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# Learning from Parkinson's patients: Usability of the Cyclops dry powder inhaler

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ABSTRACT

Effective inhaler therapy requires correct handling of the inhaler, including being able to prepare the inhaler for use. Motor function impairment and cognitive disabilities, may impose problems on patients with Parkinson's disease when they have to prepare medication, such as inhalers, for use. The aim of the present study was to examine whether Parkinson's patients are able to correctly prepare the Cyclops inhaler for use. At first, 12 patients, 6 in an off state and 6 in an on state, were asked to open 5 inhalers with ascending peel resistance of the cover foil. It was investigated up to which peel resistance they were able to successfully pull the foil from the inhaler. For the second part of the study, 48 participants, 24 on and 24 off, were asked to open 2 pouches and the 2 inhalers selected in part 1. For pouch 1, 70.8% of the patients in an on state and 58.3% in an off state were able to open the pouch correctly. For pouch 2, this was 79.2% and 75.0%, respectively. Both Cyclops inhalers were opened correctly by 95.8% of the participants in the on state and 91.7% of the participants in the off state.

## 1. Introduction

Parkinson's disease is a neurodegenerative disorder of the central nervous system, causing a lack of dopamine in the substantia nigra in the brain. The golden standard for treatment of the motor symptoms of Parkinson's disease is administration of levodopa via the gastrointestinal tract, either as oral formulation or as suspension via a tube in the duodenum (Pedrosa and Timmermann, 2013). Administration of levodopa via the pulmonary route is a promising treatment option for Parkinson's disease patients in an off period, when the disease symptoms are poorly controlled (Lipp, 2016). Off periods are characterised by a variety of complaints, such as tremor, bradykinesia and decreased mobility. Furthermore, non-motor symptoms as autonomic, sensory and psychiatric problems can be present. During an on period, the Parkinson's symptoms are less pronounced.

Literature reports that many people experience difficulties in opening packaging from for example food and medicines (Bell, 2016; Hensler, 2015; Beckman, 2005). In patients older than 65 years, these difficulties are most apparent, due to both physical and cognitive deterioration (Beckman, 2005; Notenboom, 2017) and the presence of hand disorders (Marks, 2012). Taking into account the elder age, the impaired cognition and motor function and muscular rigidity during "off periods", it can be imagined that the preparatory steps for the use of an inhaler may be challenging for patients with Parkinson's disease. In the development stage of a levodopa inhaler plus drug combination, it is therefore important to study the physical ability and user satisfaction of Parkinson's patients in preparing the inhalers for use.

We previously studied the applicability of Parkinson's patients to use dry powder inhalers during an off period (Luinstra, 2015a). Based on the results of that study, we developed a levodopa inhalation powder for pulmonary administration (Luinstra, 2015b), using the Cyclops inhaler (Hoppentocht, 2015). Like most inhalers, the Cyclops inhaler has to be prepared for use by the patient prior to the inhalation of levodopa. This preparation involves two steps; firstly, the pouch around the inhaler is to be opened using the tear notch. The location of the notches differed between the different pouches. Secondly, the the cover strip sealing the dose compartment has to be pulled out of the Cyclops inhaler. Once the foil is removed, the drug formulation can be inhaled.

The aim of the present study was to examine whether Parkinson's patients are able to correctly prepare the Cyclops inhaler for use.

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## 2. Materials and methods

### 2.1. Sample size

This study is a non-therapeutic observational study designed to obtain information on the ability of Parkinson's patients to correctly open a pouch wherein the inhaler is stored and to correctly prepare the inhaler for use by pulling a foil out the inhaler. Since we only wanted to obtain insight in the ability of Parkinson's patients to prepare the inhaler correctly, no sample size calculations were performed. A sample size of 60 Parkinson's patients was considered to be appropriate.

### 2.2. Study site and patient recruitment

The study was performed in the 'Point for Parkinson Groningen' centre or at the homes of Parkinson's patients. "Point for Parkinson Groningen" is a care centre specialized in the treatment of patients with Parkinson's disease and Parkinsonism in the northern part of the Netherlands.

