Section 9 Anti parkinsonism medicines

Section update

Submission on behalf of Movement Disorder Society

10th January 2013
1. Summary statement of the proposal for inclusion, change or deletion

In a recently published prevalence study of Parkinson’s Disease (PD) in Tanzania the majority of the identified patients had not previously been diagnosed or treated, and those who had been diagnosed often could not afford to continue medication that was prescribed (Dotchin et al 2008). To add to their difficulties, local pharmacies would often not stock any medication for PD, but those that did would only keep Sinemet 250/25 and not the 100/25 strength. The drug strength is shown as Levodopa in milligrams / Dopamine Decarboxylase inhibitor (DDCI) in milligrams.

The Sinemet 250/25 strength is not used for initiation of treatment in PD. The 10:1 ratio of Levodopa:Carbidopa is too high to prevent the Levodopa-induced nausea for many patients. The 100/25 tablet, with its 4:1 ratio is the preferable tablet to be used for titration to effective dose. This is supported by pharmaco-kinetic studies and expert opinion (Olanow CW et al 2009). The average patient in the USA or Europe started on Levodopa would usually start at 50/12.5 twice daily, gradually working up to 100/25 three times daily and then increasing the frequency as necessary after this.

Data for the UK for 1 year from July 2008 to June 2009 inclusive show that for all prescriptions containing Levodopa (all of which also include a DDCI), prescriptions for a 10:1 ratio, either Carbidopa/Levodopa 10/100mgs or Carbidopa/Levodopa 25/250mgs, accounted for 3% of all prescriptions, with the remaining 97% having a 4:1 ratio. The 250mgs dose (only available with a 10:1 ratio) only accounted for 2% of all prescriptions. This data is from IMS Health, 7 Harewood Avenue, London and is based on 90% of all purchase made by community pharmacists and dispensing doctors and also on data from hospitals that cover 95% of acute beds.

After looking into this further, we found that this was due to the WHO essential drugs list stating that countries should have “Sinemet 250/25, Sinemet 100/10 and Biperiden, an anticholinergic”. Our colleagues in Nigeria have also come across this problem, and find that local bureaucracy suggest that the WHO guidelines should be followed leading to difficulties in getting hold of any other type and strength of PD medications. Biperiden itself is not generally available but Trihexyphenidyl another anticholinergic, is. We feel that this should replace Biperiden. The rationale for the use of anticholinergics is to decrease the effects of central cholinergic excess as a result of dopamine deficiency.

We feel that the WHO essential drugs list should be updated to reflect best practice from evidence based medicine worldwide. Firstly, the anticholinergic is outdated and very rarely used for PD in other regions of the world. In fact, anticholinergics as a whole are rarely used for the treatment of PD except occasionally in younger patients with predominant tremor problems. Indeed, their use in elderly and patients with cognitive impairment is limited by well known side effects including confusion, dizziness, memory loss and psychosis (hallucinations and agitation). We would therefore recommend that the anticholinergic on the essential drugs list be changed to Artane, which is more widely available, and make it clear that it should only be used if Levodopa or another agent is unavailable, and that it should be avoided in older patients, especially those with cognitive problems.

There are other drugs to consider which we feel should only be used by those with experience of treating PD. Ideally these should be neurologists but we realize that, for example in sub-Saharan Africa (SSA), there is a great shortage of neurologists (Bower et
There are no dopamine agonists (DAs) listed for PD. There is an ergot derivative DA which is hardly ever used for treating PD in Europe or the USA due to potential severe side effects (including retroperitoneal, pleuropulmonary and heart-valves fibrotic reactions) with risk of valve regurgitation and heart failure correlated with higher mean cumulative doses (Antonini and Poewe, 2007). Therefore, given the higher mean daily dosage and long-lasting duration of PD treatment compared to infertility, we believe that Bromocriptine is not a suitable medication to add into the anti Parkinsonian medications list. Unfortunately oral non-ergot derivative DA, even though they are now off patent, still remain expensive. Of the two widely used (Pramipexole, Ropinirole) Pramipexole appears to be the most widely available in low and middle income countries (LMICs). A summary of the evidence for Pramipexole can be found in Cochrane review (Clarke C et al 2003).

Another drug we suggest adding is Selegiline, a monamine oxidase type B inhibitor (MAOIB), which can be used both as initial, and add-on, therapy. It is available as 5mgs (usual starting dose) or 10mgs (usual maintenance dose) tablets to be taken once daily. Please see later in relation to relative costs. Like Amantadine, it has a propensity to cause hallucinations in susceptible individuals.

