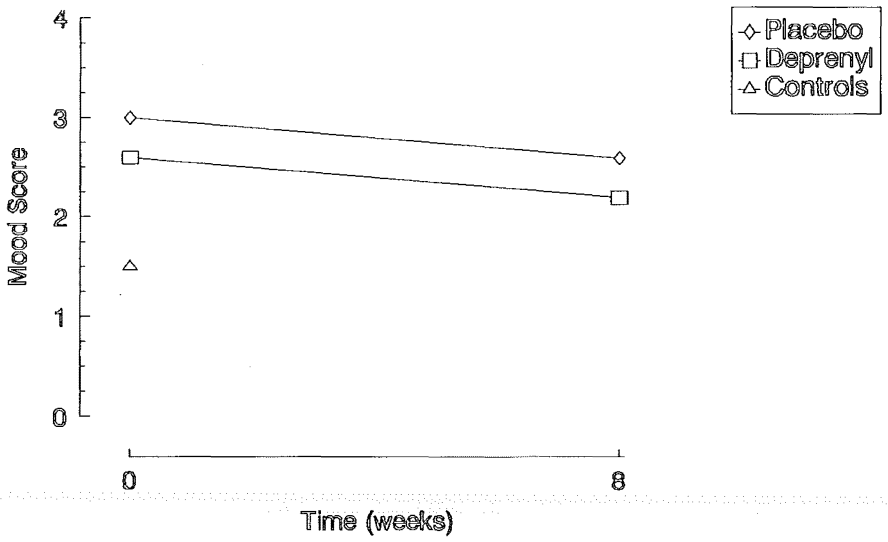


Figure 8.4.3.1: Mean scores on the Beck Depression Inventory (Mood Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

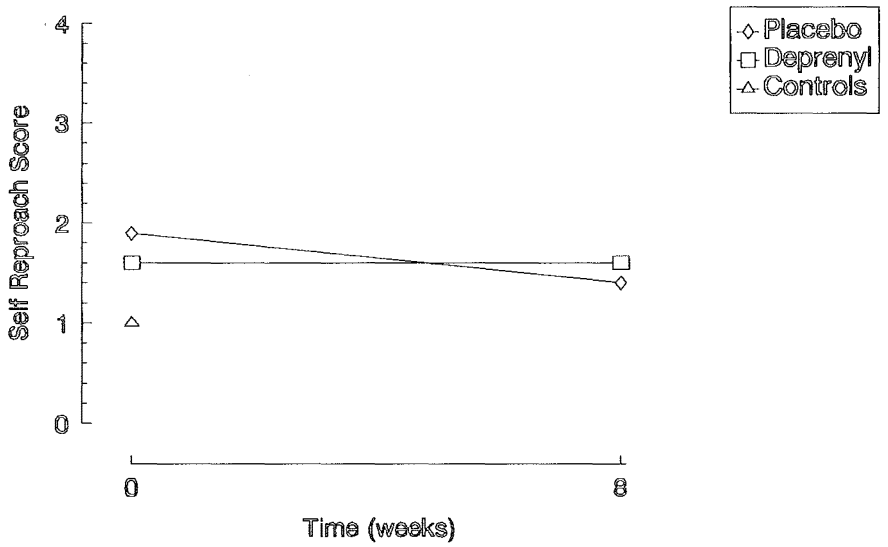


Figure 8.4.3.2: Mean scores on the Beck Depression Inventory (Self Reproach Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

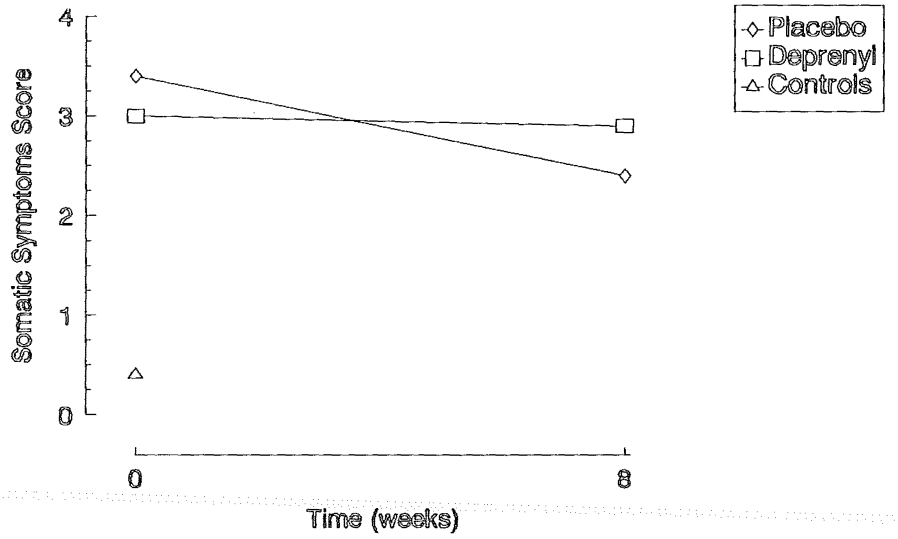


Figure 8.4.3.3: Mean scores on the Beck Depression Inventory (Somatic Symptom Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

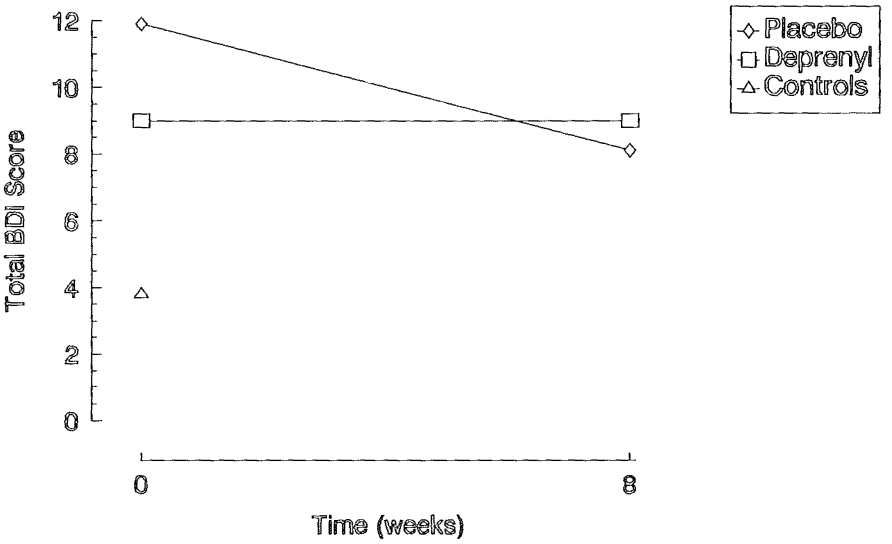


Figure 8.4.3.4: Mean scores on the Beck Depression Inventory (Total BDI Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

