The AZ-PLM Nausea Study: A Novel Patient-Centric Collaboration

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ABSTRACT

This paper describes a novel collaboration between AstraZeneca (a large, global biopharmaceutical research company) and PatientsLikeMe (a circa 50 employee patient-centric, outcomes-based online research platform). During the second half of 2012, AZ & PLM conducted a patient-centric study into nausea and vomiting as drug side effects. While the specific objective of studying the univariate and multivariate aspects of the 'shape' of these side effects was pursued, a parallel overarching aim was to assess the feasibility of direct-from-patient data collection and analysis as a complementary form of real world evidence. The authors present the motivations, context, design and analysis of the study. The pilot collaboration was considered a success, and showed that patient-reported data of this kind is amenable to medical hypothesis generation. