Patient-driven N-of-1 in Parkinson’s Disease

Lessons Learned from a Placebo-controlled Study of the Effect of Nicotine on Dyskinesia

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Summary
Background: New insights and knowledge in biomedical science often come from observation and experimentation. Methods traditionally used include self-experimentation, case reports, randomised controlled trials, and N-of-1 studies. Technological advances have lead to an increasing number of individuals and patients engaging in self-tracking. We use the term patient-driven N-of-1 for self-tracking performed with the explicit intention to disseminate the results by academic publishing.

Objectives: The aim of the study was to: 1) explore the potential role for patient-driven N-of-1 studies as a tool for improving self-management in Parkinson’s disease (PD) using the example of managing levodopa-induced dyskinesia (LID) with nicotine, and 2) based on this example; identify some specific challenges of patient-driven N-of-1 studies.

Methods: We used a placebo controlled patient-driven N-of-1 study with nicotine administered via e-cigarette to treat LID. The first author initiated and conducted the experiment on herself and noted her observations. The evaluations of the potential of N-of-1 for improving self-management of PD as well as the effects of nicotine on dyskinesia were based on the perception of the subject. During the planning and undertaking of the experiment, notes were made to identify challenges specific to patient-driven N-of-1 studies.

Results: The subject was able to distinguish a decrease of her LID from nicotine but no effect from placebo. The main challenges of patient-driven N-of-1 studies were identified to be associated with planning of the study, recruiting a suitable research team, making sure the data collection is optimal, analysis of data, and publication of results.

Conclusions: Our study indicates that nicotine administered via e-cigarette may have an effect on levodopa-induced dyskinesia in individual patients with PD. The main contribution is however highlighting the work done by patients on a daily basis for understanding their conditions and conducting self-tracking experiments. More work is needed to further develop methods around patient-driven N-of-1 studies for PD.

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1. Introduction

New insights and knowledge in biomedical science are gleaned from observation, hypothesis generation and careful experimental testing. While large-scale empirical studies garner the most attention in research, the methods and knowledge that enabled large-scale studies to be conducted in the first place are often overlooked. Historically seminal ideas occurred from a single person’s careful observation and even self-experimentation. Sometimes, prior to testing an intervention on intended populations or healthy volunteers, clinicians and researchers do self-experimentation, considering it an important element of ethical research [1]. Self-experimentation
tation (or auto-selfexperimentation) has lead to important discoveries and also a number of Nobel Prizes [2].

Experiences from single cases in the form of case reports have been used for a long time in medical education and training. From a historical perspective, descriptions of clinical cases have been found in ancient Egyptian medicine, as well as in the practices of Hippocrates and Galen [3]. Today, case reports are valued for hypothesis generation and for identifying outliers that do not fit existing models, theories, or known mechanisms. Case reports are used retrospectively to report on discoveries relating to for example new diseases, unusual manifestations of diseases or unexpected treatment side effects [4]. While case study findings are generally considered less broadly applicable across populations, researchers are beginning to acknowledge case studies as an important complement to traditional large scale empirical studies [4, 5]. Large scale randomised controlled trials (RCTs) are still considered the gold standard of clinical research. There is however an increasing awareness of the limitations of RCTs, especially when it comes to applying the results to individual patients. One only has to note the sometimes vast differences in efficacy and/or side effects between the published results of new pharmaceutical trials and actual clinical practice. One possible solution may be using N-of-1 studies [6, 7]. In N-of-1 studies, also referred to as single subject studies, the investigation is focused on the results from one individual, often aiming to see whether a specific intervention is effective for this individual [6, 8, 9]. N-of-1 studies may be especially suitable for diseases or conditions with large individual variability.

One such condition is Parkinson’s Disease (PD), which is the second most common neurodegenerative disease. It causes a large variety of motor and non-motor symptoms, resulting in significant burdens on the individuals with the condition, their family members and society [10]. The condition is highly individual in nature and requires that each person with Parkinson’s disease (PwP) collaborate closely with their clinicians to find their optimal regime, often consisting of multiple pharmacological and other treatments [11, 12]. Typically, age of onset is about 60 years but 3–5% of PwP experience onset before the age of 40 [13, 14], often referred to as Young Onset Parkinson’s Disease (YOPD). The number of PwP over the age of 50 in the world exceeds 5 million (2005) and the number is predicted to double between the years 2005 and 2030 [15].

Long term use of anti-parkinsonian drugs can lead to development of a potentially debilitating and socially disruptive side effect called levodopa induced dyskinesia (LID) [16]. LID manifests as abnormal involuntary movements with writhing and sometimes jerky movement pattern. The risk of LID is significantly higher for YOPD [12, 13, 14] and can also be difficult to manage. There are only a few approved available therapeutic options with limited patient success [12].