8.4.4 Rivermead Behavioural Memory Test (RBMT)

The Table 8.4.4.2 shows the mean values for the four measures on the RBMT, and Figures 8.4.4.1 to 8.4.4.4 the corresponding graphs, for the Placebo and deprenyl groups at baseline and eight weeks. The two way ANOVA, Group (placebo vs. deprenyl) x Time (0 vs. 8 weeks), repeated over the second factor, showed there was no significant main effect between the groups (placebo and deprenyl), but there was a main effect for time (0 vs. 8 weeks) on immediate recall of logical prose ($F = 5.6791$, $1,21$, $p < 0.05$). Mean scores improved in both groups over the eight weeks with no Group x Time interaction ($p > 0.10$). The delayed recall of prose also revealed a main effect for time ($F = 14.5939$, $df = 1,21$, $p < 0.001$) but no interaction effect was demonstrated.

Table 8.4.1

Summary of ANOVA for Rivermead Behavioural Memory Test - placebo vs.. deprenyl group subjects at baseline and at eight weeks.

Measure	Source	df	F	p
RBMT				
Standardised Profile Score	P v D	1, 21	0.2639	0.6183
	0 v 8	1, 21	1.9737	0.1718
	P/D x 0/8	1, 21	0.7746	0.3927
Screening Score	P v D	1, 21	0.7631	0.3963
	0 v 8	1, 21	2.8531	0.1026
	P/D x 0/8	1, 21	2.3173	0.1396
Immediate Recall	P v D	1, 21	0.0635	0.7909
	0 v 8	1, 21	5.6791	0.0253 *
	P/D x 0/8	1, 21	0.5960	0.4547
Delayed Recall	P v D	1, 21	0.0028	0.9122
	0 v 8	1, 21	14.544	0.0013 *
	P/D x 0/8	1, 21	0.1642	0.6907

Note. * $p < 0.05$

Table 8.4.4.2

Placebo vs. Deprenyl at Baseline and at eight weeks. Rivermead Behavioural Memory Test

	Placebo (N = 11)		Deprenyl (N = 12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
Standardised Profile					NS
Mean	19.6	20.0	18.4	20.0	
SD	2.8	4.3	2.6	3.2	
Median	20.0	21.0	17.5	20.0	
Range	14 - 24	10 - 24	14 - 24	13 - 24	
Screening Score					NS
Mean	8.7	8.8	7.1	8.9	
SD	1.9	2.7	2.4	2.3	
Median	9.0	9.0	6.5	9.5	
Range	5 - 12	4 - 12	4 - 12	4 - 12	
Immediate Recall					0.064
Mean	6.5	7.5	6.2	8.2	
SD	2.2	3.3	2.6	3.4	
Median	5.5	8.0	5.0	8.0	
Range	4 - 10.5	3 - 12.5	2.5 - 13	3 - 15	
Delayed Recall					NS
Mean	4.2	6.9	4.5	6.7	
SD	3.1	3.6	2.5	2.6	
Median	4.0	7.5	4.3	6.0	
Range	0 - 9	0.5 - 14.5	1.5 - 11	4 - 13	

Note: NS = Not Significant

Standardised Profile Score
22 - 24 = normal.
17 - 21 = poor memory.
10 - 16 = moderately impaired.
0 - 9 = severely impaired.

Screening Score
10 - 12 = normal.
7 - 9 = poor memory.
3 - 6 = moderately impaired.
0 - 2 = severely impaired.

Immediate and Delayed Recall Maximum Score = 21

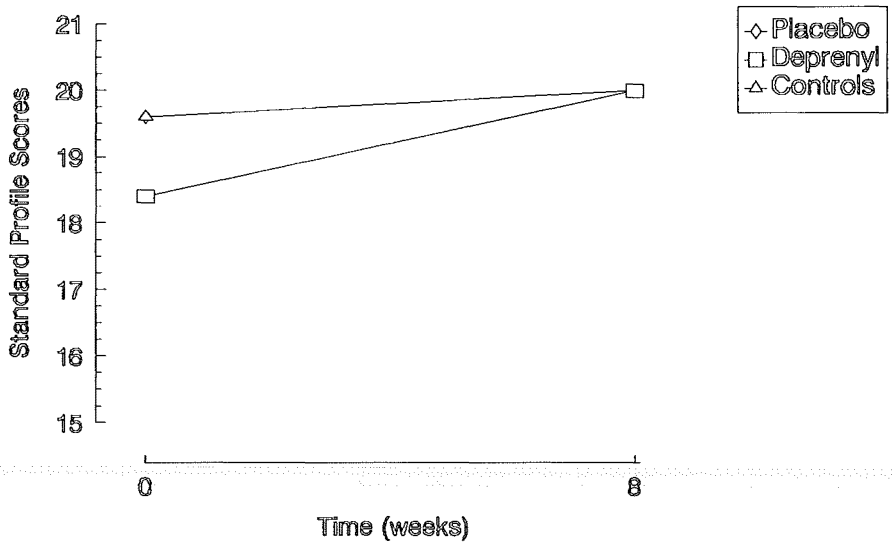


Figure 8.4.4.1: Mean scores on the Rivermead Behavioural Memory Test (Standardised Profile Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

