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## THE RELATIONSHIP OF CLINICAL TREATMENT TO QUALITY OF LIFE IN A PATIENT WITH VASCULAR PARKINSONISM: A CASE REPORT FROM A PHARMACIST'S PERSPECTIVE

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### ANNOUNCEMENT

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## The Relationship of Clinical Treatment to Quality of Life in a Patient with Vascular Parkinsonism: A Case Report from a Pharmacist's Perspective

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### Abstract

Vascular Parkinsonism (VP) is different from Parkinson's disease (PD). The etiology is still unclear, and clinical diagnosis is often difficult. The present study followed up on the medical treatment after hospital admission of a patient with VP, i.e. from the juncture when the patient was diagnosed with VP until his death. An 82-yr-old male patient who had a history of hypertension and heavy smoking was diagnosed with VP after admission to the hospital with multiple cerebral infarctions. He manifested poor quality-of-life (QoL) with major symptoms and adverse drug reactions (ADRs) such as incontinence, symmetrical gait difficulties, dementia, daytime drowsiness, dysarthria, micrographia, salivation, insomnia, and constipation. He was treated with multiple medications (12 agents from 21 month post-intervention) to maintain a life-sustaining yet low-risk blood pressure (range: systolic/diastolic range: 143/88-94/49 mmHg), which resulted in various adverse events and exacerbated QoL, making the patient feeling 'low' and resigned. The patient suffered from drowsiness and hypotension before succumbing 40 months after the initial intervention. During the follow-up period (from 20 months after intervention), the rehabilitation he participated in improved his mood and his motivation to carry out daily life activities (i.e. it led to higher QoL), although previously observed ADRs remained unchanged. Certain drugs used for a similar target outcome were used, and it is unclear if prescribing multiple medications was useful. However, physical activity may be useful for establishing a higher QoL in VP, and should have been started at the early-stage treatment. Further study is warranted on the use of multiple drugs in the elderly with VP.