While clinical research is traditionally initiated by clinicians or researchers, new modes of research are unfolding. Emerging technologies enable an unprecedented data collection, which has been utilized in conventional research as a tool for data collection e.g. Apple ResearchKit [17, 18]. Furthermore, the prospect of learning from data collected by patients, e.g. PwP, in their daily lives using for example wearable devices and/or smartphones for improving clinical management and research is attracting growing interest [19, 20, 21, 22, 23, 24, 25]. Technology, such as for example smartphones, apps, sensors and other devices can also be used to facilitate data collection for individuals wanting to find answers to their own questions. This form of study can be called self-tracking [26, 27, 28, 29], self-experimentation [30, 31], Quantified Self [32] or self-quantification [33, 34] and may also be done without technical assistance. A U.S. study reports that 69% of American adults track an indicator relating to health for themselves or a family member [35]. When exploring the mode of tracking, the same study shows that the use of technology is not mandatory for tracking: 49%, track ‘in their heads’, 34% use pen and paper, and 21% track their health using some form of technology.

Self-tracking can be applied to any personal aspect of life, but in the context of this article we focus on health or illness related factors. It can be seen as a parallel to the self-experimentation, N-of-1 studies and case reports utilized by medical professionals to learn from data or information emanating from one or a few individuals. In this article, we consider self-tracking to include any form of data-collection, observation or experiment made by an individual with or without the use of technology, concerning aspects relating to their own health or disease. We will use the term patient-driven N-of-1 for self-tracking performed with the explicit intention to disseminate the results by academic publishing. We would argue that for patients’ self-tracking practices and insights to reach their full potential and result in changes to clinical practice, scientific publication and clinical validation is necessary.

Patients are beginning to report the results of their own N-of-1 studies in a wide variety of health conditions including diabetes type 1 [36], Crohn’s disease [37], and food intolerance [38] and such reports are seen as a potentially important contributor to personalised clinical care [39]. Even though there are examples of patient-driven smaller studies in PD [40, 41] we were unable to find any scientific articles reporting specifically on patient-driven N-of-1 in PD. The lack of scientifically published reports does not necessarily mean that they do not exist. The first author has engaged in self-tracking to better understand the variations of her PD for a number of years and also writes about it on her personal blog (http://www.riggare.se). Her self-tracking work has been described in the popular press [42, 43] but not in academic journals. She had been looking for an example suitable for an academic paper to demonstrate the usefulness of self-tracking for improving self-management and came across the work of one of the co-authors (Sturr) on social media. Sturr had been self-tracking her own PD and a collaboration was initiated.

2. Objectives

The objectives of the study were to: 1) explore the potential role for patient-driven N-of-1 studies as a tool for improving self-
management in PD using the example of managing LID with nicotine, and 2) based on this example, identify some specific challenges of patient-driven N-of-1 studies.

3. Methods

To meet the aims of the study, a placebo controlled patient-driven N-of-1 study was designed using e-cigarettes to administer nicotine.

The first author (Riggare) initiated the experiment and recruited other researchers, clinicians and patients to participate in conducting the study, including design, data collection, analysis, and reporting. The first author was also the subject of the study; she is an experienced self-tracker, had not smoked before and was on stable doses of PD medication at the time for the experiment. Subject characteristics are listed in Table 1.

Nicotine has been demonstrated as effective against LID in an animal model of PD (primates) without an increase in parkinsonian symptoms [44] and in a paper by Quik and colleagues [16] there is mention of a small trial on human subjects (phase I/II). Quik et al. states that four months of oral nicotine treatment in PwP with moderate disease decreased several measures of LID [16] but we have not been able to find any separate article reporting on the results from that trial.

Two identical sets of e-cigarettes (KangerTech mini starter kit) were purchased together with two bottles of e-juice of identical flavour, one with nicotine (3 mg/ml) and the other without. The subject took additional levodopa (25 mg) an hour before the start of the experiment to increase the likelihood of dyskinesia. The e-cigarettes were used as therapeutical intervention.

In order to minimize exposure to LID, which is an uncomfortable and unwanted side effect, the experiment was conducted during as short a time span as possible.

Based on prior experience by one of the authors (Sturr) with managing LID with e-cigarette, nicotine was expected to reduce LID within less than 30 seconds after administration of a few puffs. The subject took two to four puffs from the e-cigarette each time and took notes of her perception of the effect. Depending on the exploratory nature of the experiment, the number of puffs was not standardised. During the planning and undertaking of the experiment, notes were made to identify challenges specific to patient-driven N-of-1 studies.