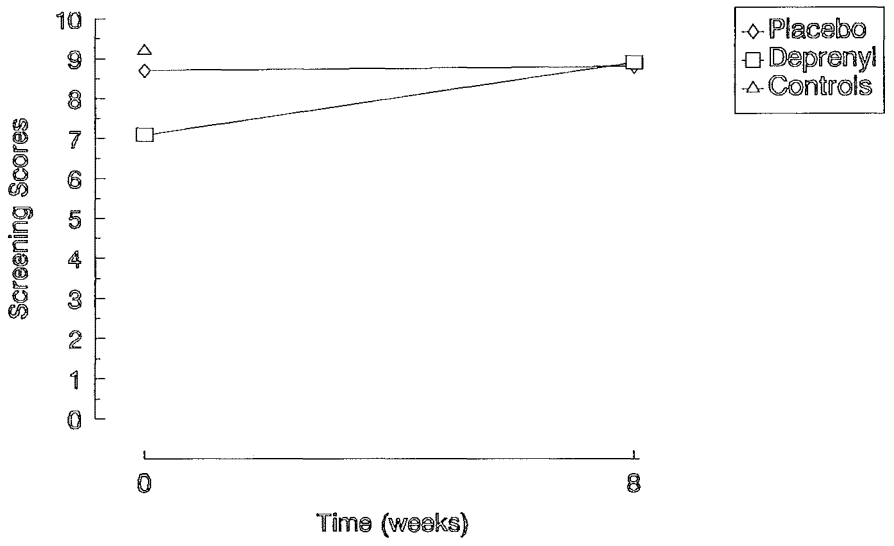


Figure 8.4.4.2: Mean scores on the Rivermead Behavioural Memory Test (Screening Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

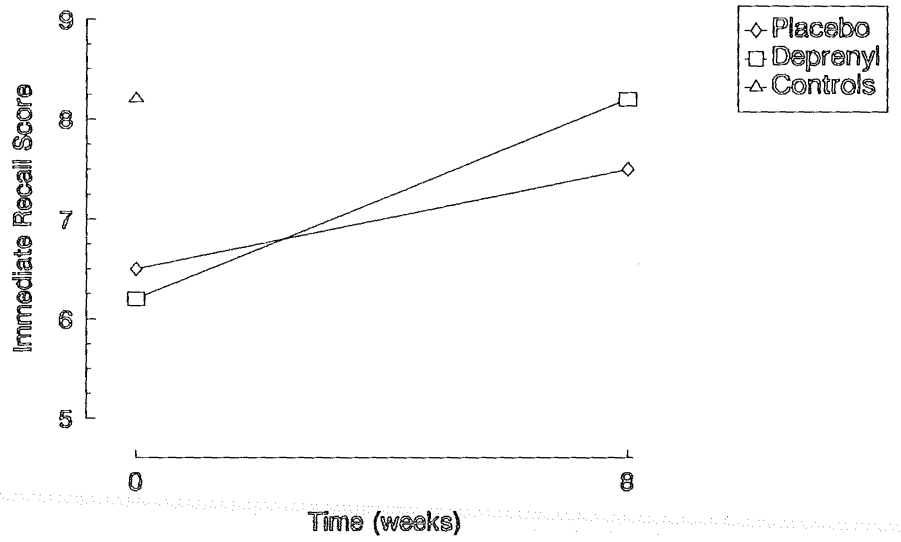


Figure 8.4.4.3: Mean scores on the Rivermead Behavioural Memory Test (Immediate Recall Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

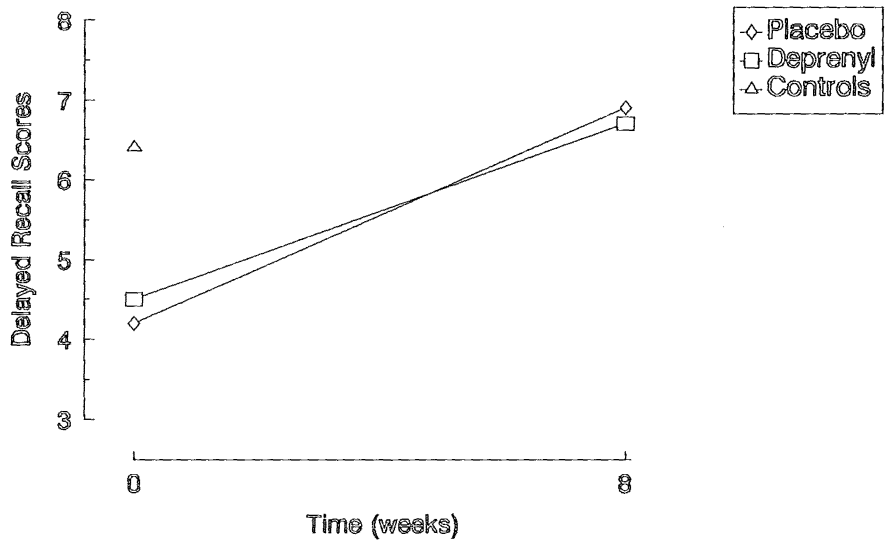


Figure 8.4.4.4.: Mean scores on the Rivermead Behavioural Memory Test (Delayed Recall Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

8.4.5 Advanced Progressive Matrices

Table 8.4.5.2 presents mean scores and Figures 8.4.5.1 to 8.4.5.2 for Placebo and deprenyl groups at baseline and eight weeks. Although there was a slight trend towards lower scores in both groups at eight weeks, the two ANOVAs revealed no significant main effects or interactions.

Table 8.4.5.1

Summary of ANOVA for the Advanced Progressive Matrices - placebo vs. deprenyl group subjects at baseline and at eight weeks.

Measure	Source	df	F	p
Advanced Progressive Matrices				
Set One	P v D	1, 21	0.0464	0.8140
	0 v 8	1, 21	1.0602	0.3159
	P/D x 0/8	1, 21	0.2919	0.6006
Set Two	P v D	1, 21	0.7380	0.4044
	0 v 8	1, 21	2.2957	0.1414
	P/D x 0/8	1, 21	0.0000	1.0000

Table 8.4.5.2

Placebo vs. Deprenyl at Baseline and at eight weeks. Advanced Progressive Matrices.

