The Parkinson’s disease death rate: carbidopa and vitamin B6

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Abstract: The only indication for carbidopa and benserazide is the management of L-dopa-induced nausea. Both drugs irreversibly bind to and permanently deactivate pyridoxal 5′-phosphate (PLP), the active form of vitamin B6, and PLP-dependent enzymes. PLP is required for the function of over 300 enzymes and proteins. Virtually every major system in the body is impacted directly or indirectly by PLP. The administration of carbidopa and benserazide potentially induces a nutritional catastrophe. During the first 15 years of prescribing L-dopa, a decreasing Parkinson’s disease death rate was observed. Then, in 1976, 1 year after US Food and Drug Administration approved the original L-dopa/carbidopa combination drug, the Parkinson’s disease death rate started increasing. This trend has continued to the present, for 38 years and counting. The previous literature documents this increasing death rate, but no hypothesis has been offered concerning this trend. Carbidopa is postulated to contribute to the increasing Parkinson’s disease death rate and to the classification of Parkinson’s as a progressive neurodegenerative disease. It may contribute to L-dopa tachyphylaxis.

Keywords: L-dopa, levodopa, vitamin B6, pyridoxal 5′-phosphate

Introduction
Parkinson’s disease is classified as a progressive neurodegenerative disease.1 L-3,4-dihydroxyphenylalanine (L-dopa) is the most effective treatment for Parkinson’s disease.2 Many patients who take it experience profound nausea, which may prevent them from reaching higher dosing values required for symptom relief.3 On May 2, 1975, the US Food and Drug Administration (FDA) approved carbidopa (MK-486),4,5 a drug whose only indication was the management of L-dopa-induced nausea. The Centers for Disease Control and Prevention (CDC) noted an increasing Parkinson’s disease death rate. In 2003, Parkinson’s disease was added to the top 15 causes of death; it entered the list as the 14th leading cause of death.6

The following questions are examined in this review:
1. Is carbidopa linked to the increasing Parkinson’s disease death rate?
2. Are the attributes of the nutritional collapse associated with Parkinson’s disease, L-dopa, and/or carbidopa being misdiagnosed as progressive neurodegeneration?
3. Is carbidopa involved in L-dopa tachyphylaxis?

Insight into these questions required the review of Parkinson’s disease, relative nutritional deficiencies, pyridoxal 5′-phosphate (PLP) (the active form of vitamin B6), L-dopa, carbidopa, carbidopa’s side effects, the CDC-reported Parkinson’s disease death rates, the biochemistry of L-dopa-induced nausea, and of the documented alternatives to carbidopa and benserazide.
Benserazide
Benserazide and carbidopa have identical mechanisms of action and indications. Any reference to benserazide means, “Benserazide and/or its metabolite trihydroxybenzylhydrazine.”
While the focus of this paper is on carbidopa, the attributes shared by benserazide are noted.

Drug nutrient perspective
The following definition for a nutrient is utilized: A nutrient is any substance that facilitates normal system function. A drug is any substance that induces abnormal system function. A nutrient may become a drug. A drug may not become a nutrient.

5-hydroxytryptophan (5-HP) is a nutrient. When it is administered as a single agent, dopamine depletion may occur.8–21 If it induces dopamine depletion, then 5-HP no longer functions as a nutrient; it is a drug. L-dopa may be administered as a nutrient. When it is administered as a single agent, serotonin depletion may occur.10–18,22–29 If it induces serotonin depletion, then L-dopa no longer functions as a nutrient; it is a drug.

Vitamin B6
Over 300 enzymes and proteins require PLP to function properly.30 The five PLP-dependent enzymes—glutamate decarboxylase, arginine decarboxylase, histamine decarboxylase, aromatic L-amino acid decarboxylase (AADC), and sulfoalanine decarboxylase—are:

[...] unrivaled in the variety of reactions they catalyze and the highly diverse metabolic pathways they are involved in, including the conversion of amino acids, one-carbon units, biogenic amines, tetrapyrrolic compounds, and amino sugars […] sulfur assimilation, incorporation in cysteine, biotin, and S-adenosyl methionine.11

L-dopa
The primary pathology demonstrated in Parkinson’s disease is progressive degeneration of the substantia nigra of the brain.12 The primary etiology of Parkinson’s disease is postsynaptic dopamine neuron damage caused by neurotoxins. Progressive neuron damage induces the collapse of the electrical conduction that regulates fine motor control.12 L-dopa crosses the blood–brain barrier and it is then freely synthesized to dopamine without feedback regulation. The administration of L-dopa increases synaptic dopamine levels.32–55 It is analogous to turning up the voltage; more electricity flows through the remaining viable postsynaptic neurons. Restoration of postsynaptic electrical flow optimizes regulation of fine motor control.10,56