Patients were informed about the study by their neurologist or nurse practitioner. These caregivers selected suitable patients. Patients were suitable for participation if they were at least 18 years old, diagnosed with Parkinson's disease and if they were not suffering from cognitive dysfunction that would disable them to understand the study. If a patient was willing to participate, the on or off state of the patient was judged by the neurologist/nurse practitioner. Thereafter, the researcher explained the purpose of the study again, subsequently the participant completed the study. Informed consent was noted on the form. Patients with predictable end of dose off periods were visited at home during an off period. The entire study was carried out between February 2018 and April 2019.

### 2.3. Study objectives and design

The primary objective of this study was to assess whether Parkinson's patients are able to correctly open a pouch in which the inhaler is packed in the correct way and subsequently prepare the inhaler for use by pulling the cover foil from the inhaler. Secondary objectives were to investigate whether there is an optimal seal setting for the cover foil and whether there is a difference between Parkinson's patients in an off or on state.

The study was divided in 2 parts. In the first part, 12 patients, 6 in an off state and 6 in an on state, were asked to remove the cover foil from 5 inhalers with ascending peel resistance of the cover foil. It was defined up to which peel resistance the participants were able to successfully pull the foil from the inhaler. This test allowed us to determine the bandwidth of the seal settings for the second part of the study. The greatest peel resistance that 3 or more participants could successfully remove was selected for the second part of the study. Also, the inhaler with the lowest or second lowest peel resistance was selected for the second part of the study, based on a combination of the number of patients that was able to successfully remove the foil from the inhaler and the optimal seal setting for correct storage of the powder.

For the second part of the study, 48 participants, 24 on and 24 off, were asked to open 2 pouches in which the inhaler was packed. The way of opening the pouches was scored as right or wrong by the researcher, and the participants were asked to score how easy opening of the pouch was. After opening the pouches, the participants were asked to pull the cover foils from the inhalers selected in the first part of the study, (defined as Cyclops A and Cyclops B). Similar to the pouches, the researcher recorded whether the participants were able to open the inhalers and the participants were questioned about the easiness of opening the inhaler. The order of opening pouch 1 and pouch 2 and of opening Cyclops A and Cyclops B was randomised, although all patients started with the pouches. A randomisation list was used to assign an order to a participant.

**Fig. 1.** Cyclops inhaler, with the removable cover foil pointing out at the left side of the inhaler. Before inhalation of the powder with the Cyclops inhaler, it is necessary that the patient is able to remove the cover foil by pulling it out of the inhaler. After the cover foil is removed, the powder can be released from the dose compartment and from the inhaler.

### 2.4. Score form

There were two score forms, one form for part 1 of the study and one form for part 2 of the study. For both parts, demographic information as sex, age and time since the diagnoses of Parkinson's disease were noted. For part 2 of the study, scores regarding the easiness of pulling the foil or opening the pouch were expressed as easy – neutral – hard – not able.

### 2.5. Inhaler and seal settings

The inhaler used in this study is the Cyclops (Hoppentocht, 2015), see Fig. 1. The dose compartment, located within the inhaler, is made of LDPE (low-density polyethylene) and sealed with a foil made of PET/PE (polyethylene terephalate/polyethylene).

Generally, the levodopa powder is provided in the dose compartment, but the presence of drugs it was not necessary in this study since the aim was to assess opening and preparing the inhaler. The dose compartment is the primary packaging of the levodopa inhalation powder from moisture. The Cyclops inhaler is provided in a sealed pouch (see Fig. 3A and B) made of PET/AL/PE (polyethylene terephalate/aluminium /polyethylene) film, which protects the contents from light, air and moist.

The cover foil is sealed upon the dose compartment by a heated metal die, which melts the foil two-folded onto the dose compartment for a certain time with a certain pressure and temperature. The dose compartment is shown in Fig. 2.

The metal die has a pattern, which follows the rim of the dose compartment. The shape and area of the die, together with the other parameters, determine the peel resistance of the foil.

By choosing different process parameters regarding the sealing of

**Fig. 2.** The dose compartment the inhalation powder is stored in, sealed with cover foil. For opening the dose compartment, the patient needs to pull the cover foil.