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## 1. Introduction

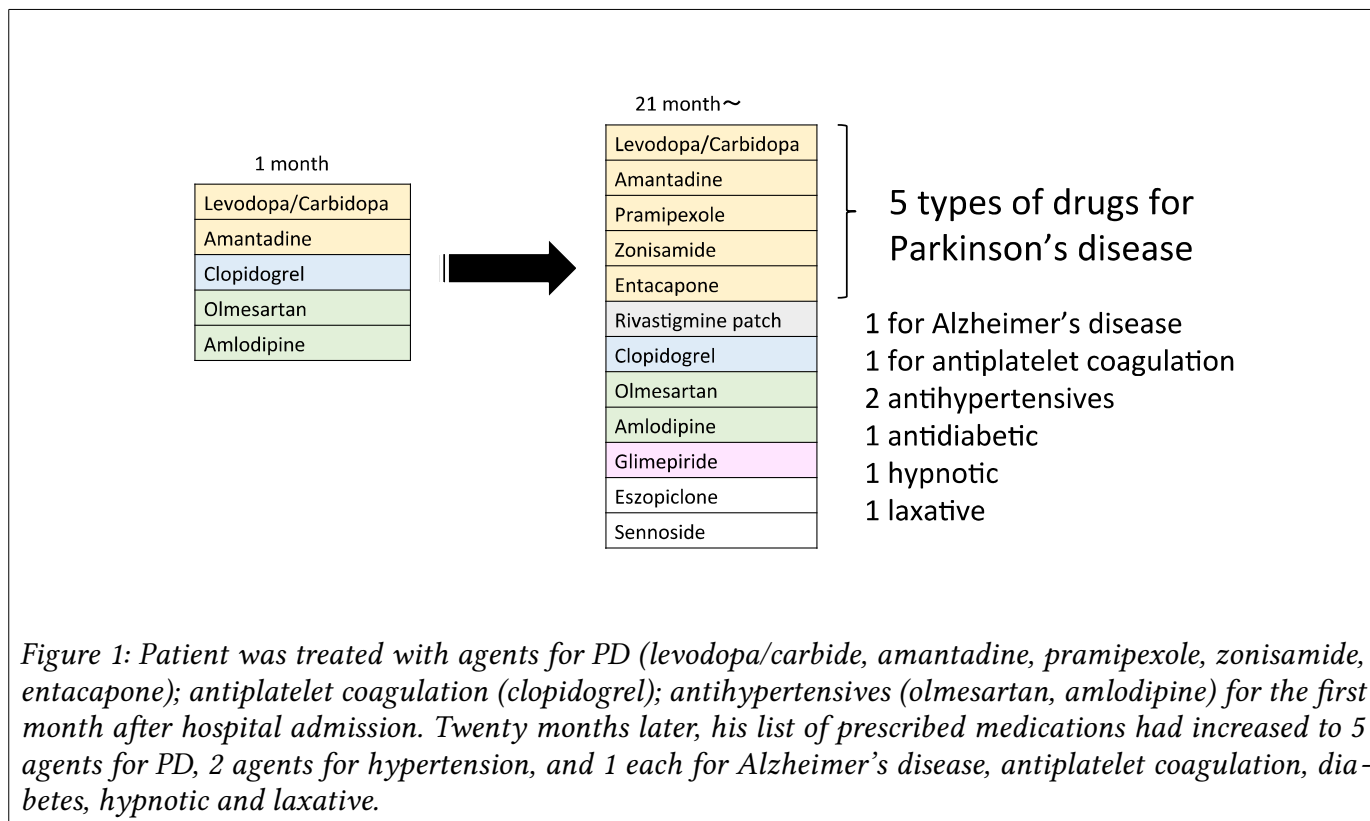
Parkinsonism is a general term that refers to a group of neurological disorders that cause movement problems similar to those observed in Parkinson's disease (PD). Tremors, slow movement and stiffness are the typical symptoms and signs of neurological disorders.<sup>1</sup> Within the various disorders categorized under Parkinsonism, certain symptoms and signs have yet to be clearly defined or named. It is often hard to know whether a person has idiopathic PD or a syndrome that mimics it during the early stages of the disease. Parkinsonisms, also known as atypical PD or Parkinson's plus,<sup>2</sup> represent about 10% of all diagnosed cases of Parkinsonism. They tend to progress more rapidly than PD, to present with additional symptoms such as early falling, sensory deficits,<sup>3</sup> sleep and cognitive disturbances,<sup>2</sup> dementia or hallucinations without external identifiable cause,<sup>4</sup> and not to respond or respond for only a short time to levodopa therapy.<sup>2</sup>

The following diseased states are some of the most common Parkinson's plus disorders:<sup>5</sup> progressive supranuclear palsy,<sup>6</sup> multiple system atrophy (also referred to as Shy-Drager syndrome), vascular parkinsonism (VP),<sup>7,8</sup> dementia with Lewy bodies,<sup>5</sup> drug-induced parkinsonism (drugs such as antipsychotics, metoclopramide, MPTP),<sup>6,7</sup> and corticobasal degeneration.<sup>7</sup> It is important to remember that many people will not exhibit the cardinal symptoms necessary for a diagnosis of a specific disorder and their condition will simply be labeled as "Parkinsonism." Typically, parkinsonism in slow-onset VP tends to be bilaterally symmetric, affecting the lower limbs more than the upper limbs ('lower-body parkinsonism'), and resting tremor is usually absent. Commonly noted lesions on brain imaging in VP are lacunes, white matter changes, and, rarely, territorial infarcts. As coincidental vascular lesions in idiopathic Parkinson's disease (PD) are common, the mere presence of these lesions on brain imaging is not diagnostic of VP. Pathological evidence of a vascular disease in the absence of typical PD lesions (e.g. Lewy bodies) is the diagnostic 'gold standard'. VP is generally considered to be poorly or non-responsive to L-dopa therapy. However, recent studies have shown a beneficial effect with L-dopa in a subset of patients.<sup>7</sup>

In the present study, we encountered a case diagnosed by the physicians as VP, although a definitive test to discriminate PD from Parkinsonism has yet to be established. For this diagnosis, doctors took a thorough medical history and performed a number of movement tests. Because of the observational nature of the diagnosis, PD can sometimes be confused with Parkinsonism, and the diagnosis may need to be revised over time based on the speed of disease progression, response to medications, and other factors. One thing is known for certain: all Parkinson's patients suffer from a loss of dopamine.