The only major advancements in Parkinson’s disease occurred in the 1950s and involved the amino acid, L-dopa. This research was awarded the Nobel Prize in Medicine in 20007,38 and the Nobel Prize in Chemistry in 2001.39 Sweet and McDowell attributed the decreasing Parkinson’s death rate that occurred between 1958 and 1975 to L-dopa (from 2.9/100,000 to 1.6/100,000 of the standard population, age-adjusted).61

The National Parkinson Foundation notes that 89% of the 1 million Parkinson’s patients in the US take L-dopa/carbidopa daily.62 While L-dopa is the most effective treatment, it is not usually the drug of choice.2 Side effects have positioned it to be one of the last drugs started in many cases.2 Parkinson’s disease is associated with the depletion of serotonin, dopamine, norepinephrine, epinephrine, thiols (homocysteine, L-methionine, S-adenosyl-L-methionine, S-adenosyl-homocysteine, cystathione, L-cysteine, and glutathione), L-tyrosine, and L-tryptophan, and these depletions represent relative nutritional deficiencies (RNDs) where systemic nutritional synthesis requirements cannot be achieved on a normal or optimal diet.12,13,28,63–68

L-dopa may induce its own unique RND and exacerbate the Parkinson’s disease RND. When administered singularly or with an improper nutrient balance, it has the ability to induce RNDs of serotonin, thiols, L-tyrosine, and L-tryptophan.12,13 We hypothesize that if the Parkinson’s disease patient is being evaluated for the signs and symptoms of progressive neurodegenerative disease without considering the potential for, as well as the existence and ramifications of RNDs associated with the disease itself, L-dopa, and/or carbidopa, then nutritional collapse components will erroneously be attributed to progressive neurodegeneration.

Carbidopa
Efficacy and safety concerns must be addressed before US FDA drug approval. Conceptualize a drug that has no treatment efficacy claims under US FDA guidelines. Its sole indication is the management of the side effect of nausea induced by improperly balanced nutrient administration.3 It irreversibly binds to and permanently deactivates free PLP and PLP-dependent enzymes while inducing PLP reserve pool depletion.7 It negatively impacts the function of over 300 enzymes and proteins.30 Administering vitamin B6 counteracts its mechanism of action.3 Drugs with these attributes are being prescribed. (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid (carbidopa) is being prescribed in the US and (RS)-2-amino-3-hydroxy-N’-(2,3,
4-trihydroxybenzyl) propanediamine (benserazide) is being prescribed outside the US.\textsuperscript{2,69}

L-dopa-induced nausea is a peripheral phenomenon. Carbidopa and benserazide inhibit peripheral L-dopa metabolism by AADC.\textsuperscript{3} This increases the amount of L-dopa available to cross the blood–brain barrier. Decreasing peripheral L-dopa levels through decreased ingestion, while maintaining its levels in the central nervous system, effectively controls nausea.\textsuperscript{12} Carbidopa and benserazide control nausea by identical mechanisms.\textsuperscript{2,66} Carbidopa and the active metabolite of benserazide, trihydroxybenzylhydrazine, irreversibly bind to and permanently deactivate PLP and PLP-dependent enzymes.\textsuperscript{18,19,70–74} Normally, a Schiff base alamine reaction catalyzes the irreversible hydrazine binding of PLP with the core protein of AADC to produce the active enzyme.\textsuperscript{5} Benserazide is completely metabolized to trihydroxybenzylhydrazine before it reaches the arterial blood. Carbidopa and trihydroxybenzylhydrazine are substrate analogues endowed with irreversible substituted hydrazine function.\textsuperscript{7}

PLP is noncovalently (reversibly) bound to approximately 300 enzymes and proteins forming the PLP reserve pool.\textsuperscript{70} The molecular weight of PLP is 247.142 g/mol\textsuperscript{70} and that of carbidopa is 244.244.\textsuperscript{76} Carbidopa irreversibly binds to PLP in a 1:1 ratio.\textsuperscript{7} The recommended dietary allowance of vitamin B6 is about 1 to 2 mg/day depending on age.\textsuperscript{77} If the lowest daily dose of carbidopa (10 mg) is administered, then the system is placed into a PLP-induced RND state on the first day.

