Parkinson’s Disease medications

In correlation to the Unified Parkinson’s disease rating scale

Ayaan Mohamed
Abstract

Introduction:
Parkinson's disease is a result of a loss of cells in the brain. It is a progressive degenerative neurological movement disorder. The exact causes of Parkinson’s disease have not been established. Parkinson’s has four distinct symptoms: tremor, rigidity, impaired coordination and balance, bradykinesia. Parkinson's cannot be detected through only laboratory or blood test and physicians have to do several examinations. Treatment with levodopa is administrated orally or through intestinal infusion. Levodopa is associated with motor fluctuations and rotigotine, entacapone as well as safinamide can be used in combination therapy with levodopa. The aim of this study is to analyze and compare the safety and efficacy of the aforementioned medications.

Method:
The database pub med was exclusively used to collect 10 clinical studies online. Recurring keywords are: Parkinson’s, medication, rotigotine, safinamide, entacapone and levodopa.

Result:
Rotigotine, safinamide, entacapone and levodopa-carbidopa intestinal infusion gel decreased the off time when used together with stable dose of levodopa. Rotigotine was well tolerated in two studies, reactions at the applications site occurred at the beginning of the study. Entacapone was reported to have improved motor symptoms by 20 % according to the unified Parkinson’s disease rating scale. Another study on entacapone reported that 30% of the patients who were administrated suffered from dyskinesia. A study on safinamide resulted in a significant difference between placebo and 100 mg safinamide. The most common adverse events with levodopa-carbidopa intestinal gel were device complications such as tube dislocation. One study compared oral administration of levodopa-carbidopa with intestinal gel infusion and no difference was discovered in motor symptoms.

Discussion:
With the exception of the study of safinamide where a different rating scale was used, all the studied medication was effective on fluctuating symptoms measured with UPDRS. Though the studies had some differences in safety profile, the most common adverse event in all the studies was nausea. Although the studies had some differences in safety profile.
**Conclusion:**
Rotigotine, safinamide and entacapone can be used in combination therapy with levodopa in order to reduce fluctuating symptoms. Levodopa-carbidopa intestinal infusion provides continuous dopaminergic stimulation, which also decreases the fluctuating symptoms.

**Keywords:** Parkinson’s disease, UPDRS, rotigotine, entacapone, safinamide.
Abbreviations:

**UPDRS** - Unified Parkinson's disease rating scale

**MAO-B** - Monoamine oxidase B

**COMT** - Catechol-o-methyl transferase

**LRRK2** - Leucine-rich repeat kinase 2

**FP-CIT-SPECT** - Single-photon emission computed tomography

**MRI** - Magnetic resonance imaging

**DRS** - Dyskinesia rating scale

**DOPA** - Aromatic L-amino acid decarboxylase inhibitor
Introduction:

Parkinson’s disease is a progressive degenerative neurological movement disorder with no cure. Physicians and researchers have known Parkinson’s since 1817 but to this day the exact cause of Parkinson’s is still unrecognized. Parkinson’s disease is a result of a loss of cells in the brain, substantia nigra in particular. It is in this region of the brain that produces the chemical messenger dopamine. The messenger transmits signals within the brain, which in turn creates coordination of movements. The lack of dopamine producing cells creates the characteristic movement disorders associated with Parkinson’s disease. The neuron impulses, which control the body movements, are regulated by dopamine and the decreased dopamine levels complicate the movement control [1].

Symptoms:
Parkinson’s has four distinct symptoms: tremor, rigidity, impaired coordination and balance and bradykinesia. Tremor appears visible in hands, legs and face while stiffness or rigidity occurs in trunk, legs and arms. The symptoms complicate the daily life of Parkinson’s patients and they develop gradually. Difficulties in walking, swallowing and speaking is common. Many patients also experience hardship when urinating and skin problems as well as constipation occur frequently. Other symptoms are not as visible, for example emotional distress and sleep disruption [2]. Cognitive impairment is another example where the ability to concentrate or multi-task deteriorates. These symptoms are usually non-motor symptoms [1]. The main risk factors for idiopathic Parkinson’s is age, the risk grows from the age 55 and onwards. It affects more men than women and approximately 1 in 100 is affected by the illness. Parkinson’s can affect younger people from age however it is not as common. [3].

Causes:
The exact causes of Parkinson’s disease have not been established. While Parkinson’s is not a genetic disease it has been discovered that mutations in the LRRK2 (leucine-rich repeat kinase 2) gene can increase the risk of Parkinson’s disease, however only in a few cases have LRRK2 mutations related to Parkinson’s been discovered. It has for example caused Parkinson’s in 1-2 % of all the case [1]. In the brain of Parkinson’s patients alpha-synuclein form plaque called lewy-bodies, which together with decreased dopamine can cause Parkinson’s disease [4].
Diagnosis:
Parkinson’s disease shares many similarities with other movement disorders, which can cause misdiagnosis. The symptoms emerge gradually and are progressive meaning that the symptoms worsen over time. Therefore a continuous assessment of the disease is needed even after many years of illness. The only way to establish a diagnosis is through interview, brain imaging and neurological examination. Repeated clinical assessment is crucial for progressive disorder in order to avoid misdiagnosis.

Differential diagnosis is done with the help of brain imaging to evaluate if the symptoms are caused by secondary causes such as tumor, stroke and atypical Parkinsonism. When other conditions have been excluded with for instance magnetic resonance imaging, a specific imaging method is used to evaluate the dopaminergic function called “single-photon emission computed tomography” (FP-CIT-SPECT or DaTscan). It differentiates Parkinson’s disease from disorders that cause motor symptoms similar to Parkinson’s. It is not a common tool to use on patients, although magnetic resonance imaging (MRI) is used frequently to differentiate from atypical Parkinsonism. Even neurofilaments from the spine could be used to separate Parkinson’s from atypical Parkinsonism. Misdiagnosis is common because of the resembling symptoms. A continuous assessment several years after first appearance of symptoms are important [5].