There are limited options for treatment of later stage PD and prevention/treatment of complications even though drugs such as Amantadine (used to treat dyskinesias) are available in generic form and relatively cheap. Dyskinesesia is a jerking involuntary movement that arises in later stage disease as a complication of treatment. It can sometimes be quite distressing. Amantadine has moderate anti Parkinsonian effects, but has been found to be potentially very helpful for dyskinesia. The initial dose is 50mgs twice daily, with the second dose no later than mid-afternoon to avoid the side effect of insomnia.

In Ghana, the use of non-dopaminergic anti Parkinson medications such as anticholinergics (Trihexyphenidyl), Selegiline and Amantadine is far higher than Levodopa, due to their relative lower cost and larger availability throughout the country. However, when prescribed to either elderly patients, or those with cognitive decline, these medications often cause side effects such as confusion, dizziness, memory loss and psychosis.

References

- Bower et al 2006

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Dr Tarun Dua, Medical officer for Neurological diseases and neuroscience
3. Name of the organization(s) consulted and/or supporting the application

This application is sent by Professor Richard Walker (UK / Tanzania), chair of the Africa Task Force of the Movement Disorders Society (MDS), along with other members of the Task Force committee: Olivier Rascol (France), Mark Gutman (Canada), Jonathan Carr (South Africa), Njide Okubadejo (Nigeria), Moussa Traore (Mali), Roberto Cilia (Italy / Ghana), Catherine Dotchin (UK / Tanzania), Jim Bower (US) and Dan Tarsy (US), Juzar Hooker (Kenya), Joaquim Ferreira (Portugal), Philip Thompson (Australia). Professor Günther Deuschl, President of the MDS is aware of this request and supports its submission, as does Professor Matt Stern, President Elect of the MDS. We have also received advice from Professor Carl Clarke (UK), author on the Cochrane Reviews we have referenced, and Professor Francisco Cardoso (Brazil).

4. International Nonproprietary Name (INN, generic name) of the medicine

In order of greatest need, taking into account cost:

Levodopa / Carbidopa – Sinemet, Syndopa
Trihexyphenidyl hydrochloride – Benzhexol

The following to be prescribed by a specialist only -
Pramipexole (Mirapexin)
Amantadine hydrochloride (Symmetrel)
Selegiline

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

1. Levodopa / Carbidopa 100/25mgs (Olanow et al 2009)
2. Pramipexole immediate release 0.7 mgs and 0.18 mgs (for drug titration purposes) (Cochrane review, Clarke et al 2003)
3. Amantadine hydrochloride 100mgs (Cochrane Review, Crosby et al 2003)
4. Selegiline 10mgs (starting at 5mgs) (Cochrane Review, Turnbull et al 2005)

References

- Crosby N, Deane KH, Clarke CE. Amantadine in Parkinson’s disease. Cochrane Database Systematic Reviews, 2003; (1):CD003468

For efficacy please see section 9, safety (section 11), and comparative effectiveness (section 10).

6. International availability - sources, if possible manufacturers and trade names
Levodopa / Carbidopa – Sinemet (Bristol-Myers Squibb), Syndopa (Sun Pharmaceuticals) – widely available throughout the world.

Trihexyphenidyl (non-proprietary) – widely available

Pramipexole (Mirapexin) (Boehringer Ingelheim), generics – appears to be the most widely available non-ergot derivative DA in LMICs.

Amantadine (Symmetrel) – Alliance

Selegiline (non-proprietary) – appears to be widely available.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicines

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Based on the Tanzanian prevalence study (Dotchin et al 2008) it is likely that the majority of people with PD in low income countries are not currently diagnosed, and therefore not treated, and yet the symptoms of PD can be effectively, and safely, treated with Levodopa which is the mainstay of PD treatment world wide. A Brazilian prevalence study (Barbosa et al. 2006) revealed similar prevalence rates of PD to those seen in elderly European and American populations but demonstrated that the majority (72%) of these patients had not previously been diagnosed. We have demonstrated that it is useable, and effective, in a resource poor environment (Dotchin et al 2011). Access to diagnosis and treatment for the condition may be affected by local health beliefs around the nature and cause of the symptoms with many people not realizing that it is a medical condition which is amenable to symptomatic treatment (Mshana et al 2011). A recent paper in Movement Disorders (Bach et al 2011) reports that for the years 2010 to 2050 there will be a near doubling of the number of people with PD in some countries. This is based on data from USA, Canada and Europe. The authors comment that data for other countries are not available, however with the projected ageing of the world’s population, especially marked in countries such as China and India (WHO ref), this is likely to hold true world wide. We have previously reported similar figures for Tanzania (Dotchin et al 2012). The main (unmodifiable) risk factor for developing PD is increasing age, with only 5% of incident cases occurring under the age of 50 in developed countries.