**Table 1**
Seal settings of the dose compartment of part 1 (1–5) and part 2 (A/B) and tear notch position of the pouches.

| Cyclops | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Seal width (mm) | 0.75 | 0.75 | 1.50 | 1.50 | 1.50 |
| Die pressure (bar) | 7 ± 1 | 7 ± 1 | 7 ± 1 | 7 ± 1 | 7 ± 1 |
| Dwell time (s) | 2 | 2 | 2 | 2 | 2 |
| Temperature (°C) | 127 | 142 | 127 | 132 | 137 |
| Cyclops | A | B | | | |
| Seal width (mm) | 0.75 | 1.50 | | | |
| Die pressure (bar) | 7 ± 1 | 7 ± 1 | | | |
| Dwelling time (s) | 2 | 2 | | | |
| Temperature (°C) | 142 | 137 | | | |
| Pouch | 1 | 2 | | | |
| Tear notch position | Acentric | Centric | | | |

the foil on the dose compartment, five Cyclops inhalers with variant sealing of the dose compartment were developed. This resulted in an ascending peel resistance that is needed to pull the foil from the dose compartment and out of the inhaler. Seal settings for every Cyclops are shown in Table 1.

The pouch is wrapped around the inhaler and provided with two 'end seals' and one 'fin seal' over the length of the inhaler. The tear notch position of pouch 1 was acentric, opposite to the side were the fin seal has been folded (Fig. 3A). The tear notch position of pouch 2 was centric (Fig. 3B).

### 2.6. Ethics

The Martini Hospital ethics committee approved the study. All participants provided informed consent for their participation in this study.

**Table 2**
Patient characteristics part 1.

| | On patients (n = 6) | Off patients (n = 6) |
|---|---|---|
| Sex (females/males) | 2/4 | 4/2 |
| Age (yr) mean ± SD | 64.2 ± 7.8 | 73.2 ± 8.2 |
| Time since diagnosis (yr) mean ± SD | 6.7 ± 4.0 | 16.0 ± 3.3 |

### 2.7. Data analysis

Correct opening of the pouch was defined as opening the pouch the way it was designed for, as shown in Fig. 3A and B. For both pouches this means using the tear notch. The tear notch of pouch 1 was located at the upper side, one third from the right corner. The tear notch of pouch 2 was located in the middle of the upper side.

Correct opening of the inhaler was defined as holding the inhaler on a flat area with one hand and pulling out the complete foil with the other hand.

## 3. Results

### 3.1. Part 1: peel resistance of the cover foil on the dose compartment

#### 3.1.1. Patient characteristics

All 12 participants (Table 2) were able to pull the cover foil from the dose compartment for each of the five ascending seal settings. The participants mentioned that there was no considerable difference between Cyclops inhaler 1 and 2. However, all participants experienced the transition between Cyclops 2 and 3 clearly. Overall, all participants experienced only a slight difference between Cyclops inhaler 3, 4 and 5. All participants except one used their dominant hand for pulling the foil. As upper peel resistance, Cyclops inhaler 5 was selected for part 2 of the study. Since the settings from inhaler 2 provide a better adherence between cartridge and foil compared to seal setting 1, the peel resistance of Cyclops inhaler 2 was selected as lowest for the second



**Fig. 3.** 3A and 3B: correct opening of pouch 1 (A) and pouch 2 (B) using the tear notch. The tear notches are at different positions for pouch 1 and 2. For correct opening of the pouch, the patient needs to rip the pouch apart by using the tear notch. This enables the patient to remove the inhaler from the pouch, as shown in 3A and 3B.

**Table 3**
Patient characteristics part 2.

| | On patients (n = 24) | Off patients (n = 24) |
|---|---|---|
| Sex (females/males) | 7/17 | 9/15 |
| Age (yr) mean ± SD | 68.2 ± 7.0 | 70.5 ± 9.4 |
| Time since diagnosis (yr) mean ± SD | 12.3 ± 8.3 | 10.0 ± 4.2 |

part of the study.

### 3.2. Part 2: opening of two pouches and two inhalers

Forty-eight Parkinson's patients participated in the second part of this study. The patient characteristics are shown in Table 3.

### 3.3. Opening the pouches

For pouch 1, 70.8% of the patients in an on state were able to open the pouch correctly. Only 2 patients (8.3%) defined opening of pouch 1 as hard, the other participants defined it as easy or as neutral. Regarding the participants in an off state, 58.3% were able to open pouch 1 correctly. Two participants (8.3%) were not able to open the pouch and get access to the inhaler. Seventeen participants (70.8%) defined opening of pouch 1 as easy (Table 4).