Parkinson’s cannot be detected through only laboratory or blood test and physicians have to do several examinations. The UK Parkinson’s disease society brain bank criteria is used to assess the symptoms, the diagnosis criteria contain both inclusion criteria and exclusion criteria when the symptoms do not correspond to the symptoms of Parkinson’s disease. The diagnosis criteria are categorized in: progress, gradual onset of disease, duration of symptoms lack of symptoms for a period of time and lasting dopaminergic effect of medication. In other words, to establish a correct diagnosis, there is a need to continually observe the progress of the disease [6].

In table 1, certain inclusion criteria are presented from the UK Parkinson’s disease society bank. These symptoms occur frequently and are common in Parkinson’s patients [7]. However patients who for instance have experienced serious signs of dementia, cerebral tumor or stroke with parkinsonian symptoms are excluded since they do not have idiopathic Parkinson’s although they can exhibit motor symptoms. The inclusion criteria are bradykinesia, rigidity and postural instability [6].
Table 1 Example of inclusion and exclusion criteria for Parkinson’s disease according to UK Parkinson’s disease society brain bank criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinesia</td>
<td>History of stroke with parkinsonian symptoms</td>
</tr>
<tr>
<td>Muscular rigidity</td>
<td>Neuroleptic medications at the time of first symptoms</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Early severe signs of dementia, cerebral tumor, lack of response to levodopa</td>
</tr>
</tbody>
</table>

Medical treatment:
Since Parkinson’s is one of the most researched neurological condition there are several effective medications. The medications addressed in this thesis are as following: levodopa intestinal infusion, rotigotine, entacapone and the newly developed safinamide.

**Levodopa**
Levodopa is widely used due to its effective nature, although it eases the symptoms it does not affect the progression of Parkinson’s. Levodopa is a prodrug to dopamine and is used in combination with DOPA decarboxylase inhibitor, which inhibits the metabolism of levodopa. In the central nervous system and in peripheral circulation levodopa is converted to dopamine. A DOPA decarboxylase inhibitor makes levodopa available to transportation to the brain. A DOPA decarboxylase inhibitor cannot pass the blood brain barrier and its mechanism of action is to hinder the enzyme DOPA decarboxylase (aromatic L-amino acid) from converting peripheral levodopa to dopamine and thus avoids gastrointestinal adverse effects. Only cerebral dopamine receptors are activated with the help of DOPA decarboxylase inhibitor [8].

Treatment with levodopa and DOPA decarboxylase inhibitor is usually administered in the form of tablets, capsules, and depots but also in the form of portable pump where levodopa is infused continuously. Since Parkinson’s disease is a chronic condition, the long-term effects of levodopa can fluctuate. 50% of older long-term patients developed dyskinesia after only 5 years. The corresponding percentage for younger people is 70-90% after 5 years. There are many theories behind why fluctuations occur, one being that patients develop tolerance in dopamine receptors against dopamine [8].
Younger patients are recommended to not use levodopa immediately because of motor fluctuations, until a continuous dopaminergic input should be established. Motor fluctuations or on and off time are episodes of good motor skills which turns into episodes of dyskinesia, tremor and worsen motor skills almost immediately [6].

Levodopa intestinal infusion is a treatment that offers a continuously dopamine stimulation. A portable pump contains a tube, which infuses levodopa together with a DOPA decarboxylase inhibitor, for example carbidopa. The treatment is offered to patients with fluctuating motor symptoms and it provides a stable and constant plasma concentration compared to oral treatments [6].

Levodopa infusion is feasible with PEG (percutaneous endoscopic gastrostomy). A tube is connected to the stomach through an endoscopic medical procedure. Levodopa and carbidopa is immediately pumped in the duodenum. Although the administration is invasive it aims to relieve the dyskinesia experienced with oral levodopa. The levodopa-carbidopa infusion gel is indicated towards patients with fluctuating motor symptoms who do not respond well to oral therapies. Levodopa is associated with on/off side effects and the purpose of levodopa infusion is to stabilize the plasma concentration. This method was introduced during 1990s and a levodopa-carbidopa infusion gel called Duodopa was approved to use 2004 [9].

**Rotigotine**

Rotigotine is a dopamine agonist who exercises its effect directly on dopamine receptors and is non-selective. The receptors in question are D₁, D₂ and D₃ in the brain [10]. Dopamine agonist can be used as a mono therapy but it is considered to have fewer efficacies than levodopa. It is therefore mainly used in combination with levodopa to reduce the off and on fluctuations. For younger patients it is often recommended to start with a dopamine agonist rather than levodopa in order to decrease the risk of dyskinesia. Many dopamine agonist have similar effect however there is a difference in chemical structure. Rotigotine is a non-ergoline while other dopamine agonists have an ergoline structure; this affects the safety and tolerability profile of the drug. Dopamine agonist with ergoline structure can cause fibrosis in the heart and lungs. A common side effect of rotigotine is sleepiness, this is something Parkinson’s patients already experience and can worsen with dopamine agonists [6].

Rotigotine is administered as a transdermal patch and delivers the administered dose during 24 hours. Although rotigotine is formulated as a transdermal patch, which is attached to the skin, it has a systemic effect. The released rotigotine is transported to
the brain where it exerts its effect. The patch is applied on the thigh, stomach, shoulder, hip or upper arm once a day. Once rotigotine passes the blood brain barrier it stimulate the brain similarly to dopamine. The transdermal patch delivers a constant flow of rotigotine into the bloodstream. Rotigotine has been permitted to be used by EMA (European medicines agency) in 2006 [11].

**Entacapone**
Entacapone is a COMT (catechol-o-methyl transferase) inhibitor and unlike rotigotine, it cannot be used as a mono therapy. The drug inhibits catechol-o-methyl transferase (COMT) enzyme specifically. The enzyme converts levodopa to 3-o-methyldopa (3OMD). Entacapone reduce the amount of converted levodopa. The drug exerts its effect in peripheral tissues and no the brain. When the COMT enzyme is inhibited, more active levodopa is available in the brain [12]. Entacapone is used in combination with levodopa (and carbidopa) in order to minimize the fluctuations that are associated with levodopa treatments. Treatment with entacapone is only used when reduction in levodopa dose is proven not effective on the sudden reappearance of motor symptoms. Entacapone is can only be used with non-released modified levodopa. Considering entacapone inhibits enzymes that break down levodopa, it is counterproductive to use with levodopa that is released later [13].