Life expectancy for patients with PD in Europe was severely limited before the introduction of Levodopa, and that is essentially the situation that still exists in sub-Saharan Africa. Although prevalence rates of age-related chronic diseases are progressively increasing because of the increasing life expectancy, most developing countries are not as rapid as this demographic transition in adapting health policies, so that PD-related economic burden is still largely under-covered by medical insurance systems. Poorer individuals living in rural areas often rely on financial support from their family members, who are themselves financially unconfident, thus possibly causing family tensions and finally leading to traditional healers or self-medication, or even quitting any form of treatment [Aikins, 2007]. The economic burden of PD includes the cost of medicines, doctor’s fees, laboratory/imaging investigations, transportations expenses, while indirect costs include...
productivity loss due to sickness or early retirement as well as home nursing care in those with advanced stages, thus further reducing familial income. Health economics data are lacking from LMICs. The economic burden of PD in developing countries with low-income has been investigated previously in India and China (Cilia et al. 2011). PD-related costs were a significant burden and in both countries represented 50-70% of patients’ income.

Need to add prevalence references for China and India.

References:


9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

In areas where there is no specialist in PD we would recommend that the only treatment that is used is Levodopa. Most patients will need Levodopa only. It is the most symptomatically effective medication available for PD. (UK NICE guidelines 2006; Fahn S et al 2004). The dosage regimen for Levodopa is starting with an initial dose of 50/12.5mgs 1 tablet twice daily, and gradually increasing up to an initial maintenance dose of 2 tablets three times daily (equivalent to 100/25mgs three times daily). This is based on the 50/12.5mgs tablets being available or alternatively the 100/25mgs tablets could be halved. Duration is life long and, as PD is a progressive disease, gradually increasing
doses, both in size and frequency, are required and are titrated according to a patient’s needs and tolerance (Carr J et al. 2009)

If a specialist is available, it would be beneficial for them to have access to a wider range of drugs. Amantadine is recommended as an agent to use if patients develop Levodopa induced dyskinesias. (Cochrane Review, Crosby et al 2003, Thomas A 2004). Amantadine is started at a dose of 50mgs twice daily (with the second dose in the afternoon), and subsequently increased up to 100mgs twice daily and then further as required. It has modest anti-Parkinsonian effect. If it needs to be withdrawn this should be done gradually.

In younger patients, Pramipexole may be considered as an option for first line treatment, and in later stage disease, if a second agent is required, Pramipexole may be of benefit. There is good evidence for the safety, efficacy and tolerability of Pramipexole (Pinter et al 1999, Clarke C et al 2003 (Cochrane review), Kieburtz K JAMA 1997).

Selegiline is given at a dose of 5 mgs or 10mgs OD and could be considered in early disease in younger patients. It is of less symptomatic benefit than Levodopa, but it can delay the time to requiring Levodopa and therefore reduce the development of dyskinesias (Cochrane review 2005 for Selegiline in early PD). It can be used as add-on therapy but its use is often limited by side effects, especially in those with cognitive impairment.

The current WHO Essential Drugs List includes “Sinemet 250/25, Sinemet 100/10 and Biperiden, an anticholinergic”.

We feel that this should be reviewed as it reflects outdated practice. Firstly, the anticholinergic is outdated and very rarely used for PD in other regions of the world. In fact, anticholinergics as a whole are rarely used for the treatment of PD except occasionally in younger patients with predominant tremor problems. The Sinemet 250/25 strength is not used for initiation of treatment in PD. The 10:1 ratio of Levodopa:Carbidopa is too high to prevent the Levodopa-induced nausea for many patients.

Parkinson’s disease is a clinical diagnosis although in many high income countries dopamine transporter (DaT) scan is available to aid diagnosis. It can generally be managed in the community.