## 2. Methods and Subject

This paper is a retrospect study of a patient diagnosed with VP after hospital admission: i.e. it covers the time from the juncture when the patient was diagnosed with VP until his death. The patient was an 82-yr-old male with a history of hypertension and heavy smoking. Three months before hospital admission, the patient had a fall, and suffered from gait difficulties thereafter. Despite the gait difficulties, he was able to actively move around in his home and neighborhood. During a consultation with an orthopedist, no abnormalities were found other than the gait difficulties. The patient was then diagnosed by a neurologist as having VP (thought to be inflicted by multiple cerebral infarctions), and was treated with therapeutic agents and regimen (Figure 1): viz., two agents for PD (levodopa/carbide, amantadine); one agent for antiplatelet coagulation (clopidogrel); and two antihypertensives (olmesartan, amlodipine) for the first month after hospital admission. Family members deemed the treatment unsatisfactory, and transferred the patient to another hospital under the care of another neurologist, who added more therapeutic agents (Figure 1). Thereafter, his list of medications was gradually increased, whereupon he was given five agents for PD (levodopa/carbide, amantadine, pramipexole, zonisamide, entacapone); one for Alzheimer's disease (rivastigmine patch); one antiplatelet coagulation (clopidogrel); two antihypertensives (olmesartan, amlodipine); one antidiabetic (glimepiride); one hypnotic (eszopiclone); and one laxative (sennoside) which began 21 months after his initial therapeutic treatment. Long-term care started 16 months after hospitalization, and the level of care was considered category 1 until 27 months after hospitalization. His condition did not improve, and the care level was raised to category 2 for 2 months (28-29), progressing to care level 5 from 30 months until his death. Although he could move around, he found it hard to walk even with a walker from 29 months on.



Rehabilitation started 17 to 29 months after admission. Patient was eager to participate in rehabilitation. In post-admission month 30, he was discharged from the hospital, and received home-care nursing thereafter. Patient began to experience insomnia after the termination of rehabilitation. He ate lunch and dinner with family members once a week.

### 3. Results

After the first month of medical treatment, he manifested poor quality-of-life (QoL) with onset of symptoms such as incontinence, symmetrical gait difficulties, dementia, daytime drowsiness, dysarthria, micrographia, salivation, insomnia, and constipation. His poor QoL as well as the symptoms and signs exacerbated when, to relieve his signs and symptoms, he was given additional types and doses of drugs with overlapping and/or complementary pharmacological actions.

He was treated with multiple medications (average; 12 agents by 21 months) to maintain a life-sustaining and yet low-risk blood pressure (systolic/diastolic blood pressure range: 143/88-94/49 mmHg), which resulted in various adverse events and decreasing QoL: he tended to feel 'low' and resigned. Patient suffered from dementia, drowsiness, constipation, depression, and hypotension before succumbing 40 months after the initial intervention

Intriguingly, rehabilitation adopted from 17 months after intervention improved his mood, bowel movements, and motivation to carry out daily life activities (i.e. improved QoL), although previously observed adverse events and/or probable adverse drug reactions (ADRs) remained apparently unchanged (events were neither qualitatively or quantitatively monitored).