**Safinamide**
Safinamide is a MAO-B (monoamine oxidase B) inhibitor used in combination with levodopa to treat motor fluctuations in Parkinson’s patients. Safinamide is used for patients with advanced Parkinson’s or mid-stage Parkinson’s. Safinamide is very specific to MAO-B enzymes. Its mechanism of action is to inhibit the enzyme and in turn the degrading of levodopa is reduced. Safinamide was recently approved the EMA in 2015 [14]. Dopamine levels in the brain's striatum increase due to inhibition of MAO-B enzyme. Safinamide has some non-dopaminergic action; it is linked to release of the neurotransmitter glutamate for instance. Nonetheless, it has not yet been established how the non-dopaminergic action contributes to the efficacy of Safinamide [15].

**The unified Parkinson’s disease rating scale**
The unified Parkinson’s disease rating scale (UPDRS) is used frequently to evaluate the efficacy of different active substances [16]. The rating scale consists of questionnaire with questions divided into three parts. Physicians that interview the patients also use
the UPDRS and every question has points, which are added together. 199 points are possible, no points equals to no disability due to Parkinson’s symptoms. All the parts in UPDRS each assess different aspects of Parkinson’s disease:

- Part I: mental activity, mood and behaviour. The questions concern intellectual impairment, initiative, depression, thought disorder (due to medication)

- Part II: activities of daily living. This part deals with the patient’s ability to speak, swallow, salvation, handwriting, handling utensils, hygiene turning in bed and adjusting bed sheets, walking and lastly dressing. Many other areas are covered by the questionnaire.

- Part III: motor symptoms. The patient’s movement coordination is assessed with question regarding rigidity, speech, facial expression, tremor at rest, postural tremor of hands, the ability to open and close hands quickly and body bradykinesia to name a few examples of question themes [16].

**Dyskinesia rating scale**

Another rating scale that is frequently used is Dyskinesia rating scale (DRS). It measures the dyskinesia and how severe it is. DRS is also used to detect the most disabling dyskinesia.
Objective

This study was undertaken in order to examine common medications for Parkinson’s disease treatment: levodopa, rotigotine entacapone and safinamide. The UPDRS and its reliability as an instrument to compare different medications will be treated as well. The aim of this analysis is to address the following thesis questions:

- Is there a difference in efficacy and adverse effects in patients with motor symptoms, treated with levodopa and transdermal rotigotine patch (dopamine receptor agonist), levodopa and safinamide (MAO-B inhibitor), levodopa and entacapone (COMT inhibitor) in correlation to UPDRS?
- What is the maximum safe dose of transdermal rotigotine in advanced Parkinson’s disease patients?
- To what extent is the long-term use of Levodopa/Carbidopa intestinal infusion safe in advanced stages of Parkinson’s disease?
- How effective is levodopa/carbidopa intestinal infusion compared to oral levodopa/carbidopa therapy?

Method:

This literature study is based on original research articles. The database pub med was exclusively used to collect clinical studies online. Recurring keywords are: Parkinson’s, medication, rotigotine, safinamide, entacapone and levodopa. Table 2 illustrates the articles used and the search terms were in most cases specific to one medication. Inclusion criteria for the studies in this analysis were study subjects with moderate to advanced stages of Parkinson’s disease and fluctuating motor symptoms caused by the use of levodopa. Mostly recent studies were selected based on their publishing date. However some of the studies have an earlier publishing date and were selected based on their abstract, which contained relevant information.

Study number 8 is one example of a somewhat older study. Since the levodopa-carbidopa treatment is not as usual as oral therapy, a broader search term was used in order to get as many relevant studies as possible. As a consequence, large number of hits appeared. The selected studies were chosen firstly based on their title and whether
it included levodopa as intestinal infusion. Secondly they were chosen based on their abstract. Other recourses were used as well to gather medical information such as the website Fass.se and lakemedelsverket.se

Table 2. Literature search in Pub med.

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<thead>
<tr>
<th>Date</th>
<th>Search term</th>
<th>Number of chosen articles</th>
<th>Limitations</th>
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<th>Selected references</th>
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<td>2017-01-27</td>
<td>Rotigotine AND off-time</td>
<td>2</td>
<td>clinical study</td>
<td>6</td>
<td>17,21</td>
</tr>
<tr>
<td>2017-01-16</td>
<td>Safinamide AND parkinson</td>
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<td>clinical study</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>2017-01-19</td>
<td>Entacapone AND off-time</td>
<td>2</td>
<td>clinical study</td>
<td>23</td>
<td>18,19</td>
</tr>
<tr>
<td>2017-01-27</td>
<td>Rotigotine AND parkinson</td>
<td>1</td>
<td>clinical study and free full text</td>
<td>44</td>
<td>22</td>
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<td>Parkinson’s AND medication</td>
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<td>clinical trial and free full text</td>
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<td>2017-01-26</td>
<td>Parkinson’s AND intestinal</td>
<td>2</td>
<td>clinical trial</td>
<td>27</td>
<td>24,26</td>
</tr>
</tbody>
</table>
Results

Effect

1. *Transdermal rotigotine in advanced Parkinson's disease: a randomized, double blind, placebo-controlled trial [17]*

A fairly recent study that was published in 2014 studied the efficacy of transdermal Rotigotine in patients who suffer from on and off time because of levodopa treatment as well as declining effects of levodopa. This randomized double-blinded study was conducted on 172 Japanese patients. Half of the subjects received a placebo transdermal patch and the other half received the dopamine receptor agonist, rotigotine. A daily dose of rotigotine was administered to the patients. The researchers set the daily dose at 16 mg/24 hours.