For pouch 2, 79.2% of the participants in an on state and 75.0% of the participants in an off state opened pouch 2 correctly. Fourteen on state participants (58.3%) and 10 (41.7%) off state participants rated opening of the pouch as easy. One off state participant was not able to open pouch 2. Six participants in the on state (25%) and 5 (20.8%) in the off state defined it as hard. These participants mentioned that tearing the pouch was hard due to the mouthpiece of the inhaler they bounced into during tearing, causing resistance during tearing.

### 3.4. Opening the inhalers

95.8% of the on state participants and 91.7% of the off state participants opened both Cyclops A and Cyclops B correctly. For Cyclops A, two off state participants were not able to pull the foil from the inhaler, instead of one off state participant for Cyclops B. Regarding the ease of pulling the foil, 75.0% of the on state participants and 70.8% of the off state participants defined Cyclops A as easy. For Cyclops B, this was 62.5% and 54.2% respectively.

**Table 4**
Results of opening pouch 1 and 2 and Cyclops A and B.

| | On patients; n (%) | Off patients; n (%) |
|---|---|---|
| Results opening pouches | | |
| *Correct opening P1* | 17 (70.8) | 14 (58.3) |
| Ease of opening P1 | | |
| Easy | 21 (87.5) | 17 (70.8) |
| Neutral | 1 (4.2) | 3 (12.5) |
| Hard | 2 (8.3) | 2 (8.3) |
| Not able | 0 (0) | 2 (8.3) |
| *Correct opening P2* | 19 (79.2) | 18 (75.0) |
| Ease of opening P2 | | |
| Easy | 14 (58.3) | 10 (41.7) |
| Neutral | 4 (16.7) | 8 (33.3) |
| Hard | 6 (25.0) | 5 (20.8) |
| Not able | 0 (0) | 1 (4.2) |
| *Correct opening Cyclops A* | 23 (95.8) | 22 (91.7) |
| Ease of opening Cyclops A | | |
| Easy | 18 (75.0) | 17 (70.8) |
| Neutral | 2 (8.3) | 5 (20.8) |
| Hard | 4 (16.7) | 0 (0) |
| Not able | 0 (0) | 2 (8.3) |
| *Correct opening Cyclops B* | *23 (95.8)* | 22 (91.7) |
| Ease of opening Cyclops B | | |
| Easy | 15 (62.5) | 13 (54.2) |
| Neutral | 6 (25.0) | 4 (16.7) |
| Hard | 3 (12.5) | 6 (25.0) |
| Not able | 0 (0) | 1 (4.2) |

### 3.5. On versus off state

For both pouches and both inhalers, more on state patients than off state patients were able to correctly open it. Also, more on state participants defined opening as being easy.

### 3.6. Participant suggestions

Regarding the pouches, a few participants suggested to improve the visibility of the tear notch by adding a coloured sign next to the tear notch. For the foil, suggestions were to use coloured foil instead of transparent foil, and to increase surface roughness, since it is currently smooth.

## 4. Discussion

Effective inhaler therapy requires correct handling of the inhaler, including being able to prepare the inhaler for use. It is known that usability is a key factor in ensuring safe and efficacious medication use by patients (Notenboom, 2017). Difficulties in use can turn into use errors and this may result in dangerous situations for which the user applies a strategy to overcome the inconvenience, for example using a sharp knife for opening a pouch. This may cause harm to the patient. If a patient is not able to easily prepare the inhaler for use, this may also result in decreased medication adherence (Notenboom, 2017). Further, the patient may suffer negative effects of poor disease control due to the decreased self-management ability (Philbert, 2014). Packaging development should therefore target for high patient satisfaction to ensure convenient use (Braun-Münker, 2016). Guidelines for packaging manufacturers recommend that 95% of the consumers must be able to handle the products adequately (Marks, 2012).

This study identified the user ability and convenience of the Cyclops inhaler and the pouch in a representative panel of Parkinson's disease patients. The results show the relevance of testing the ability and user convenience, since, especially for the pouches, several patients did not open the pouch the way it was designed to be opened. Even though some of them were able to open the pouch another way and grab the inhaler out of the pouch, they used the 'wrong' method, indicating a failure in the design. Pouch 2 was more often opened correctly than pouch 1, but more participants defined opening pouch 2 as hard or difficult. For a 'convenient' pouch in daily practice, almost all patients should be able to open the pouch correctly and, opening must be defined as easy by most of them. For the pouches used in this study, it may be worth improving the pouch by developing a pouch with two tear notches, one tear notch located at the position of pouch 1 and the other tear notch at the position of pouch 2. Based on suggestions of the participants, the visibility of the tear notches should be improved.