### 4. Discussion

According to various population-based and clinical cohort studies, vascular parkinsonism (VP) accounts for 4.4-12%<sup>7</sup> or 2.5-5%<sup>8</sup> of all cases of parkinsonism. VP develops as a result of ischemic cerebrovascular disease, and therefore – etiologically – it is classified as secondary parkinsonism. It has been variably referred to in the literature as arteriosclerotic parkinsonism, vascular pseudoparkinsonism, and lower-body parkinsonism.<sup>9,10,11</sup> The most important consideration in diagnosis is that it is critical to differentiate VP from Parkinson's disease (PD) because of prognostic and therapeutic implications.<sup>12</sup> The salient clinical features in VP which differentiate it from PD are postural instability and falls (in contrast to upper-limb rest tremor or bradykinesia), short shuffling parkinsonian gait accompanied by a wider

base of stance and variable stride length (parkinsonian-ataxic gait), absence of festination, frequent occurrence of pyramidal signs, and early dementia, as seen in the present case study. In a patient where the clinical features are suggestive of VP, the clinical diagnosis can be supported by demonstration of diffuse white matter lesions and/or strategic subcortical infarcts on an MRI of the brain (which was not conducted in the present case). The therapeutic options in VP are limited to levodopa, and a poor or non-sustained response to levodopa is another differentiating feature between VP and PD.<sup>13</sup>

Similar to other cases reported on in the literature,<sup>13</sup> the present case of VP was caused by clotting in the brain due to multiple cerebral infarctions. The patient had more problems with gait than with tremor in the lower body. The disorder could have developed much earlier, and progressed very slowly and indicated an abrupt onset of symptoms or stepwise deterioration immediately before and after hospital admission (symptoms get worse then plateau for a while). The pharmacologic treatment in the present VP case was strategized via a trilateral major approach: viz., symptomatic, protective, restorative. Although the goal of therapy is to reverse the functional disability using the aforementioned trilateral concept, abolition of all symptoms and signs was not possible even with the high doses of medication used in the present case. Symptoms in VP did not respond well to levodopa for long, and primary care-providers had to prescribed various complementary agents (use of amantadine, pramipexole, zonisamide, and entacapone in the present case) to extend the effect and enhance brain dopamine levels.

The use of levodopa (L-DOPA) has been considered one of the success stories of modern medicine.<sup>14,15</sup> It has remained the most efficacious drug available for the relief of symptoms in PD since its first introduction in the 1960s.<sup>14</sup> Only 5-10% of L-DOPA crosses the blood-brain-barrier, and the remainder is often metabolized to dopamine elsewhere, inducing a variety of ADRs (e.g. nausea, dyskinesia, joint stiffness, etc.). The drug and its derivatives have produced dramatic results even in patients as severely affected as the one in the present case. However, in this case, the patient had VP without responding well to levodopa over time despite high dosage and corresponding regimen. L-DOPA is converted into dopamine in the dopaminergic neurons by dopa decarboxylase,<sup>16</sup> and as a result, motor symptoms due to lack of dopamine in the substantia nigra are temporarily diminished. Carbidopa, a peripheral dopa decarboxylase inhibitor,<sup>16</sup> helps to prevent metabolism of L-DOPA before it reaches the dopaminergic neurons, reducing the ADRs and also increasing bioavailability. Pharmacologic advances during the last three decades have significantly augmented the treatment approach and concept of antiparkinsonian agents: viz., dopamine agonists (pramipexole in the present case), inhibitors of catechol-o-methyltransferase (COMT) inhibitor (entacapone in the present case) to increase the effect of L-DOPA/carbidopa in brain, antagonists of the NMDA-type glutamine (amantadine in the present case), antiseizure agents (zonisamide in the present case), and monoamine oxidase type B (MAO-B) inhibitors, have added to the list of treatment medications. However, except for entacapone and pramipexole, the use of other anti-PD drugs has not been all that impressive in terms of outcome and economic viability.<sup>4,15</sup> Superimposed upon the disease-related problems are the additional burden of on-off movements,<sup>15</sup> dyskinesias, and visual hallucinations. In our present study, symptoms - or probably adverse drug reactions (ADRs) - such as incontinence, symmetrical gait difficulties, dementia, daytime drowsiness, dysarthria, micrographia, salivation, insomnia, and constipation were encountered, and the relevant agents were therefore prescribed to reduce these unwanted effects, resulting in a vicious cycle of multiple drugs being prescribed.