The efficacy was measured with the help of UPDRS part III that is motor examination. The Part III scores changed throughout the baseline to the end of the study. For rotigotine the changes were -10.1 ± 9.0 (mean standard deviation) and for the placebo, it was -4.4 ± 7.4. The authors discovered that the patients treated with rotigotine had a significant decrease (p=0.014) in the off time experienced with levodopa medication. The tolerability of transdermal rotigotine was good, however three patients in each group experienced severe adverse effects. The authors concluded that doses up to 16 mg per day are safe for patients with severe Parkinson’s disease[17].

2. *The efficacy and tolerability of Entacapone versus Cabergoline in parkinsonian patients suffering from wearing-off [18].*

The authors compared the efficacy and safety of entacapone and cabergoline, however this analysis will focus only on entacapone. This study is randomized and rater blinded meaning that the person assessing the result is blinded. It was conducted in several medical centers during 12-week period and the study is an open-label trial. 161 older patients who suffer from Off-time were examined. They were given entacapone up to 5 times with a maximum daily dose of 6 mg per day or cabergoline, with the same maximum dose.

43 % of the patients in the entacopone group experienced dyskinesia at baseline, the number declined at the final stage of the study where 35% experienced dyskinesia. The off time was reduced with two hours in both groups; furthermore the decrease was recorded to have happen faster with patients treated with entacapone. A roughly 20 %
decrease in motor symptoms and “activities in daily living” was measured according UPDRS part II and III with entacapone.

Frequently occurring adverse event was nausea, which occurred in both treatment groups. 7.3% of the patients treated with entacapone reportedly suffered from nausea and 8.5% suffered from adverse events, which stopped the patients from participating in the study, and the only severe adverse event was dehydration. Dyskinesia was experienced by 43% of the patients treated with entacapone at baseline and that figure decreased to 35 % at the final visit. Both entacapone and cabergoline effectively reduced motor symptoms but a faster clinical effect was obtained with entacapone [18].

3. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson’s disease: a randomized, placebo controlled, double blind, six month study [19]

Another study from 2003 examined the efficacy and safety of entacapone in fluctuating and non-fluctuating patients. The study design used was a double blinded, randomized, placebo-controlled study with subjects from several neurological centers from the United Kingdom as well as Republic of Ireland. 172 fluctuating patients and 128 non-fluctuating patients were treated with either entacapone or placebo. All patients were treated with not only with levodopa but other medications for their Parkinson’s disease was permitted as well. Their dose regime was stabilized and optimized prior to the study.

Non-selective monoamine oxidase inhibitors or drugs with an antidopaminergic effect were not permitted during the six month study. The patients were divided into two groups depending on their symptoms, those with fluctuating motor symptoms into a fluctuating group and patients without these symptoms into a non-fluctuating group. Within these groups the subjects were randomized to either a placebo treatment or entacapone treatment. Each patient with motor symptoms was asked to document when off time and on time occurred during their treatment. 200 mg of entacapone and a corresponding placebo tablet was given to the patients. The tablet was administered at the same time as their levodopa administration. The daily dose differs from two to ten tablets per day.

The study resulted in a significantly prolonged on time for the fluctuating group who were given entacapone compared to placebo (p< 0.05). The mean on time rose from 9.5 hours with standard deviation 2.5 hours to 10.8 hours, standard deviation 2.4.
Simultaneously, the mean off time dropped from 7.0 (SD 2.6) to 5.9 hours (SD 2.5). A difference of 1.2 hours of on time was recorded between the placebo group and the entacapone group. Regarding UPDRS, no serious difference was noted in part III between placebo and entacapone group. The need of high dose of levodopa dropped with entacapone treatment according to patient's home journals. On the contrary, the placebo group increased their levodopa dose with 26 mg. With entacapone treatment the dose decreased with 33 mg.

The patients experienced several adverse events, diarrhea in particular occurred often in the entacapone group. 5 % of the subjects could not continue with the treatment. Furthermore, dopaminergic effects led to 3% of the entacapone group not being able further participate in the study. In the entacapone group, 30 % of the patients with fluctuating motor symptoms commonly experienced dyskinesia escalation and 10 % experienced it has a new adverse event. On contrary, only 12% of the fluctuating patients experienced it in the placebo and 8 % acquired dyskinesia as a new adverse event.

Some improvement could be seen in terms of dyskinesia with 10-20 % levodopa dose reduction in half of the fluctuating patients treated with entacapone. Another adverse event reported was hallucinations in the fluctuating entacapone group (6 patients) as well as the placebo group (three patients). A total of 3 patients discontinued the study because of the hallucinations. When the daily dose of levodopa was reduced, the adverse event ceased for one patient [19].

4.Long-Term Effects of Safinamide on Dyskinesia in Mid- to Late-Stage Parkinson’s disease: A Post-Hoc Analysis [20].

A study published in 2015 studied the efficacy and safety of the safinamide, a α-aminoamide, which was recently developed. This study is an extension of a comprehensive study, which lasted 24 weeks, and the duration of this particular study is 2 years after the original study.

In this double-blinded and placebo-controlled study, patients from different neurological centers in India, Romania and Italy were permitted to participate if they completed the preparatory study. Similarly to the previous articles, the patients suffered fluctuating motor symptoms during their levodopa medication.
The study design is a post-hoc analysis of the previous randomized study, where a part of the 669 patients were given different doses of safinamide (50 mg and 100 mg) and the other part given placebo. The aim of the study was to assess patients based on their dyskinesia and whether it has decreased or increased. All the patients were organized into two groups: patients with dyskinesia and patients were dyskinesia was absent. The dyskinesia changes during on time were evaluated with the help of the dyskinesia rating scale (DRS). The post-havoc analysis subsequently evaluated how safinamide in the long term, effects dyskinesia. Patients were not only categorized into groups based in their dyskinesia or lack thereof, but also into subgroups where the patients’ levodopa was changed during the 2-year treatment. The DRS was also used here and the Wilcoxon rank-sum test was used to compare the different doses of safinamide, 50 mg and 100 mg as well as placebo.