The scarcity of neurological diagnostic imaging facilities in rural settings in most parts of sub-Saharan Africa make it difficult to diagnose other causes of parkinsonism, such as cerebrovascular disease or brain tumors. Moreover, national health systems do not usually cover imaging investigations further lowering the availability of instrumental data on patients with possible secondary parkinsonism (for example, in Ghana brain CT scan costs 200-300 USD, while brain MRI costs 400-800 USD, with average salary of about 60 USD/month). This is likely to be representative of most LMICs. In this context, more sophisticated and expansive investigation such as dopamine transporter SPECT imaging are obviously unfeasible cost wise. It is also unfeasible as the isotope has to be used within 24 hours of production (in Europe). However, in the UK clinical practice would not be to consider this imaging in all patients. In most cases a clinical diagnosis is based on the UK PD Society Brain Bank Criteria (Hughes et al 1992) and treatment is commenced. Imaging is reserved for those in whom there is diagnostic uncertainty. In current practice DaT scans are carried out on average in less than 1/5 of all patients. If patients are
mistakenly diagnosed and treated they may experience short term side effects, eg nausea and dizziness, but are very unlikely to have any long term complications.

References:


10. Summary of comparative effectiveness in a variety of clinical settings:

- Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Levodopa has been in use now for over 40 years for the treatment of PD and still remains the most effective symptomatic treatment (Parkinson study group, 2000). Levodopa treatment has shown to reduce overall mortality in patients with PD in comparison the pre-Levodopa era (Uitti et al, 1993; Di Rocco et al, 1996), mostly by reducing falls and bone fractures as well as delaying bedridden status. Risk of death following initiation of Levodopa is significantly reduced in Parkinson disease, regardless of pre-Levodopa duration of illness (Uitti et al., 1993). Newer drugs, such as non-ergot DAs (DA), cathechol-O-methyl transferase inhibitors and monoamine oxidase inhibitors (MAOIB) can be used in addition to Levodopa as Levodopa sparing agents and, in the case of DAs and MAOIBs, as initial monotherapy to delay the use of Levodopa. In patients with advanced PD on Levodopa, motor fluctuations and dyskinesias emerge and need to be carefully managed. Optimization of Levodopa-to-DA agonist ratio by relatively reducing Levodopa dosage and increase DA to achieve a more continuous dopaminergic stimulation is the first therapeutic option. In the second instance, Amantadine is so far the only approved compound with evidence of providing a sustained antidyskinetic benefit in the absence of unacceptable side effects (Gottwald and Aminoff, 2011). In 2011 The Movement Disorders Society published recommendations for the treatment of PD based on a review of high-quality published trials (Fox et al, 2011). This work concluded that there was strong evidence to
support levodopa, Selegiline and Pramipexole as efficacious treatments for the control of motor symptoms in PD. In addition they concluded that Amantadine was a proven, efficacious treatment for dyskinesia.

Summary of available data* (appraisal of quality, outcome measures, summary of results)

Table 1 – Options for initial pharmacotherapy in early PD

<table>
<thead>
<tr>
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<th>First-choice option</th>
<th>Symptom control</th>
<th>Motor complications</th>
<th>Other adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>✓</td>
<td>+++</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Dopamine agonists</td>
<td>✓</td>
<td>++</td>
<td>↓</td>
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<tr>
<td>MAOB inhibitors</td>
<td>✓</td>
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<tr>
<td>Anticholinergics</td>
<td>x</td>
<td>Lack of evidence</td>
<td>Lack of evidence</td>
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<tr>
<td>Amantadine</td>
<td>x</td>
<td>Lack of evidence</td>
<td>Lack of evidence</td>
<td>Lack of evidence</td>
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</tbody>
</table>

+++ = Good evidence of symptom control.
++  = Moderate degree of symptom control.
+   = Limited degree of symptoms control.
↑    = Evidence of increased motor complications/other adverse events.
↓    = Evidence of reduced motor complications/other adverse events.