Systemic vitamin B6 concentrations inversely correlate with mortality induced by coronary artery disease, colorectal cancer, stroke, heart failure, and atherosclerosis.\textsuperscript{78–83} We hypothesize that if carbidopa and benserazide significantly deplete PLP, then an increased death rate will be observed. During the first 15 years of prescribing L-dopa (1960–1975) it was administered without carbidopa, a practice that was associated with a decreasing death rate.\textsuperscript{61} On May 9, 1975, the US FDA approved carbidopa for concomitant administration with L-dopa.\textsuperscript{3} Between 1976 and 2011, the there has been an increase in the general Parkinson’s disease death rate. While numerous etiologies have been postulated to explain the increasing Parkinson’s death rate, none have impacted this 38-year trend. Parkinson’s disease is most prevalent in white males. Figures 1 and 2, when viewed together, demonstrate that the Parkinson’s death rate increase is occurring across all ages, sexes, and ethnic groups.

Concomitant L-dopa/carbidopa preparations have been positioned by the manufacturers to permeate treatment to the point that prescription L-dopa as a single ingredient is no longer available (Table 1). Prior to 1999, three pharmaceutical companies distributed a US FDA-approved brand name prescription forms of L-dopa as a single-ingredient drug: Bendopa\textsuperscript{®} (Valent Pharm Intl); Dopar\textsuperscript{®} (Shire plc, St Helier, Jersey); and Larodopa\textsuperscript{®} (Hoffman-La Roche Ltd, Basel, Switzerland).\textsuperscript{22} There is no public documentation explaining the reasoning behind these SmithKline Beecham actions, as SmithKline Beecham owned the rights to the other L-dopa preparations at that time.\textsuperscript{42,84–86}
behind the virtually simultaneous discontinuation of these drugs by the three companies.

When these drugs were approved, each was described as a decarboxylase inhibitor. Documentation submitted in 1997 noted significant central and peripheral PLP depletion after limited ingestion time of carbidopa. Now the full mechanism of action of PLP is known, giving rise to more serious concerns. It is documented that PLP freely crosses the blood–brain barrier. Carbidopa prescribing information states that it “[…] does not affect the metabolism of levodopa within the central nervous system.” This is not correct. If PLP freely crosses the blood–brain barrier allowing a peripheral and central equilibrium to exist, then both peripheral and central PLP depletion will be induced by carbidopa and benserazide. Theoretically, complete PLP depletion of the central and peripheral systems may occur. If carbidopa-induced PLP depletion is great enough for compromise of central AADC function to occur, then there will be an impairment of central dopamine synthesis. This is a previously undocumented potential etiology of L-dopa tachyphylaxis.

Carbidopa prescribing information lacks full disclosure. There is no reference to PLP, PLP depletion, irreversible binding to and permanent deactivation of PLP and PLP-dependent molecules, depletion of PLP reserve pools, risks induced by PLP depletion, potential functional compromise of over 300 enzymes and proteins, or RND induction. Simply describing carbidopa and benserazide as decarboxylase inhibitors is analogous to describing a nuclear blast as a window breaker. Chronic administration affects virtually every system in the body.

The mechanism of action of carbidopa and benserazide is PLP depletion. Carbidopa prescribing information only notes, “Pyridoxine hydrochloride (vitamin B6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.” PLP depletion is an RND event. PLP can reverse the nausea control of carbidopa and ameliorate the clinical effects of L-dopa, requiring caution during concomitant administration. We hypothesize that if these drugs are stopped and then ample vitamin B6 is administered, PLP function, PLP-dependent enzyme function, and PLP reserve pools will return to normal.

The exact size of the PLP reserve pool, which is reversibly bound to about 300 enzymes and proteins, is a matter of speculation. We postulate that when normal PLP pool reserve function exists at the start of treatment, it may take 5 or more years of chronic carbidopa or benserazide ingestion, depending on the daily dosing value, before progressive clinical deterioration is demonstrated. We further postulate that without a PLP reserve pool, carbidopa or benserazide ingestion would induce PLP collapse in days.

### Carbidopa side effect profile

L-dopa active ingredient products may be administered as a nutritional supplement or a drug. Nutritional supplements are generally recognized as safe (GRAS), allowing over-the-counter sales. Due to side effects, carbidopa is not GRAS. It may induce life-threatening events including myocardial infarction, neuroleptic malignant syndrome, agranulocytosis, hemolytic and nonhemolytic anemia, gastrointestinal bleeding, thrombocytopenia, and hypokalemia (Table 2). While carbidopa side effects require its discontinuation when the continuation of L-dopa is indicated, nutrient products are the only option. Most physicians are unaware of the availability of this L-dopa form.