This analysis spanning 2 years has resulted in improved scores in DRS in the subgroup where levodopa dose was not changed during the treatment. The improvement was higher in the safinamide groups (50 mg and 100 mg) compared to the group who received placebo. There was a significant contrast between placebo and safinamide 100 mg (p= 0.0488). In this subgroup there was both patients with dyskinesia at baseline and those without. In another subgroup where dyskinesia was absent at baseline, no changes in DRS occurred during the 2 yearlong treatments for 75% of the patients. There was however a significant improvement or decrease in DRS for patients in the subgroup where dyskinesia was present at baseline and for patients with or without levodopa dose changes (p=0.0153 vs. placebo). The long-term study illustrates a good tolerability as an add-on drug to levodopa. Few patients experienced a worsening dyskinesia [20].

Table 3. Percentage of patients with different DRS changes within the subgroup “no changes in levodopa dose during the study period” [20].

<table>
<thead>
<tr>
<th>Variable (DRS changes)</th>
<th>Placebo</th>
<th>safinamide 50 mg</th>
<th>safinamide 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>27.2% (37/136)</td>
<td>33.8% (50/148)</td>
<td>39.5% (58/147)</td>
</tr>
<tr>
<td>no change</td>
<td>43.4% (59/136)</td>
<td>41.9% (62/148)</td>
<td>36.7% (54/147)</td>
</tr>
<tr>
<td>increase</td>
<td>29.4% (40/136)</td>
<td>24.3% (36/148)</td>
<td>23.8% (35/147)</td>
</tr>
</tbody>
</table>
5. High doses of rotigotine transdermal patch: results of an open-label, dose-escalation trial in patients with advanced-stage, idiopathic Parkinson disease [21].

Rotigotine transdermal patches were studied in order to evaluate the maximum safe dose and tolerability. The patients were randomized to two titration treatments; one group received a slow titration while the other received a faster titration. The total amount of participating patients was 34. The inclusion criteria were the minimum age of 30 and the patients had to have a daily dose of levodopa. The off time had to be at least 2.5 hours per day. A starting dose of 4 mg per day was given to all the patients. In the slow titration group, a gradual dosage of 2 mg/24 h was given each week. The patients in the fast titration group were given the dose 4-mg/24 h per week. The dosage was gradually increased to 24 mg/24 h.

After the titration, both groups maintained that same dose, the fast group maintained the same dose for a minimum of 42 days and the slow group for a minimum of a week. During 4 days the dose was reduced gradually and the safety as well as the tolerability was evaluated. The detected adverse events varied from mild to moderate. 12% of the patients experienced reaction in the local application site and 9% experienced hallucinations. Other common adverse events included nausea and dyskinesia. In the fast group the total mean UPDRS score was decreased with 18.9 (SD 14.2) and in the slow group it decreased by 17.8 (SD 14.0). An equally important discovery was reported; the mean off time was reduced by 2 to 3 hours per day. Furthermore, the on time increased with 2 hours per day. Overall rotigotine transdermal patch was well tolerated with doses up to 24-mg/24 h [21].

6. Rotigotine transdermal system for long-term treatment of patients with advanced Parkinson’s disease: results of two open-label extension studies, CLEOPATRA-PD and PREFER [22]

The result of two open-label studies (SP16 and SP715) illustrated the safety and tolerability of rotigotine transdermal patch. This article was published 2013 and contains studies that continued for a total of 6 years. In study SP516 patients underwent double-blinded test where they received a maximum daily dose of 16 mg rotigotine for 4 years. In SP715 the study lasted 6 years and the patients were also given maximum dose of 16 mg/24 h. In the former study 395 patients participated and 258 patients in the SP715 study. The total amount of patients that completed the SP516 study was 48% and in the SP715 45% completed. Patients enrolled in the study had to have Parkinson’s for a minimum of 3 years and 2.5 hours of off time per day. All patients had a stable dose of levodopa and other medications such as rasagiline, anti-
cholinergic drugs, atypical neuroleptics, entacapone and drugs for nausea treatment were permitted as well.

In the study SP516, the patients had their rotigotine dosage reduced from 16-mg/24 h to 4-mg/24 h during a time period of 6 days. Meanwhile the patients in SP715 had their daily dose reduced to the same amount in 8 days. Patients who had received placebo went through a dose reduction in the same manner. Thereafter a titration was gradually introduced during 7 weeks, the dosage increased with 2 mg /24 h every week (±3) up to the maximum dose of 16 mg /24 h. The 7 weeks of titration was followed by maintenance where the rotigotine dosage was more flexible in order to maintain the optimal dose for each patient.

Adverse events were reported from both studies, in SP516, 90% of the subjects experienced and reported a minimum of one adverse event. For the SP715 the percentage was higher, 100% of the participants reported at least adverse event. Serious adverse events, which were linked to death, occurred in both studies. 17 adverse events caused the death of 15 patients in SP516, furthermore, 148 patients experienced serious adverse events. Meanwhile, in study SP715, 165 patients reported serious adverse events and 28 patients passed away because of the adverse events. However only one death was related to the transdermal rotigotine in SP516 where the patient in question suffered from myocardial infarction. Additionally two deaths in SP715 occurred because of rotigotine, one death caused by circulatory collapse and urosepsis. The patients in both studies frequently experienced reactions at application site, fall and sleepiness. 17% of the falls in SP516 was serious and no patient experienced serious sleepiness in both studies.

Most reports of nausea occurred at the beginning of SP516 and SP715. In the first study 46 patients (12%) suffered from nausea compared to the last and fourth year where none of the patient reported nausea. Same tendencies could be found in the SP715 study, 44 patients (17%) reported nausea meanwhile only two patients (3%) suffered from nausea in the sixth final year.