For the inhaler > 95% of the on state participants and > 90% of the off state participants were able to open the inhaler by pulling the foil from the dose compartment. This step is required for use of the inhaler, since the inhaler cannot release the powder formulation if the foil is still on the dose compartment. It is therefore necessary that all users are able to pull the foil from the inhaler. The off state participant that was not able to pull the foil from inhaler B was not able to pull the foil from inhaler A as well. This participant was in a severe off state and was suffering from serious rigidity. One other participant that was not able to pull the foil from inhaler A was able to pull the foil from inhaler B. This participant mentioned that after practicing opening the inhaler, he expected himself to be able to open both inhalers. Since Cyclops A

was easier to open for both on and off state participants, this one is preferred over Cyclops B for use in daily practice. It is, however, worth assessing the effect of the participants' suggestions of improving the grip of the foil on the ease of opening of the inhaler.

The levodopa inhalation powder we developed is intended for use during off periods. In daily practice, this means that patients in an off period must be able to prepare the inhaler for use. For this reason, we included 30 patients in an off period. On the other hand, we were interested if there was a difference between patients in an off period and patients in an on period. Since it is hard to include off state patients in trials since off periods are often unexpected, it would be convenient if future usability studies can be performed in on state patients. However, for both pouches and both inhalers, more on state patients than off state patients were able to correctly open it. Also, more on state participants defined opening as being easy. These results indicate that differences exist in the experienced and measured suitability for use between off state and on state participants, and although the differences were small, in our opinion the worst-case assessment is the best for rating the usability. We therefore suggest to assess the effects of further packaging optimisation in off state patients. They indeed experience more difficulties in opening the pouch and pulling the foil from the inhaler, and in the end they are the intended users.

The evaluation of usability needs to have a crucial role in the development and design for medical devices such as inhalers. Sometimes, multiple doses are needed, increasing the difficulty of use even more since the number of steps needed is multiplied. These multiple steps can be challenging for Parkinson's disease patients (Stocchi Fabrizio, 2018), especially during an off period, when motor function is impaired. Our study shows that, even a relatively simple operation like opening a pouch, which was at first sight considered to be relatively easy, is already challenging for Parkinson's patients. In our opinion, it is therefore necessary that preparing the inhaler is achieved within the fewest steps possible. The data obtained in this study will help the developers to further improve the packaging of the Cyclops inhaler.

### 4.1. Study limitations

The first part of the study was performed in only twelve patients. This number is too small to draw firm conclusions. Since all twelve patients were able to open all the inhalers with different peel resistances, we assumed that this number of patients was sufficient for selecting the seal parameters for the second part of the study. However, for firm conclusions, larger patient numbers are recommended.

Further, since the intended users of this inhaler are Parkinson's disease patients in an off period, we only assessed usability in Parkinson's disease patients. However, for future improvement of the packaging, it would have been useful to incorporate a control group without Parkinson's disease in this study, since that group could clarify whether the issues regarding opening of the inhaler or the pouch were the result of the Parkinson's disease or the result of the design of the packaging, or a combination of both. Last, in our study, the physician / nurse stated whether a patient was in an off state or not. We did not distinguish regarding the seriousness of the off state between the different patients. Although the type of complaints during an off state varies between Parkinson's disease patients, it is known that in (almost) all patients, the motor function is impaired during an off state.

## 5. Conclusion

Successful dry powder inhalation depends on the interaction between inhaler, formulation and user. Usability thus is a key factor in ensuring safe and efficacious medication use by patients. Since difficulties can turn into use errors and decreased medication adherence, it is of importance that user ability of packaging is studied in a representative panel of the intended user group during the development of the packaging. This study investigated the usability of the Cyclops inhaler and pouch in a representative sample of patients suffering from Parkinson's disease. The data obtained will help the developers of the inhaler to further improve the usability of inhaler and pouch.

## Contributors

All authors contributed to the design of this study. ML, VI and LJ categorized the data. ML wrote the manuscript. All authors contributed to the interpretation of the analysis, critically revised the manuscript and approved the final manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2019.118493.

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