The carbidopa side effects and adverse reactions listed in Table 2 are a direct result of irreversible drug-induced PLP depletion, irreversible PLP-dependent enzyme binding, PLP reserve pool collapse, along with RND-induced collapse of serotonin and catecholamine synthesis. If, when equilibrated, central PLP depletion occurs as a result of peripheral PLP depletion, then central compromise, side effects, and adverse reactions are inevitable – a phenomenon not previously documented.
Table 2 Side effects and adverse reactions associated with carbidopa

<table>
<thead>
<tr>
<th>Effect</th>
<th>Carbidopa</th>
<th>Benserazide</th>
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<tbody>
<tr>
<td>Glossitis</td>
<td>Upper respiratory infection</td>
<td>Phlebitis</td>
</tr>
<tr>
<td>Leg pain</td>
<td>Bruxism</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Hiccups</td>
<td>Hemolytic and nonhemolytic anemia</td>
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<tr>
<td>Falling</td>
<td>Common cold</td>
<td>Rash</td>
</tr>
<tr>
<td>Gait abnormalities</td>
<td>Urinary tract infections</td>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Blepharospasm (which may be taken as an early sign of excess dosage)</td>
<td>Diarrhea</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>Trismus</td>
<td>Urinary frequency</td>
<td>Henoch–Schönlein purpura</td>
</tr>
<tr>
<td>Increased tremor</td>
<td>Flatulence</td>
<td>Decreased hemoglobin and hematocrit</td>
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<tr>
<td>Numbness</td>
<td>Prapism</td>
<td>Leukopenia</td>
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<tr>
<td>Muscle twitching</td>
<td>Pharyngeal pain</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Abdominal pain</td>
<td>Urticaria</td>
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<tr>
<td>Myocardial infarction</td>
<td>Bizarre breathing patterns</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Stomach or abdominal pain</td>
<td>Burning sensation of tongue</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Palpitation</td>
<td>Increased sweating</td>
<td>Dark sweat</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Syncope</td>
<td>Abnormalities in alkaline</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Orthostatic hypotension</td>
<td>Phosphatase</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Asthenia</td>
<td>Abnormalities in SGOT (AST)</td>
</tr>
<tr>
<td>Constipation</td>
<td>(weakness)</td>
<td>SGPT (ALT)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>Dysphagia</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Horner’s syndrome, mydriasis</td>
<td>Coombs’ test</td>
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<tr>
<td></td>
<td>Dry mouth</td>
<td>Abnormal uric acid</td>
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<td></td>
<td>Sialorrhoea</td>
<td>Hypokalemia</td>
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<tr>
<td></td>
<td>Neuroleptic malignant syndrome</td>
<td>Abnormalities in blood urea nitrogen</td>
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<td></td>
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<td>Increased creatinine</td>
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<td>Increased serum LDH</td>
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<td></td>
<td></td>
<td>Glicosuria</td>
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Note: Data from Hinz et al.\textsuperscript{12,13} Abbreviations: SGOT, serum glutamic oxaloacetic transaminase; AST, aspartate aminotransferase; SGPT, serum glutamic pyruvic transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase.

Nutritional management of nausea

It was previously documented that L-dopa-induced nausea, along with Parkinson’s disease, L-dopa-associated, and carbidopa-associated RND, is definitively controlled with properly balanced administration of the nutrient 5-HTP, along with L-tyrosine, a thiol (L-cysteine, glutathione, S-adenosylmethionine, or L-methionine), and cofactors (vitamin C, vitamin B6, and calcium carbonate), as facilitated by organic cation transporter type-2 functional status analysis.\textsuperscript{12,13}

AADC inhibition may be reversible or irreversible. The irreversible inhibition of AADC is the mechanism of action whereby carbidopa and benserazide control L-dopa-induced nausea.\textsuperscript{3,18,19,70–74} Reversible inhibition of AADC in the competitive inhibition state is the mechanism of action whereby 5-HTP controls L-dopa-induced nausea. If 5-HTP effectively controls L-dopa-induced nausea, then carbidopa or benserazide is no longer indicated, and all detrimental effects discussed herein no longer apply. If 5-HTP is not administered in proper balance with amino acid precursors of other systems, then it will become a drug due to its depilation of dopamine.\textsuperscript{12,13}

Due to the increased frequency of the onset of new drug-induced side effects, carbidopa, monoamine oxidase inhibitors, and catechol-O-methyl transferase inhibitors need to be stopped as 5-HTP and other nutrients are started under the nutrient protocol. If carbidopa is administered with expectations of controlling L-dopa-induced nausea, then vitamin B6 cannot be replenished while taking the drug since PLP reverses the drug effects. If there is a patient history of carbidopa or benserazide ingestion, then vitamin B6 (100–300 mg/day) is indicated at the initiation of the nutrient protocol.