Hallucination was experienced by many patients and caused 6 patients to discontinue the study in SP715. However only seven of the 76 reported cases of hallucination was considered serious. In study SP516, 39 cases were reported and the majority of them were mild to moderate stages of hallucination and only four were serious. Compulsory behavior occurred as well throughout the study. In study SP516, 22 (6%) patients experienced impulsive-compulsive behavior and it was assessed that of the 22 patients
16 (4%) suffered from it because of rotigotine. The dose was adjusted for four patient and all four the impulsive-compulsive behavior were gone. 10 (4%) patients experienced impulsive-compulsive behavior caused by rotigotine in the study SP715. Examples of serious cases of impulsive-compulsive behavior which some of the study participants experienced were pathological gambling addiction and compulsive behavior symptoms. Nevertheless the majority of the cases were mild to moderate.

Many of the patients who did not suffer from dyskinesia have during the studies established dyskinesia, 80% of the patient of the study population in SP715 and 69 % in SP516. The development was measured with UPDRS part IV. Overall, transdermal rotigotine has an adequate safety profile and was well tolerated by patients for up to 6 years [22].

7. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson’s disease: a randomized, controlled, double-blind, double-dummy study [23].

In this 12 week study, 71 patients age 30 or older with advanced Parkinson’s disease and motor fluctuations, were randomized into different groups. The patients received infusion of levodopa-carbidopa intestinal gel and placebo capsules or levodopa-carbidopa capsule and placebo infusion; depending on which group they were randomized to. 66 patients completed the study. The patients had to be on a stable dose of levodopa and experience at least 3 hours of off time per day in order to be included in the study.

At the beginning of the study the infusion gel was administered according to the optimal daily dose for the patient. No infusion occurred during nighttime. The intestinal gel contained 20-mg/mL levodopa and 5-mg/mL-carbidopa-monohydrate solution. A morning bolus of 5-10 ml was firstly administered and thereafter the patients received a continuous constant rate infusion. The placebo capsules and levodopa-carbidopa capsules were given at the same time as the infusion, in several doses during the day and at the same dose. Titration occurred during four weeks and was followed by 8-week maintenance period.

According to UPDRS part II (activities of daily life) the intestinal infusion gel and placebo capsule group presented a significant improvement compared to the group with placebo infusion and levodopa-carbidopa capsule. Although no difference was
detected between placebo infusion and intestinal gel infusion in UPDRS part III (motor symptoms) [23].

8. Duodenal levodopa infusion mono therapy vs. oral polypharmacy in advanced Parkinson disease [24].
Intraduodenal infusion was studied in a randomized crossover study, on 24 patients who suffers from advanced Parkinson’s. All the patients experienced motor fluctuations as well as dyskinesia. Levodopa-carbidopa was given as intestinal gel. The UPDRS score decreased from 53 to 35 (median, (p < 0.05)) when the patients were administered continuous infusion compared to conventional oral treatment [24].

9. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson’s disease patients; 12-month interim outcomes [25].
This prospective study was conducted in 18 countries (Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Romania, Slovenia, Spain, Switzerland and United Kingdom). A total amount of 375 patients with advanced Parkinson’s disease and motor fluctuations were included. The treatment with infusion of levodopa-carbidopa intestinal gel was given continuously through a portable pump. Some patients were on other medications as well, for example a COMT-inhibitor or dopamine agonist. The infusion occurred only during the day for about 16 hours. The UPDRS part IV and mean off time decreased significantly, it decreased by 4.7 hours (SD 3.4) when maximum reduction occurred. The on-time score decreased from baseline according to UPDRS II and III. The mean UPDRS for dyskinesia was reduced from baseline 1.7 (SD 1.2) to 0.9 (SD 1.2). UPDRS part II decreased as well by 3.1 (SD 8.7). The overall efficacy of the intestinal infusion according to UPDRS improved the fluctuating motor symptoms and non-motor symptoms [25].

Safety

10. Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease: Final 12-Month, Open-Label Results [26].
This study was conducted in order to assess the safety of levodopa-carbidopa intestinal gel in patients with advanced Parkinson’s. All the patients suffered from motor fluctuations. During the 12 month long study several adverse events have been reported. The most frequently reported adverse event was insomnia in 166 patients out
of 354 and device complications during insertion occurred in 7.3% of the participants. Many described their adverse events as moderate (43.8%). Abdominal pain occurred in 31.2% of the study population and other procedural pain was reported in 20.7%. However no changes in vital signs and laboratory findings showed a clinical significance

7. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson’s disease: a randomized, controlled, double blind, double-dummy study [23].

In this study both the placebo group and the intestinal infusion gel group received a pump with either placebo infusion of levodopa-carbidopa. 94.6% reported in the levodopa-carbidopa infusion group and 100% of the oral levodopa-carbidopa participants experienced adverse events. One patient from the infusion group experienced psychosis. However the device caused most of the adverse events. Although the adverse events were not serious it, caused 2.8% of the patients to leave the study because of the complications. Complications such as tube dislocation was reported in 23.9% of the study population, other common complication were pump malfunction and stoma insertion issues [23].

9. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson’s disease patients; 12-month interim outcomes [24].

Of the 159 patients that participated in this study 75 or 47.2% reported a minimum of one adverse event and 37 or 23.3 % reported serious events. Device dislocation, infection after surgical procedure, fluctuating motor symptoms and hallucinations were considered serious adverse events. Four patients experienced device dislocation and two patients suffered from postoperative infection. Additionally two patients suffered hallucinations and two other experienced fluctuating symptoms. Throughout the duration of the study 8 patients passed away and none of the death were related to levodopa-carbidopa infusion [24].

Summarization

To summarize the results, rotigotine transdermal patch and entacapone reduced the off time the patients experienced. Safinamide (study 4) and entacapone (study 3) also increased the on time (see table 4). Two studies states different doses as the safest maximum dose of rotigotine transdermal patch. Study 1 reported rotigotine dose up to
16 mg/24 h was well tolerated while study 5 state the maximum dose of 24 mg/24 h as a safe and well tolerated therapy.