	Placebo (N = 11)		Deprenyl (N = 12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
Total Correct (Set I)					NS
Mean	3.9	3.7	4.0	3.4	
SD	1.3	2.1	1.1	1.3	
Median	4.0	4.0	4.0	3.0	
Range	2 - 6	1 - 7	2 - 6	1 - 6	
Total Correct (Set II)					NS
Mean	4.3	4.1	5.2	4.6	
SD	2.1	1.6	2.9	2.5	
Median	5.0	4.0	4.5	3.0	
Range	1 - 7	0 - 7	1 - 10	0 - 13	

Note: Set I maximum score = 7

Set II maximum score = 18

NS = Not Significant

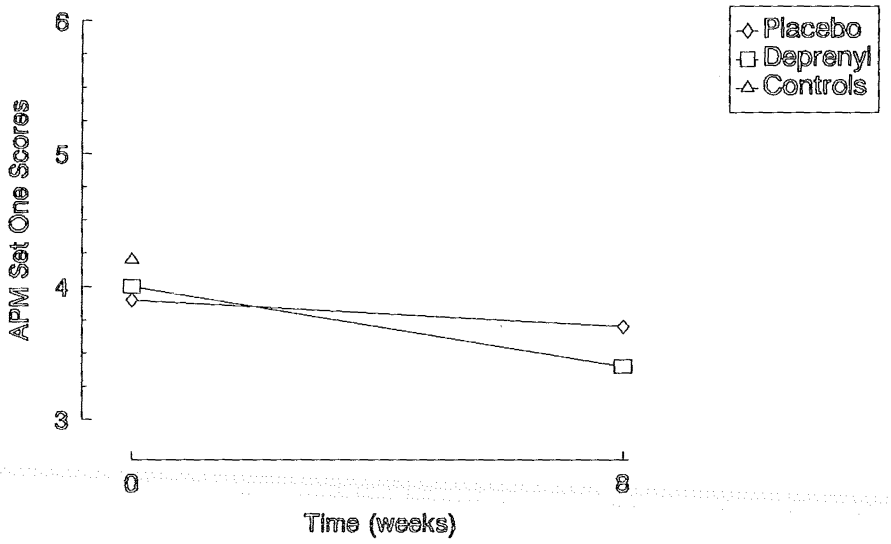


Figure 8.4.5.1: Mean scores on the APM (Set One Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

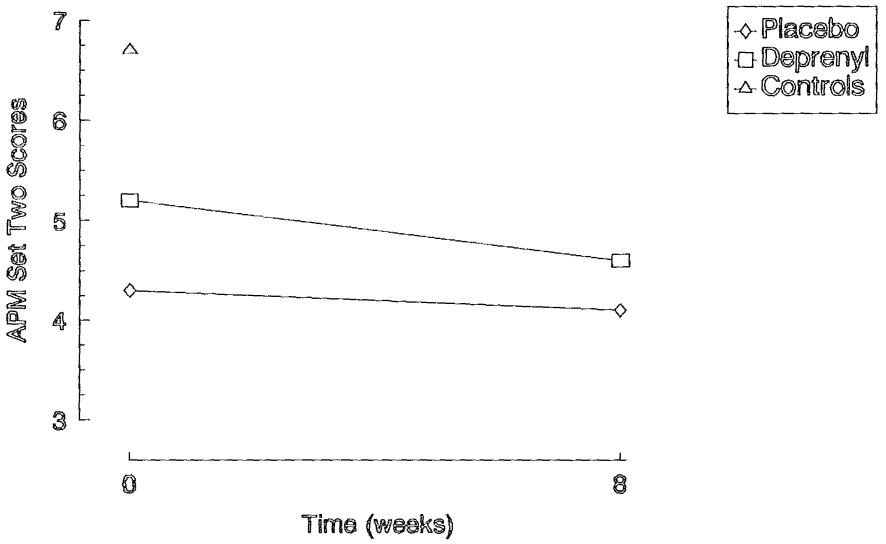


Figure 8.4.5.2: Mean scores on the APM (Set Two Score) for placebo, deprenyl at 0 and 8 weeks and controls at baseline only.

8.4.6 Unified Parkinson's Disease Rating Scale (UPDRS)

Activities of Daily Living

Table 8.4.6.3 lists the mean scores for the ADL scale of the UPDRS. The ANOVA, reveals a main effect for time ($F = 13.451$, $df = 1, 21$, $p < 0.005$). The placebo and deprenyl groups reduced scores at eight weeks, indicating increased independence in daily living.

Motor

Data presented in Table 8.4.6.3 summarise the motor scale of the UPDRS at baseline and eight weeks. ANOVAs indicated no main effects or interactions on this measure.

Table 8.4.6.1

Summary of ANOVA for the UPDRS - placebo vs. deprenyl group subjects at baseline and at eight weeks.

Measure	Source	df	F	p
UPDRS				
ADL	P v D	1, 21	0.9143	0.3522
	0 v 8	1, 21	13.451	0.0017 *
	P/D x 0/8	1, 21	0.5380	0.4777
Motor	P v D	1, 21	0.0499	0.8088
	0 v 8	1, 21	0.0303	0.8394
	P/D x 0/8	1, 21	0.3103	0.5895

Note. * $p < 0.05$

Table 8.4.6.2

Placebo vs. Deprenyl at Baseline and at eight weeks. Hoehn & Yahr

	Placebo (N = 11)		Deprenyl (N = 12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
					0.184
Mean	1.9	1.8	2.1	2.2	
SD	0.83	0.87	0.57	0.62	
Median	2.0	2.0	2.0	2.0	
Range	1 - 3	1- 3	1 - 3	1 - 3	

Note: Higher scores indicate increased severity of symptoms.

Table 8.4.6.3

Placebo vs. Deprenyl at Baseline and at eight weeks. UPDRS

	Placebo (N = 11)		Deprenyl (N = 12)		p
	0 weeks	8 weeks	0 weeks	8 weeks	
Mood, Mentation and Behaviour					NS
Mean	2.7	2.4	3.1	2.1	
SD	1.7	2.2	1.6	1.3	
Median	3.0	2.0	3.0	2.5	
Range	0- 7	0 - 8	0 - 5	0 - 4	
Activities of Daily Living					NS
Mean	12.5	10.5	11.3	8.3	
SD	4.5	4.8	4.3	4.8	
Median	12.0	10.0	11.0	9.5	
Range	6 - 19	6 - 24	1 - 19	3 - 17	
Motor					NS
Mean	14.0	13.3	14.1	14.5	
SD	9.4	7.6	6.1	5.7	
Median	13.0	11.0	13.5	14.0	
Range	2 - 38	6 - 30	8 - 27	6 - 23	

Note: NS = Not Significant

9.0 DISCUSSION

The aim of this investigation was to examine the effects of 10mg/day of deprenyl on the putative cognitive and affective disorders associated with mild to moderate idiopathic Parkinson's Disease. The results indicated that eight weeks of deprenyl therapy did not lead to improved scores across the cognitive, affective and motor assessments used to measure its effect. These findings are consistent with a recent investigation by Heitanen (1991) who also failed to detect any statistically significant differences in a double-blind placebo controlled trial, on a range of general cognitive assessments, reaction and movement times, and the BDI and HDRS.

IPD subjects compared with matched controls.