Discussion

Responsible physicians create an environment where optimal symptom control nurtures healing. Two medications with no efficacy claims have been prescribed for the iatrogenic mismanagement of a nutrient, L-dopa, turning it into a drug which depletes other systems.\textsuperscript{3,12,13,69} Their only indication is to alleviate nausea, a benign condition, while having the ability to profoundly compromise hundreds of system functions.\textsuperscript{3,66} In our opinion, use of these medications is a violation of the physician's oath to first, do no harm. These drugs can create fatal events, clinical deterioration, drug-induced sequelae, and risks where none previously existed due to profound multisystem nutritional collapse.\textsuperscript{12,13,18,19,70–74,78–83} Nausea induced by improper administration of the nutrient L-dopa should not be addressed with drugs whose mechanism of action is system-wide vitamin B6 RND, which is especially true when a drug-free nutrient management approach is available.

In 1941, almost 20 years before the dawn of L-dopa, Baker described a subgroup involving 25% of Parkinson's disease patients who achieved “definite objective improvement” with vitamin B6 administration.\textsuperscript{85} In 2012, the literature noted, “Multifactorial neurological pathologies such as [...] Parkinson’s disease [...] have also been correlated to inadequate intracellular levels of PLP.”\textsuperscript{86} Administration of carbidopa and benserazide should be contraindicated in these patients.
Conclusion
Between 1960 and 1974, the only prescription form of L-dopa available was the single-ingredient form that was associated with a decreasing death rate. In 1975, the original combination L-dopa/carbidopa drug (Sinemet®) was approved by the US FDA. Between 1976 and 2011, the CDC documented a progressive increase of 328.7% in Parkinson’s disease deaths that crossed age, sex, and ethnic boundaries. In addition, no effective way has been discovered to truly stop what has been described as neurodegeneration.

The mechanism of action for carbidopa and benserazide induces irreversible binding to and permanent deactivation of PLP and PLP-dependent enzyme molecules, potentially inducing a negative impact on over 300 enzymes and proteins. Without the induction of PLP deficiency, the clinical effects of carbidopa and benserazide are not observed. It is a documented fact that these drugs may induce system-wide PLP depletion, representing an RND that is reversed with vitamin B6 administration. Administration of carbidopa may play a role in the escalating Parkinson’s disease death rate, the exacerbation of symptoms exclusively attributed to progressive neurodegeneration, and L-dopa tachyphylaxis. The full list of biochemical compromises can only be speculated due to the ability of carbidopa and benserazide to induce hundreds of intertwined peripheral and central PLP function collapses, many of which may not be fully understood at present. It is illogical to assert that an increased carbidopa-induced death rate will not occur under these circumstances. In an attempt to control a benign condition (nausea – caused by the improperly balanced administration of a nutrient, L-dopa), the patient has been exposed to the devastating consequences of these drugs. While a formidable number of studies may still be needed to define all of the PLP depletion ramifications, they become unnecessary in the effective management of Parkinson’s disease when the nutrient protocol is implemented, since carbidopa and benserazide are no longer indicated.

The administration of properly balanced nutrients, under a documented nutritional protocol for the definitive control of L-dopa-induced nausea, should raise no more concern with the caregiver or patient than administration of a multivitamin; all are GRAS. Physicians should fully understand the mechanism of action of the drugs they prescribe rather than relying on the described indications provided by the drug company. Efficacy concerns relating to the discontinuation of carbidopa and benserazide are unfounded since they have no efficacy; they only deal with L-dopa side effects. Before 1976, in the pre-carbidopa era, ample studies were published documenting the efficacy of L-dopa without carbidopa.

Three questions are raised: 1) Is progressive neurodegeneration observed with Parkinson’s disease intrinsic to the disease, or may some symptoms be attributed to carbidopa or benzerazide-induced RND? 2) Does iatrogenic drug-induced poisoning, which may result in irreversible binding to and permanent deactivation of PLP and PLP-dependent enzyme molecules throughout the system, play a role in the increasing death rate noted by the CDC since 1976? 3) Is carbidopa or benserazide potentially involved in L-dopa tachyphylaxis? If the answer to these questions is yes, or even maybe, a greater focus on nutrition is indicated while discontinuing drugs such as carbidopa or benserazide. The doctrine of res ipsa loquitur (the thing speaks for itself) applies.

There is much fertile ground presented here for furthering this research started in 1997. The authors encourage continued investigation, along with dialogue, into the ramifications of carbidopa and benzerazide use and the known RNDs that plague the Parkinson’s disease patient.

Disclosure
MH discloses his relationship with DBS Labs, Inc. and NeuroResearch Clinics, Inc. The other authors report no conflicts of interest in this work.

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