Table 4. Summary of the result.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Study length</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>174</td>
<td>Not stated</td>
<td>Significant reduced off time (p=0.014). Up to 16mg/24h is safe.</td>
</tr>
<tr>
<td>2</td>
<td>161</td>
<td>12 weeks</td>
<td>Significant 2 hours decrease in off time. Common adverse event was nausea.</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>6 month</td>
<td>Significant increase in on time by 1.3 hours and off time reduced by 1.1 hours (p&lt;0.05 vs. placebo).</td>
</tr>
<tr>
<td>4</td>
<td>669</td>
<td>24 month</td>
<td>Significant improvement in dyskinesia with 100-mg/24 h compared to placebo.</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>Not stated</td>
<td>Off time reduced by 2 to 3 hours per day. Most common adverse event was reaction at the application site (12%). Maximum safe dose was 24 mg/24 h</td>
</tr>
<tr>
<td>6</td>
<td>653</td>
<td>6 years*</td>
<td>In study SP516, 148 patients experienced serious adverse events. In study SP715, 165 patients reported serious adverse events. The safety profile is relatively good.</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>12 weeks</td>
<td>No difference between placebo infusion and intestinal gel infusion in UPDRS part III.</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>6 weeks</td>
<td>UPDRS score decreased from 53 to 35 (p &lt; 0.05) in favor of infusion.</td>
</tr>
<tr>
<td>9</td>
<td>375</td>
<td>12 month</td>
<td>Off time reduced by 4.7 hours.</td>
</tr>
<tr>
<td>10</td>
<td>354</td>
<td>12 month</td>
<td>Most common adverse event was insomnia (166 patients). Abdominal pain occurred in 31.2% of the patients.</td>
</tr>
</tbody>
</table>

*The two studies were conducted for 4 respectively 6 years.
Discussion

Method
10 articles were included in the analysis. A literature study was conducted in order to gather a variety of studies. The majority of the studies were randomized clinical trials, however a post-hoc analysis and a global prospective study were included. This ensures a long-term perspective on the efficacy and safety on the newly developed medication safinamide (study 4) and the invasive levodopa-carbidopa intestinal infusion gel (study 9). A literature study was a good choice of method since it gave the possibility to analyze the efficacy and safety of Parkinson’s medication. The long-term studies in particular gave valuable insight into the tolerability and how safe the treatment was for the patients in the long run since Parkinson’s disease is a chronic disorder.

Different medications in combination therapy with levodopa were evaluated in order to grasp the effect of different medication groups had on the declining effects of levodopa. Safinamide was not included only to analyze MAO-B inhibitors but to also assess the efficacy of the relatively new drug which is why a study spanning 2 years was included in the analysis. Levodopa-carbidopa intestinal infusion is considered an invasive treatment and is the last option when all other oral therapies fail. This literature study aims to gather articles and analyze its effect and safety in order to assess whether it is can be considered equal, if not better treatment option for patients with advanced stage of Parkinson’s disease.

Since the subject of this analysis is to evaluate which levodopa combination therapy is safe and effective in fluctuating patients, the requirement was that the test subjects must have had to used levodopa for a period of time before the clinical trials. The literature search with specific search terms, such as Parkinson’s and entacopone yielded limited but relevant results. For general terms such as Parkinson’s and medication, the search resulted in huge collection of studies. This provided clinical studies as well as global prospective study on levodopa-carbidopa intestinal infusion, which is not as common as the oral treatments. The number of studies on Parkinson’s disease medications are many and could not be covered in this analysis, however it gives a broader perspective on the efficacy and safety of different medication groups as well as levodopa intestinal infusion gel.
Results

Is there a difference in efficacy and adverse effects in patients with motor symptoms treated with levodopa and transdermal rotigotine patch, safinamide and levodopa, entacapone and levodopa in correlation to UPDRS?

All the studied medication had an effect on fluctuating symptoms measured with UPDRS. One exception was safinamide where a different rating scale was used [20]. According to the dyskinesia rating scale it had significant improvement in patients with dyskinesia compared to placebo. The higher the dose, the bigger the difference between the placebo and safinamide. It was also noted that the improvement of dyskinesia was not because of changes in the patients’ levodopa dose but a direct result of safinamide. The fact that a different scale was used complicates the comparison to other studies. However the mean UPDRS results will differ regardless because of size difference in study population. Other medications apart from levodopa were permitted to be used by the study subjects. An example of such medication is dopamine agonists and the study did not mention how those medications could possibly affect the result. Nevertheless this post-hoc analysis is special since it highlights the long-term effects of safinamide [20]. It is also not linked to worsening of dyskinesia like entacapone, however this is a newly developed drug that needs more time to evaluate the adverse events.

The two studies on rotigotine respectively presented significant changes on the UPDRS. Study 1 and 5 both decreased the UPDRS score, study 1 decreased part III in UPDRS [17] and study 5 the overall UPDRS score [21]. Meanwhile the off time where the levodopa effect started to wear off decreased by 2 hours in study 2 of entacapone [18].

Although study 3 about entacapone also presented reduction in off time [19], only study number 2 showcased improvement in motor symptoms according to UPDRS [18]. A decrease of 20% occurred in motor symptoms. Meanwhile the second entacapone study reported only a decrease in off time but no improvement for part III in UPDRS was reported compared to placebo [19]. It is worth to note that the first study was conducted in only 12 weeks while study 3, which reported no significant changes in UPDRS, lasted 6 month. This means that the longer the treatment lasted; the motor symptoms did not improve according to UPDRS compared to study 1 where rotigotine presented improvement on the UPDRS part III score [17]. Study 1 on rotigotine was a double-blinded clinical trial while study 2 was only rater blinded, which could affect the reliability of the result.
In terms of adverse events rotigotine have better safety profile. In study 3 entacapone was linked to 30% of dyskinesia escalation in patients that already suffered from dyskinesia [19]. Rotigotine can therefore be regarded as a better option for advanced Parkinson’s patients since it is not connected to dyskinesia escalation and it improves the motor symptoms according to UPDRS part III. It has also better documentation about adverse events than safinamide, which was released in 2015.