Ten age-, sex-, and education-matched control subjects were also included in this investigation to make comparisons with the IPD subjects, which is especially important for less frequently used tests such as the ROT where IPD subjects are reportedly impaired (Hovestadt, 1990)

Affect

This study found that as a group IPD subjects were significantly more depressed than controls, which is a frequently documented finding (Huber et al, 1990). The specific features of depression, ie. mood, self-reproach, somatic and vegetative symptoms had only been analysed in one investigation previously (Huber et al, 1990) in which it was reported that IPD subjects differed from controls in all four subscales. The present study found differences between IPD subjects and controls in somatic and vegetative symptoms, whereas mood and self reproach scores were not significantly different from controls. The range of scores in the IPD group was rather large, which suggests the IPD subjects were a heterogeneous group with respect to affect.

Executive Functions

Consistent with Lees & smith (1983) the IPD subjects in this investigation were significantly more impaired than controls on the total number of errors and perseverative errors made on the WCST. The number of categories and number of trials to achieve the first category were close to significance and indicated a trend towards further differences between the IPD and control subjects. The pattern of impairments in IPD subjects in the study is similar to that reported by Cooper et al, (1991) except in the number of categories score. IPD subjects in the investigation of Cooper et al. (1991) had the some number of categories as controls. The study of Caltagirone, Carlesimo, Nocentini & Vicari (1989) includes a similar composition of IPD subjects to the present study and produced a pattern of results very similar to that of the present study. A greater sample size in the control group might have yielded further differences between controls and IPD subjects on the WCST.

Visuospatial Functioning

Hovestadt (1990) reported early IPD subjects had impaired visual and tactile spatial perception as measured by the ROT. His claim of an impairment was based on comparisons with the normative data provided by Meerwaldt & Van Harkamp (1982) who used normal subjects but with a younger mean age. Hovestadt (1990) did not use age, sex and education matched controls. The present study failed to find a statistically significant difference between IPD subjects and age-, and education-matched controls. It is important to note that the IPD subjects from Hovestadt (1990) and this investigation were similar on mean error scores in the visual vertical, visual horizontal and tactile vertical measures of the ROT, they differed on tactile horizontal in that, subjects in the present study were superior on the latter measure.

The second measure of visuospatial functions employed in this study also failed to reveal a difference between IPD subjects and controls. Although deficits have been reported in the Standard and Coloured Progressive Matrices with IPD subjects (Pillon et al, 1989a; Pillon et al, 1989b; Caltagirone et al, 1989), no study has used the Advanced

Progressive Matrices (APM). The more difficult version of this test, was chosen to limit ceiling effects reported in the Standard Progressive Matrices but the similarity in scores between the IPD subjects and controls indicates that the Advanced Progressive Matrices was difficult for both groups and therefore not able to differentiate IPD subjects from controls.

Memory

The Rivermead Behavioural Test (RBMT) is newer than the WMS and the Rey Auditory Verbal Learning Test traditionally used in IPD research. Consequently only one other study has used it in the context of investigating IPD (Hovestadt, 1990), but the procedure used in that study for scoring differed from the present study making it difficult to compare findings. The present study used the screening and standardised profile scores (a combination of all subtests) and these indicated that IPD subjects performed as well as controls on the RMBT. The immediate and delayed recall of prose subtests were examined in addition to total scores. Although statistical significance was not reached, there was a strong suggestion of impairment on immediate recall ($p = 0.51$) and delayed recall ($p = 0.62$) of prose. Cooper et al, (1991) also reported on impairment in immediate and delayed recall, digit span backwards and paired associate learning in de novo IPD subjects. Mohr et al. (1990) found a similar impairment in highly educated subjects, which suggests that the memory deficits are independent of age, education or IPD severity and duration. Mohr et al. (1990) have suggested tasks must be sufficiently difficult to discriminate between IPD and control subjects.

Early vs. Established IPD subjects

The motor function assessments showed established IPD subjects were significantly more impaired than early subjects on the crude measure of the Hoehn and Yahr scale, but the more sensitive motor subscale of the UPDRS failed to demonstrate a statistical significance difference between these groups. The most likely reason for this finding is that established subjects were optimally controlled on levodopa and anti-Parkinson's disease preparations, whereas early subjects had washed out of

anticholinergics to fulfil the inclusion criteria for this trial and several had inadequate symptom control. As indicated in Appendix A, several of the early subjects required extra symptomatic treatment in addition to deprenyl therapy. There were no differences between early and established IPD subjects in scores on the WCST, ROT, RBMT and APM. Gotham, Brown and Marsden (1988); Taylor et al. (1987); Mohr et al. (1989) and Hovestadt (1990) have compared various cognitive functions in early and established IPD subjects and results from these studies suggest that disease and levodopa therapy have little if any impact on cognitive deficits. The lack of any significant differences across the present study is therefore in keeping with the above mentioned investigations. Huber et al. (1990) were the first group to report the qualitative features of depression in IPD subjects in addition to total cut-off scores on measures such as the BDI and HDRS. According to Huber et al (1990) the pattern of depression varies with the progression of the motor symptoms in IPD. The present investigation also used the qualitative analysis of depression and found that established IPD subjects were significantly more depressed than early subjects, but only on the mood subscale of the BDI. The investigation of Huber et al. (1990) reported that somatic symptoms were more common in early IPD subjects but vegetative symptoms developed as the IPD advanced and that self reproach and mood did not differ with disease severity. Findings in the present study were generally in keeping with Huber et al. (1990) except in the mood subscale scores, which were higher in established IPD subjects in the present investigation.

Relationship between affect, motor and cognitive functioning in IPD subjects.

The cognition and motor function correlation analyses in this study indicated that there was no significant relationship between motor functioning and cognition. The studies by Cooper et al. (1991) and Jankovic et al. (1989) (who analysed the DATATOP baseline data) also failed to find a link between cognitive deficits and motor functioning in IPD subjects. Jankovic et al, (1989) suggested the lack of a relationship between motor and cognitive variables may indicate that cognitive deficits in IPD are the result of non-dopaminergic lesions. However, Mortimer et al. (1982) suggest motor and cognitive

deficits in IPD may be caused by the same lesions. The present study found that motor function was not a reliable predictor of cognitive status in IPD subjects and that the early and established subjects were similar cognitve functioning.