Ethical considerations are an essential part of all research. Our study can be considered analogous to the self-experimentation performed by clinicians and researchers prior to testing interventions on the intended populations or healthy volunteers. Self-experimentation of that kind has previously been regarded as an essential part of ethical research [1]. Our study has not been reviewed by any ethical review board and there is support in the literature that N-of-1 studies often do not require IRB [45]. Nevertheless, ethical issues have been considered. The idea for the study came from the subject who was well-informed, knowledgeable and chose not only to participate voluntarily but also took a leading role in the planning, performing and analysis of the study. The potential risks for coercion or peer pressure were considered negligible. The subject was planning to conduct the experiment regardless of whether it was going to be submitted for publication or not. However, in order to share the results of the experiment as well as the experience of utilizing the patient-driven N-of-1 method to a wider audience, it was considered ethical to publish the results in a scientific journal.

4. Results

The experiment was conducted between 10 and 11 am local time on 23rd September in the Oregon Convention Centre during the 4th World Parkinson Congress. The assessments of the perceived effects of the e-cigarette by the subject together with notes taken by the subject are listed in Table 2.

During the first test (test A in Table 2), the subject could perceive no effect. At the start of test B however, a sense of calm spread through her body, leading to a reduction of dyskinesia. Furthermore, she experienced a clearness of mind that she had

Table 1 Subject characteristics.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Time since onset (years)</th>
<th>Time since diagnosis (years)</th>
<th>Type of PD</th>
<th>Hoehn &amp; Yahr stage</th>
<th>PD medication incl daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>45</td>
<td>32</td>
<td>13</td>
<td>Juvenile onset PD (Parkin genetic form with a 3 year history of falls and occasional LID)</td>
<td>3</td>
<td>Levodopa/benserazid, 150 mg Entacapone, 1,000 mg Rasagiline, 1 mg Rivastigmine, 3 mg</td>
</tr>
</tbody>
</table>

Table 2 Assessment of effects by the subject.

<table>
<thead>
<tr>
<th>Subject assessment</th>
<th>Subject notes</th>
<th>Key</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test A</td>
<td>Placebo</td>
<td>No effect</td>
</tr>
<tr>
<td>Test B</td>
<td>Nicotine</td>
<td>Sense of calm spread through body, brain fog lifted</td>
</tr>
<tr>
<td>Test C</td>
<td>Nicotine</td>
<td>Less dyskinesia</td>
</tr>
<tr>
<td>Test D</td>
<td>Nicotine</td>
<td>Sense of calm, less dyskinesia</td>
</tr>
<tr>
<td>Test E</td>
<td>Placebo</td>
<td>No effect</td>
</tr>
<tr>
<td>Correct (%)</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
not felt in a long time. During tests C and D, the dyskinesia was also reduced but during test E the subject experienced no effect.

When the tests were unblinded, it was clear that the subject was able to distinguish a decrease of her LID from nicotine but no effect from placebo.

During the planning, design, execution and analysis of this experiment a number of challenges specific to patient-driven N-of-1 studies were noted, which are listed below. The list is not intended to be exhaustive but gives some examples of considerations.

1. Planning. To develop the research idea, you have to make sure that the research you want to do fits the current state of research in that area. Hence, it is necessary to familiarize yourself with the research area in question, both state-of-the art and some of the history in the area. To be able to do this, it is important to have access to published papers, also beyond open access articles. The research question(-s) has to be developed and the study as a whole planned.

2. Research team. If you don’t have all the necessary skills and knowledge yourself, a suitable research team has to be recruited. The team as a whole has to be able to plan, design, and conduct the study, as well as collect and analyse data.

3. Data collection. How can data best be collected and what are the best tools to use?

4. Analysis. How can the data best be interpreted? Are other experts needed to interpret the findings?

5. Publication of results. In order to publish the research, you have to conform to the guidelines and restrictions of scientific journals, which can be a challenge in itself. The cost for publishing may also be an issue as well as choosing the appropriate journal.

5. Discussion

Our aim was to explore the potential role of patient-driven N-of-1 studies as a tool for improving self-management in PD by conducting an experiment using nicotine to reduce LID. The subject experienced a reduction in LID from nicotine and not from placebo which supports the notion that N-of-1 is potentially useful for enabling PwP to better understand and manage their condition. We also want to highlight that advanced technology was not necessary in order to achieve important insights.

5.1 Levodopa-induced Dyskinesia and Nicotine

LID is a potentially troublesome and common side effect of long-term anti-parkinsonian treatment with significant negative impact on quality of life and few effective and available treatment options.