**What is the maximum safe dose of transdermal rotigotine in advanced Parkinson’s disease patients?**

In study 5, the maximum dose of 24 mg / 24 h was well tolerated by the patients. However the study length is unknown which makes it difficult to interpret the severity of the adverse events if they would continue to use the patch for an extended time period. 12% of the patients experienced reaction in the local application site and 9% experienced hallucinations [21]. Study 6 presents the long-term use of rotigotine transdermal patch and the dose 16 mg/ 24 h were deemed more suitable for long-term use and the study length spans for 6 years. 3 deaths were linked to the transdermal patch and during the 6 years the study progressed some patients developed dyskinesia [22]. However it is a tolerated medication [22]. Rotigotine has a good safety profile but some caution is needed for doses up to 24 mg /24 h. If the lower dose of 16 mg/ 24 h can cause dyskinesia and other severe adverse events, it is unlikely that a maximum dose of 24 mg/ 24 h is safer than 16 mg/ 24 h. In other words 16 mg/24 h safer maximum dose.

**How effective is levodopa/carbidopa intestinal infusion compared to oral levodopa/carbidopa therapy?**

Regarding the efficacy of levodopa-carbidopa intestinal gel infusion, two articles compared oral therapies to infusion gel. Study 7 and 8 are two of the few studies where a randomized study was conducted in order to compare oral therapy to intestinal infusion [23][24]. Both studies reported significant benefits to fluctuating patients with advanced Parkinson’s. In study 7 the patients experienced an improvement in UPDRS part II (activities of daily life) where the everyday life was easier with portable pump compared to oral therapy. However in terms of motor symptoms, no difference was detected between oral levodopa-carbidopa and levodopa-carbidopa infusion gel [23].
In study 8, the overall UPDRS score decreased more with infusion gel. It decreased from 53 to 35 (median, (p < 0.05)). In conclusion the patients experienced that with the portable infusion pump, the daily activities were simplified compared to oral therapy. This could be explained by the constant plasma concentration of levodopa-carbidopa with the infusion compared to the oral administration. However the difference between oral and intestinal infusion gel in terms of motor symptoms was not great. If they have similar effect on fluctuating motor symptoms, the daily life of advanced Parkinson’s disease patients could be taken into consideration. This will give the patients options in their treatment in the future as opposed to today where the intestinal infusion is a last resort.

To what extent is the long-term use of Levodopa-Carbidopa intestinal infusion safe in advanced stages of Parkinson’s disease?

Despite the advantages of intestinal infusion gel, it is an invasive process. The majority of the adverse events had to do with the device and abdominal pain. In study 7, 94.6% reported adverse events in the levodopa-carbidopa infusion group and 100% of the oral levodopa-carbidopa participants experienced adverse events [23]. In study 10, the patients experienced their adverse event as moderate. The safety profile for oral therapy and intestinal infusion do not differ much with the exemption of the device complications. Intestinal infusion also caused less dyskinesia and fluctuating motor symptoms. The infusion gel is safe in terms of fluctuating symptoms however the device malfunctions and the invasive nature is worrisome.

**UPDRS**

This rating scale has been exclusively used from 1980 and is still widely used today. UPDRS can be used in all stages of Parkinson’s disease but it has been discovered that the score measures moderate to advanced Parkinson’s and is weaker in assessment of early and mild symptoms. Its reliability has been questioned to a certain degree. For example part II of UPDRS is limited to some cultures and displays cultural bias [27]. Questions about dressing as well as handling utensils are limited to metropolitan environment and cannot be used in some rural regions. UPDRS is however still widely used. A modified version of the scale, MDS-UPDRS was developed in 2009 by an organization called “Movement disorder society”. The new scale was made in order to adjust the limitations of UPDRS. The symptoms can be graded in its intensity rather than the absence or presence of symptoms [27].
Bias
Companies and organizations financed several studies. This could influence the outcome of the studies and bias is fully possible, particularly in reports of adverse events. Pharmaceutical companies funded the following studies:

Table 5. A list of studies financed by pharmaceutical companies.

<table>
<thead>
<tr>
<th>Title of article</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>High doses of rotigotine transdermal patch: results of an open-label, dose-escalation trial in patients with advanced-stage, idiopathic Parkinson disease</td>
<td>Schwarz Pharma</td>
</tr>
<tr>
<td>Transdermal rotigotine in advanced Parkinson's disease: a randomized, double-blind, placebo-controlled trial</td>
<td>otsuka pharmaceutical</td>
</tr>
<tr>
<td>Long-Term Effects of Safinamide on Dyskinesia in Mid- to Late-Stage Parkinson’s Disease: A Post-Hoc Analysis</td>
<td>Zambon Pharma</td>
</tr>
<tr>
<td>The efficacy and tolerability of Entacapone versus Cabergoline in parkinsonian patients suffering from wearing-off</td>
<td>Orion Pharma</td>
</tr>
<tr>
<td>Rotigotine transdermal system for long-term treatment of patients with advanced Parkinson's disease: results of two open-label extension studies, CLEOPATRA-PD and PREFER</td>
<td>UCB Pharma</td>
</tr>
</tbody>
</table>

Conclusion:
Different types of studies were consciously chosen to be included in this thesis paper. Randomized double-blinded studies, open-label extension studies and post-hoc analysis were all important to get an understanding of the safety and efficacy in the treatments. The Post-hoc analysis and the extension studies unveiled insight into long-term benefits and side effects of safinamide and the intestinal infusion. It is important because of the invasive nature of levodopa-carbidopa infusion gel and it’s potential to
bypass fluctuating motor symptoms. Safinamide is a new drug on the market the adverse effect need to assessed for a longer time period than 2 years. To conclude, different medications can be used in combination therapy with levodopa. Rotigotine and entacapone both decrease the off time and are both well tolerated by patients. The incidence of dyskinesia escalation lowers the safety profile of entacapone, in that aspect rotigotine have better safety profile according to the studies. All the mentioned treatments had also documented decreased motor fluctuations. The newly modified UPDRS should be considered to be used in clinical trials and in neurological centers.

Acknowledgement

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