Affect and Motor Function

A significant relationship between affect and motor functioning in IPD was found in the present study. Studies using detailed multiple regression analysis (eg Cooper et al, 1991) have reported a similar relationship between depression and motor symptoms. In a longitudinal investigation Starkstein et al. (1990) have shown that IPD subjects who are depressed have a more rapid progression of motor symptoms than subjects who are not depressed. Santamaria et al. (1986) have postulated that subjects with IPD and depression form a subgroup of the IPD syndrome.

Affect and Cognitive Function

The present investigation found a positive correlation between affect and impaired cognitive functioning. Starkstein et al. (1990) and Cooper et al. (1991) have also reported that depressed IPD subjects tend to perform worse than non depressed subjects on cognitive tests. Taylor et al. (1986) on the other hand claim that depression in IPD does not impair cognitive functioning in the same way as it does in primary endogenously depressed patients. Taylor et al (1986) were unable to demonstrate any short term memory deficit in a group of depressed IPD subjects of the type found in people with endogenous depression.

The relationships between motor, cognitive and affective functions in this study are consistent with large scale analyses such as DATATOP. Taken together, the findings of the present study, those of Cooper et al. (1991), Jankovic et al. (1989) and of Starkstein et al. (1990) suggest that the presence of depression in IPD may be a marker for cognitive deficits.

Placebo vs. Deprenyl

The present study did not find any significant benefit following eight weeks of deprenyl therapy, compared to placebo in subjects with mild to moderate IPD. Results from this trial are consistent with Heitanen (1991), but are in contrast with those of Portin & Rinnie (1983) and Lees (1991) who indicated that deprenyl improves cognitive functioning in IPD subjects. The present study was prompted by the possibility that deprenyl might enhance cognitive functioning in IPD subjects, as it has done in subjects with SDAT (Tariot et al, 1987a, 1987b; Finali et al, 1991). Each measure used in the present investigation failed to yield any specific change that could be attributed to deprenyl therapy. There is no evidence that subjects treated with deprenyl failed to comply with faking deprenyl therapy. Each measure is discussed separately.

Memory

The Rivermead Behavioural Memory Test (RBMT) was used to examine the expected influence of deprenyl in this study. The failure to detect any improvement on the RBMT, that could be attributated to deprenyl, was unexpected given the evidence of deprenyl's benefit in SDAT subjects (Tariot et al, 1987a). Scores on the immediate recall of prose increased from baseline in subjects treated with placebo, as well as deprenyl, which indicates either a learning effect occurred or the baseline performances were hindered by anxiety. There was no evidence that the prose test used at eight weeks was easier than that used at baseline as the RBMT has good alternate form reliability.

Visuospatial Functioning

The present investigation failed to demonstrate a baseline visuospatial deficit in IPD subjects relative to matched controls on the ROT and the APM. Consequently, after eight weeks of deprenyl therapy, two scores on the two measures of visuospatial function remained unchanged. Early and established IPD subjects had similar performances on the APM and ROT which indicates reported decrements in visuospatial functions may be related to a simultaneous dementia. All subjects in the

present study were dementia-free, which may explain why no visuospatial deficit was detected. Furthermore, the preliminary findings from Como (1990) indicate deprenyl prevents deterioration, rather than improves cognitive functioning. Given that cognitive decline in IPD is probably insidious, only a longer term study could monitor possible decrements in visuospatial functioning, if any were likely to arise.

Executive Functioning

Although subjects treated with deprenyl showed a slight reduction in the mean number of non-perseverative errors made on the WCST (20.5 at baseline and 16.3 at eight weeks) and although the subjects given placebo increased their non-perseverative error score (24.4 at baseline and 28.0 at eight weeks) the failure of these results to reach statistical significance indicates it would be inappropriate to suggest that deprenyl had any effect compared to placebo. The large standard deviations on this measure reflect the considerable variability in both groups of subjects, and are in keeping with Hietanen (1991) who also reported considerable intra-group variability. Although not explicitly stated the findings from the DATATOP study with respect to executive functions appear to be consistent with the present investigation. "Odd-man-out" Test was used by Flowers & Robertson (1985) to assess the ability of IPD subjects to maintain a mental set. DATATOP investigators also used the "Odd-man-out" Test. The lack of data regarding this test suggests that deprenyl had no significant impact on the executive functions, as measured by that test. Taken together, findings from DATATOP and the present study strongly suggest that deprenyl's action in IPD is independent of the cognitive functions assumed to be executed by the frontal lobes.

Affect

Ten mg/day of deprenyl failed to produce a significant change in affect as measured by the BDI and by its four subscales in this investigation. This may be because, as a group subjects treated with deprenyl were not depressed at baseline, in fact their mean scores were almost static. Two of the 12 subjects treated with deprenyl did reduced their total scores on the BDI by five and eight points respectively, however

a further two subjects indicated that they were more depressed following eight weeks of deprenyl as scores on the BDI rose by six and seven points. Portin & Rinnie (1983) and Lees et al. (1989) are the only investigators to report improvements in affect with 10 mg/day of deprenyl and both studies have small sample sizes, limited duration and open designs. The lack of an anti-depressant effect in the present study is not surprising given that Nappi et al (1991), Parkinsons Study Group (1989) and Prztuntek & Kuhn (1987) have also failed to detect an effect using 10 mg/day with IPD subjects. Heitanen (1991) did not detect changes at 30 mg/day, which suggests that a dosage of at least 40 mg/day is necessary to achieve a significant mood elevating effect, inhibition MAO-A as well as "B" needs to occurs if deprenyl is used for its anti-depressant properties.

Interestingly mean scores on the BDI reduced from 11.9 at baseline to 8.1 at eight weeks in subjects given placebo. An interaction emerged in the ANOVA which showed a main effect for time. This means that a placebo effect occurred in subjects treated with placebo. Such a finding reinforces the importance of double-blind investigations.