The kind of dementia associated with the present VP case has been estimated to affect at least 20% of PD patients, with a higher prevalence among older patients, and lower prevalence among those with young-onset disease. An estimated 40-60% of PD patients suffer from depression (for example, zonisamide very commonly induces depression: <https://en.wikipedia.org/wiki/Zonisamide>), which was observed and treated for accordingly in the present case as well. Adverse psychiatric effects are much more likely to occur in patients with predisposing characteristics such as dementia, advanced age, premorbid psychiatric illness, and exposure to high daily doses of levodopa. Although currently popular surgical interventions include pallidotomy, chronic deep-brain stimulation of the subthalamic nucleus, and globus pallidus internus using an implantable pulse generator are available,<sup>16</sup> these methods were not attempted for treatment in our present patient probably in consideration of his advanced age.

Drug-induced Parkinsonism can be difficult to distinguish from PD, although the tremors and postural instability may be less severe. It is usually the ADRs that affect dopamine levels in the brain; ADR

inducing drugs include antipsychotics, certain calcium channel blockers (the antihypertensive amlodipine used in the present case treatment is a calcium ion blocker) and stimulants like amphetamines/cocaine. These ADRs may take as long as 18 months to disappear. Dopamine dysregulation syndrome is induced by the hypnotic eszopiclone,<sup>16</sup> which is in the category cyclopyrrolones used in the present VD case. Eszopiclone is a non-benzodiazepine receptor agonist that inhibits noradrenalin, dopamine, and serotonin turnover in the brain, possibly by direct action in the gamma-aminobutyric acid (GABAergic) pathway.<sup>18,19</sup>

There is an overlap in treatments for PD and Parkinsonisms. Dopaminergic therapy (the first line treatment for PD) can be effective in some Parkinsonisms. Other common treatments for both PD and Parkinsonisms include physical, occupational, or speech therapy, antidepressants, and botulinum toxin (Botox) for dystonia.<sup>20</sup> Affected by the QoL-related conditions, health care providers focally treated the symptoms to improve QoL of the elderly VP case.

It is worthy of note that the current patient's physical activity via physiotherapy in the rehabilitation program improved his mood and his motivation to engage in daily life activities,<sup>21,22</sup> although ADRs and physical events remained unchanged. Regular physical exercise with or without physiotherapy is beneficial to maintaining and improving mobility, flexibility, strength, gait speed, and QoL.<sup>23</sup> An exercise program performed under the supervision of a physiotherapist leads to improvements in mental and emotional function, engagement in daily living activities, and QoL.<sup>24</sup> Other effective techniques to promote flexibility include slow rotational movements of the extremities and trunk, rhythmic movements, diaphragmatic breathing, and even meditation techniques.<sup>25</sup> Besides predominantly mental improvements, rehabilitation enhanced bowel movements as well.<sup>26</sup>

As this is a retrospective study, impossibility of communication with the deceased patient was a limitation of this study. In addition, limited experience with or history of treating such cases by the primary caregivers, and restricted understanding by the primary healthcare provider of the clinical situation were also possible factors. Furthermore, it should be noted questions to the provider about the use of multiple-medication prescription went unanswered. The patient was in such a dire state that more could not be extracted from his poor physical condition and adverse drug reactions. All in all, the patient was definitely feeling more positive and affirmatively elated with physical activity. As such, physical activity should be incorporated as early as possible to make patients have a more positive in the outlook on life and the treatment process.

## 5. Conclusion

Although certain drugs used for complementary treatment to yield a target outcome were used, some of these were used without exhibiting clinical benefit and might have even produced adverse drug effects. Therefore, further studies are warranted to pursue an understanding of treatment outcomes under multiple medications using agents with different mechanisms. On the other hand, physical activity was definitely useful for establishing a higher QoL in VP, and should be started at the early treatment stage. Further study is warranted on the use and combination of multiple-drug regimens and rehabilitation in the treatment of elderly with VP.

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