Adapted from the National Collaborating Centre for Chronic Conditions. Parkinson’s disease: national clinical guidelines for diagnosis and management in primary and secondary care. London: Royal College of Physicians, 2006

In sub-Saharan African countries, once the diagnosis of Parkinsonism is made, some issues need to be taken into consideration for the initiation of anti-Parkinsonian treatment, where the choice of drug and the success of long-term treatment is limited by local availability and by the cost. Outcome and side effects of Levodopa [Girard et al, 1972; Harries et al., 1972] and the DA Bromocriptine [Ndaiye et al., 1980] have been addressed in PD cohorts from Kenya and Senegal. Compared to developed countries, national health insurance systems of most low-income countries may either cover only a minority of individuals (as for example in India [Ragothaman et al., 2006]) or even do not cover any anti Parkinson medication at all (as for example in Ghana, Zambia, Tanzania, Nigeria, Ethiopia, etc), so that pharmacological treatment remains out of reach of most people living in rural communities. In this context, patients who cannot afford treatment may take Levodopa only once a day instead of the prescribed three times or even stop drug consumption for weeks before being reviewed. In advanced disease stages, it becomes
even more challenging to manage motor fluctuations as DAs, that help in reducing motor complications, are largely unavailable (Dotchin et al., 2007 and 2011). This has been demonstrated elsewhere as well (Dotchin C and Walker R 2012). There is no comparative evidence on efficacy, side effects and health economics but this should be helped when the PD MED later results become available (Carl Clarke, personal communication).

• Summary of available estimates of comparative effectiveness

Despite Levodopa being the most effective drug in reducing motor disability in PD, initial treatment with a DA (such as Pramipexole) results in significantly less development of motor complication (such as wearing off, dyskinesias, or on-off motor fluctuations) compared with Levodopa (the Parkinson study group 2000). Moreover, patients initially treated with the DA Pramipexole demonstrated a reduction in loss of substantia nigra neurons compared with those initially treated with Levodopa, during a 46-month period (the Parkinson study group 2002). However, recent evidence from the UK (Gray et al 2012) from the PD MED study where patients were randomized at the time of first commencing medication to either Levodopa, DA or MAOIB has just become available. Initial data suggests that Levodopa is the most effective, with lower side effects than previously demonstrated. This is likely to be due to the lower doses used (mean Levodopa dose of 450mgs per day at 5 years (Carl Clarke, personal communication)).

As a result of a twinning arrangement between the Parkinson Institute (ICP, Milan, Italy) and three hospitals in Ghana (Korle Bu Teaching Hospital in Accra, Komfo Anokye Teaching Hospital in Kumasi and Comboni Hospital in Sogakofe) ongoing since 2008, approximately 100 individuals with Parkinsonism have been put on chronic treatment with Levodopa/Dopa decarboxylase 200/50 mgs (provided for free) and regularly followed-up. About 15% of these cases received anti-Parkinson treatment for the very first time; all of those with a diagnosis of Parkinson’s disease showed a significant motor improvement (mean improvement of the UPDRS motor scores of about 40% compared to baseline condition) with a very low rate of side effects (all reversible after reducing the dosage, none had to drop out treatment). More than 90% of cases who were already on Levodopa Carbidopa 1:10 ratio (100/10 or 250/25) and switched to the same daily dosage of chronic Levodopa-Dopa decarboxylase 1:4 ratio reported a significant further and long-term improvement of motor performance. Levodopa-induced motor complications (wearing-off and dyskinesias) have been successfully managed with optimization of Levodopa regimen, amantadine was added in some cases to reduce dyskinesias and Pramipexole have been helpful in two cases with long-standing disease (Cilia et al personal communication).

References:


11. Summary of comparative evidence on safety*:

- **Estimate of total patient exposure to date**

  Levodopa (UK NICE guidelines 2006) has been in use now for over 40 years and is the most widely used medication for PD throughout the world.

  For Pramipexole, Selegiline and Amantadine please see Cochrane Review referenced above. For anticholinergics (including trihexyphenidyl) there are many years experience of usage since before the time of Levodopa.

- **Description of adverse effects/reactions**

  In the short term Levodopa can lead to nausea and dizziness but both of these effects usually settle down. In the longer term people can get problems with wearing off and dyskinesia, and also potentially hallucinations. Wearing-off and dyskinesias are not caused by Levodopa itself but rather reflect an interaction between advanced disease stages and Levodopa treatment.
Selegiline - side effects are similar to other PD drugs, but the main additional side effects of note are postural hypotension and hallucinations, especially in older patients or those with cognitive problems. It is contraindicated in women who are pregnant or breast feeding.

Amantadine - again the main additional side effects of note are visual hallucinations, and older and cognitively impaired patients are particularly at risk. It can also cause insomnia and so should not be taken later than mid-afternoon.

Pramipexole - other side effects are similar to other PD drugs. The main additional potential side effects of note are excessive daytime sleepiness, leg oedema and impulse control disorders (about which patients should be warned).