Motor Function

The lack of significant change in motor function in this investigation was a little surprising given the evidence that deprenyl has some positive effect on motor symptoms (Myllyla et al, 1989). Indeed, several subjects reported feeling energetic, and able to accomplish more since receiving deprenyl. Deprenyl's failure to improve motor function in this study might be explained by the finding that deprenyl is only of symptomatic value in the earliest months of IPD (Elizan et al, 1989), and that it does not prevent the progression of existing symptoms. In the present study early and established groups were combined on the basis of equivalent cognitive status, but in terms of motor function, this may have eliminated the likelihood of detecting a symptomatic benefit from deprenyl, particularly in the de novo, recently diagnosed subjects. Several of the de novo subjects had severe symptoms, especially tremor and

bradykinesia, but had delayed seeking medical assistance or had washed out of anticholinergics and were thus unmedicated. In reality, some of the de novo subjects would have benefited from seeking symptomatic therapy earlier, and, indeed, subjects in both placebo and deprenyl groups were given additional symptomatic control whilst the trial was in progress (see Appendix A), which reinforces the idea that deprenyl needs to be commenced very early in the course of IPD if it is to be of any symptomatic benefit, and it is probably most effective when used in conjunction with amantadine or dopamine receptor agonists in early IPD (Nappi et al, 1991). Furthermore, most of the established IPD subjects had good symptom control. Scores on the activities of daily living subscale of the UPDRS indicated that subjects receiving placebo and deprenyl improved, but not significantly from baseline. As the scale is a somewhat crude measure of daily living and the changes were not statistically significant, the likely explanation is that the symptoms in IPD are somewhat dynamic and can be influenced by a variety of factors, including anxiety and fatigue.

9.1 Contributions and Limitations of the present study

Portin & Rinnie (1983) and Lees (1991) have raised the possibility that deprenyl's effect on cognitive functioning in IPD is more positive than results in the present study suggest. However Lees et al. (1989) and Eatough et al. (1990) have only reported improvements in simple reaction times, on a computer based assessment which measures simple, two- and three, choice response reaction times. Three published summaries of these reaction time studies with IPD subjects on either deprenyl or placebo show that deprenyl does not improve choice reaction times, the measure Lees (1991) suggests is a measure of cognitive processes. In view of the findings of improved motor functioning following deprenyl therapy (Parkinsons Study Group, 1989; Tetrud & Langston, 1989) the results of Lees et al. (1989) should probably be interpreted as a result of improved motor, rather than cognitive function. Preliminary results from DATATOP suggest that at best, deprenyl delays cognitive deterioration in early untreated IPD (Como, 1990) and it appears that cognitive improvements should not be expected. The present study found that 10 mg/day of deprenyl did not change

baseline motor, affective or cognitive measures. This finding is of value because the present study used a range of focussed evaluations, which assessed cognitive deficits believed to be inherent in IPD. Heitanen (1991) also failed to detect any significant cognitive effect in IPD subjects following eight weeks of deprenyl therapy and the present results are consistent with those of Heitanen (1991). It is now obvious that studies with IPD subjects should focus on measuring decline - not improvement-in in cognition. Although SDAT subjects treated with 10 mg/day of deprenyl have improved selective aspects of memory (Monteverde et al, 1990), the present investigation suggests deprenyl has a different effect in IPD.

A further contribution of this investigation was the finding that IPD subjects are not impaired on the ROT relative to age and education matched controls. Hovestadt (1990) reported the ROT was a sensitive measure of spatial functioning in IPD and reported IPD subjects were impaired on the test relative to normative data. This investigation is the first to use age appropriate controls with IPD subjects and the present findings suggest that Hovestadt's claim of a deficit, would benefit from re-evaluation with matched controls.

Findings in this study may be limited by the sample size (n = 23) but comparisons with investigations by Heitanen (1991) who had 18 subjects, and Nappi et al. (1991) with 20 subjects suggests the results were not biased by sample size, as findings in the three studies are consistent. The study of Lees et al. (1989) with nine subjects also failed to reveal cognitive benefits with 10 mg/day of deprenyl, despite improved simple reaction times. Reports of deprenyl's effect in SDAT subjects and laboratory rats indicated that cognitive functions in IPD might be improved by deprenyl but the preliminary evidence from Como (1990) suggests studies into the cognitive effects of deprenyl need to be of an adequate duration (ie. at least three months) to detect any possible declines.

A major limitation of the present investigation may have been its limited duration, but with respect to ethical issues eight weeks is probably as much as would be acceptable, any longer would amount to withholding treatment for the obvious motor deficits in IPD.

The lack of significant improvement in motor function scores on the UPDRS was in conflict with the subjective reports of increased energy in this and similar investigations (Elizan et al, 1989; Portin & Rinnie, 1983; Lees, 1987). A more objective way of evaluating the anecdotal reports would have been a valuable addition to the tests used in the present study. The Profile of Mood States assessment used by Menza et al. (1990) or the subjective Affect/Arousal State Visual Analogue Scale used by Brown et al. (1984) may be of value in future studies.

Memory impairments in the IPD subjects relative to controls, was extremely close to significance ($p = 0.051$), which indicates that a greater number of subjects might have changed this to a more significant result. However, the test used to assess memory in this study may not have been sufficiently sensitive to distinguish between IPD and control subjects, thus contributing to the result.

9.2 Recommendations for Future Studies

All exiting research into the cognitive effects of deprenyl, and much of the general cognitive research in IPD is limited by a failure to make use of any theoretical approach. Future studies using deprenyl in IPD subjects would benefit from an even more focussed approach than the present study. The "outflow model" proposed by Taylor et al. (1986) would provide a useful structure to examine executive functions in IPD subjects. Future memory investigations with deprenyl would benefit from structure provided by Baddeley's Model of Working Memory (Baddeley, 1986) and the Brown-Peterson Paradigm is one example of a memory task that is consistent with Baddely's Model. Bradley et al. (1989) have reported a deficit in the visuospatial subsystem of working memory in IPD subjects, which may explain the existence of visuospatial

deficits reported by some investigators. Future research into cognitive effects of deprenyl would be enhanced by the specific focus and structure provided by the working memory and "outflow" models.

Deprenyl seems to effect the cognitive functions of SDAT and IPD subjects in differing ways, and a future investigation, with matched IPD and SDAT subjects might clarify these seemingly differing effects. The possibility of a neuropsychological dissociation between IPD and SDAT would also be highlighted by the suggested comparative study.

The final recommendation made by this study is that future investigations with IPD subjects seek to quantify cognitive decline, rather than improvements. No study, thus far, including the present investigation, has conclusively shown that deprenyl is of any value in improving cognition in IPD subjects which suggests that the emphasis of further studies should not be to expect an improvement. To reiterate, the main conclusion of the present study is that 10 mg/day of deprenyl did not lead to improvements over baseline in a range of focussed cognitive and affective evaluations. This finding is consistent with Heitanen's (1991) findings, which were published after the present study commenced.