The e-cigarette was invented in 2003 and has since spread rapidly across the world. It consists of a battery, an atomizer and a reservoir containing the e-liquid. A heating coil inside the atomizer generates the aerosol. The e-liquid is available in a large number of flavours, both with and without nicotine. E-cigarettes can be a way to facilitate smoking cessation although health and safety are not fully understood and the long-term effects of inhaling vapours of nicotine and solvents are not currently known [46]. Further work is therefore needed in this area.

5.2 Benefits and Challenges of Patient-driven N-of-1

In PD, conventional N-of-1 studies have been used to explore effects of substances showing potential in primate studies [47, 48]. We found two articles describing studies of PD symptomology (e.g. LID) and in one case the effects on primates were also seen in human subjects [47]. An N-of-1 design has also been used to study the effect of espresso coffee on daytime somnolence in PD [49]. Espresso was considered efficacious compared to decaffeinated coffee in two of the four PwP included.

The use of patient-driven N-of-1 for PD should be further explored because PwP have relatively limited options for treatment, especially in the long term. Levodopa was first used to treat PD in 1961 [50] and remains the gold standard treatment 50+ years later, despite the common side effects. The highly individual aspects of PD also means that it can be a challenge to find an optimal treatment regime and the progressiveness of the condition means that adjustments to the regime may be necessary also between clinical visits. N-of-1 studies offer a potential opportunity for PwP to be proactive in the management of their disease and learn more about their individual condition and treatments. The method can be used to generate hypotheses grounded in personal experience followed by testing on an individual basis. With access to methods to evaluate individual effects of various interventions, PwP may explore different treatments, both pharmacological and other available conventional and alternative interventions. If data and information can be collected in a structured way, this can also contribute to clinical research and practise. There is however more work needed on developing robust and scientifically sound methods for patient-driven N-of-1 studies.

Increasingly, patients of today are active in the management of their health and well-being, they find valuable health information online [51, 52], connect with fellow patients in online communities [29] and use the information they find when communicating with healthcare [53]. Networks of patients connect online, test different ideas and share results, experiences and lessons learned. Social media enables patients to connect with and learn from other patients, clinicians and researchers all over the world. There are also scientific conferences that leverage this potential and one prominent example is the World Parkinson Congress (WPC), organised by the World Parkinson Coalition (http://www.worldpdcoalition.org), a non-profit organisation working to provide an international forum for knowledge and learning about PD actively engaging all stakeholders, physicians, scientists, nurses, rehabilitation specialists, caregivers and PwP. Our study originated from social media and was made possible through the work of WPC. The first author (Riggare) came across a video on social media of a fellow PwP and co-author (Sturr) using nicotine distributed by means of an e-cigarette to manage her LID. Contact was made and the resulting collaboration led to conducting this study at WPC. We see that the combination of social media and conferences...
where patients can meet other patients as well as clinicians and researchers has a strong potential for new findings and collaborations.

The distinction we make between self-tracking and patient-driven N-of-1 has implications. Both have the benefit of drawing on motivation from the participant/researcher, something that has been identified as a key factor for success [54]. One main difference is that self-tracking can be conducted easily and can provide important insights without much planning or time for writing up the results. However, if you want to make your self-tracking publicically known via academic journals, according to our definition of patient-driven N-of-1, there are considerations to be made, as listed in the Results section. The main challenges of patient-driven N-of-1 studies were identified to be associated with planning of the study, recruiting a suitable research team, making sure the data collection is optimal, analysis of data, and publication of results. This process is of course not linear but rather iterative and explorative. For patients who are interested in performing N-of-1 studies, there are many hurdles to overcome in order to be able to share your results with the scientific community.

5.3 Limitations

Our study is not without limitations. Results from N-of-1 studies cannot be extrapolated beyond the subjects in the study. Results from multiple N-of-1 conducted in a standardised way can however generate results applicable to a wider population [45]. Another challenge is related to the demographics and effects of PD. PwP are often older and may not be able to engage as actively in their self-management as our subject. The apathy that often is associated with PD can also make it difficult to expand the use of patient-driven N-of-1 into the wider PwP population. However, for each PwP that can be motivated to manage their condition more proactively, healthcare resources may be reallocated to those in more need of help. We therefore believe that the potential benefits justify further work in this area.

6. Conclusions

In conclusion, this study indicates that nicotine administered via e-cigarette may have an effect on levodopa-induced dyskinesia in individual patients with PD. The main contribution of this paper is however highlighting the work done by patients on a daily basis for understanding their conditions and conducting self-tracking experiments. These experiments and observations are rarely disseminated in academic journals in the form of patient-driven N-of-1 studies and therefore do not reach medical professionals in clinical practise in a validated manner. More work is needed to further develop methods for patient-driven N-of-1 studies for PD.

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