• Identification of variation in safety due to health systems and patient factors

Ideally diagnosis should be made by a specialist in movement disorders but in many LMICs there is a dearth of such specialists. Therefore, most patients are diagnosed and looked after by non-specialists. Most patients will show a good therapeutic response to Levodopa, with the highest benefit-to-risk ratio compared to all the other anti Parkinson medications. Effectiveness of Levodopa in alleviating PD motor symptoms significantly improves quality of life of patients and caregivers and reduces PD-related morbidity and mortality.

• Summary of comparative safety against comparators

Levodopa is generally a very safe medication and the main limit to its use is the development of wearing off and dyskinesia. It can be used throughout the course of PD. In later stage disease it is often better tolerated than other medications. Wearing-off and dyskinesias are not caused by Levodopa itself but rather reflect an interaction between advanced disease stages and Levodopa treatment.

Reference


12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

• range of costs of the proposed medicine (cost accessed from British National Formulary March 2012)

The average cost of treating someone with Levodopa for 1 year is about USD 300 but this is very much dependent on the dose of medication required..

Trihexyphenidyl – 100 x 5mgs tablets = £15.60. Therefore yearly cost 5mgs three times daily is approximately £170. NB, this is a relatively high dose.

Pramipexole – 0.7mgs x 100 = £71.82 therefore 0.7 three times daily for 1 year = £786.
Amantadine (Symmetrel) – 100mgs x 56 tablets = £9.90. Therefore 1 year treatment of 100mgs twice daily is approximately £17. NB only those with dyskinesia will be eligible for Amantadine treatment so this is likely to be less than 10% of overall patients.

Selegiline – 10mgs x 30 = £7.51 – therefore 1 year treatment of 10mgs daily is approximately £104

• comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality adjusted life year gained)

While PD is much more expensive to treat than say epilepsy or hypertension in LMICs, the treatment costs are comparable to highly active anti-retroviral therapy. The effects can be dramatic with patients who are virtually bedbound becoming mobile again. It therefore has major implications for the individual and for caregivers who are prevented from working as they have to look after the patient. In Ghana, the average cost of Sinemet 100/10mgs for 1 year (at 100mgs three-times/day regimen) is about 700 USD (90 GH Cedis), with the average monthly salary being approximately 60-70 USD.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Levodopa is available in virtually all countries. All the other drugs appear to be available in most countries.


Available in British pharmacopoeia and US pharmacopoeia. Check re international pharmacopoeia

15. Proposed (new/adapted) text for the WHO Model Formulary

Parkinson’s disease should be treated with Levodopa. The formulations available are 100/25mgs and 200/50mgs (the 25mgs and 50mgs refers to the dopadecarboxylase inhibitor, respectively). Patients should be started at a low dose (50 mgs Levodopa, ie half of a 100/25mgs tablet, twice a day) and then gradually titrated up to an initial maintenance dose of 100 mgs three times daily. They should be warned about the initial side effects of nausea and dizziness which tend to settle over time. The size and frequency of the dose will need to be titrated up further as the symptoms progress over time.

Anticholinergics have been available for a long time and are relatively cheap. They may be useful in young people whose main problem is tremor and rigidity, but they have little effect on bradykinesia, and their side effects preclude widespread use and they are now only infrequently used in developed countries. They should not be used in those already showing signs of cognitive impairment. Trihexyphenidyl hydrochloride (Benzhexol) should be started at 1mgs daily and slowly increased to a maintenance of 5 – 15mgs per day in 3 – 4 doses (maximum 20mgs / day). Most patients cannot tolerate the higher doses.

The following drugs should only be used by specialists:
DAs can be used alone or in association with Levodopa to reduce the risk of motor fluctuations and dyskinesias. Titration should be slow. Pramipexole is easier to titrate than ropinirole, starting from 0.18mgs tablet twice a day and then gradually titrated to an initial maintenance dose of 0.7mgs tablet three times/day. However, DAs are more expensive than Levodopa.

In patients who have significant problems with dyskinesias, Amantadine can be used in the form of 100mgs tablet, starting at ½ tablet twice daily and increasing up to a usual maintenance dose of 1-2 tablets twice daily (maximum dose of 400mgs / day). The second dose should be taken in the afternoon to avoid insomnia. The patients (especially elderly and those with cognitive decline) should be warned about potential onset, or increase of, visual hallucinations.