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10. APPENDICES

APPENDIX A

PD GROUP - CLINICAL CHARACTERISTICS.

AGE	SEX	H & Y	PD DURATION	CURRENT TREATMENT
36.1	M	2	12 months.	Propranolol (+)
43.1	M	2	120 months.	Disipal Sinemet Propranolol (-)
51.2	F	3	96 months	Sinemet Amantadine Disipal
56.6	F	1	2 weeks.	Nil
57.0	M	1	2 weeks.	Nil
59.6	F	3	38 months.	Anticholinergic (-) Amantadine (+)
59.9	M	2	60 months.	Sinemet Amantadine Disipal Propranolol
60.4	M	1	2 months.	Nil
61.6	F	2	11 months.	Madopar
64.2	M	2	24 months	Madopar Bromocriptine
66.2	F	2	9 months.	Amantadine
66.4	F	1	4 months.	Anticholinergic (-) Propranolol (+)
67.1	M	1	18 months.	Amantadine

Key:	
Age	Years and Months.
(-)	Washed Out
(+)	Added in during trial regain symptomatic control.
Disease Duration	Time of diagnosis by GP or Neurologist. NB: Differs from duration of symptoms.

PD GROUP - CLINICAL CHARACTERISTICS ....CONTINUED

AGE	SEX	H & Y	PD DURATION	CURRENT TREATMENT
68.1	M	2	1 month.	Nil
68.4	M	3	192 months.	Madopar Amantadine Nortriptyline
70	F	2	24 months.	Anticholinergic (-) Amantadine (+)
70.3	F	3	36 months.	Doxepin (-)
71.6	F	2	2 weeks.	Bromocriptine (+)
72.4	M	2	15 months.	Amantadine Lisuride Nortriptyline (-) Immovane (+)
73.3	M	3	96 months	Sinemet Disipal
73.5	F	2	54 months.	Anticholinergic (-) Bromocriptine (+)
75.0	M	3	120 months	Madopar
78.4	M	2	24 months.	Lisuride

Key:	
Age	Years and Months.
(-)	Washed Out
(+)	Added in during trial regain symptomatic control.
Disease Duration	Time of diagnosis by GP or Neurologist. NB: Differs from duration of symptoms.

APPENDIX B

DEPRENYL STUDY: PATIENT INFORMATION

M	F

SURNAME: _____ FIRST NAME: _____

ADDRESS: _____

TELEPHONE: PRIVATE BUSINESS

NEXT OF KIN: TELEPHONE

PARKINSONS SUPPORT GROUP MEMBER: Y N

Neurologist: _____ GP _____ Telephone: _____

EDUCATION: (Years completed) Secondary school: Tertiary:
Highest qualification completed:

CURRENT MEDICATION REGIME:

NAME:	DOSAGE/DAY:	TIME TAKEN:

PREVIOUS RELEVANT MEDICATIONS (eg; anti depressants).

VISION: Glasses. Yes No DISTANCE: READING:
HAND DOMINANCE: LEFT: RIGHT:
PARKINSON'S DISEASE SIGNS/SYMPTOMS:
Duration. Years: Months:
Age of onset. Date of Diagnosis:

Place a tick in the relevant box .

TREMOR	Y		N
BRADYKINESIA	Y		N
ON/OFF	Y		N
FINE MOTOR SKILLS	Y		N
BILATERAL SYMPTOMS	Y		N
L > R	Y		N
R > L	Y		N
L = R	Y		N
RIGIDITY	Y		N
FREEZING	Y		N
DYSKINSEA	Y		N

HOEHN AND YAHR STAGING

(Place a tick in a box to indicate the appropriate stage)

☐ Stage I: Unilateral involvement only, usually with minimal or no functional impairment.

☐ Stage II: Bilateral or midline involvement, without impairment of balance.

☐ Stage III: First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when the person is pushed from standing.

☐ Stage V: Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

☐ StageV: Confinement to bed or wheelchair unless aided.

COMMENTS:

ASSESSOR: _____ DATE: / / 1991

TIME: AM | PM

APPENDIX C

UNIFIED PD RATING SCALE, VERSION 3.0 (FEBRUARY 1987) DEFINITIONS OF 0-4 SCALE

I MENTATION, BEHAVIOUR, AND MOOD

1. Intellectual Impairment:

0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 =Severe memory loss with disorientation for time and often place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2 Thought Disorder (Due to dementia or drug intoxication):

0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3 Depression :

0 = Not present.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4 Motivation/Initiative :

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (non-routine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

1 2. Turning in Bed and Adjusting Bed Clothes:

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (Unrelated to Freezing):

0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Fall more than once daily.

14. Freezing When Walking:

0 = None.
1 = Rare freezing when walking; may have start-hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing; occasionally, falls from freezing.
4 = Frequent falls from freezing.

15. Walking:

0 = Normal.
1 = Mild difficulty; may not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor:

0 = Absent.
1 = Slight and infrequently present.
2 = Moderate ; bothersome to patient.
3 = Severe ; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory Complaints Related to Parkinsonism:

0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech:

0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression:

0 = Normal.
1 = Minimal hypomimia, could be normal "poker face."
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed faces with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at Rest:

0 = Absent.
1 = Slight and infrequent)y present.
2 = Mild in amplitude and persistent. Or moderate in amplitude but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands:

0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude ; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored):

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession\tab with widest amplitude possible, each hand separately):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands: (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 in.):

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in on-going movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straight-backed wood or metal chair, with arms folded across chest):

0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to rise without help.

28. Posture:

0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait:

0 = Normal.
1 = Walks slowly, may shuffle with short steps, but not festination or propulsion.
2 = Walks with difficulty, but requires little or not assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared):

0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness hesitancy, decreased armswing, small amplitude, and poverty of movement in general):

0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

(Lang,1990 p 16-21).

II. ACTIVITIES OF DAILY LIVING (DETERMINE FOR "ON/OFF")

5. Speech:

0 = Normal.
1 = Mildly affected; no difficulty being understood.
2 = Moderately affected; sometimes asked to repeat statements.
3 = Severely affected; frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation:

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have night-time drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing:

1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrostomy feeding.

8. Handwriting:

0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected ; not all words are legible.
4 = The majority of words are not legible.

9. Cutting Food and Handling Utensils:

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone , but can still feed slowly.
4 = Needs to be fed.

10. Dressing :

0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene :

1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.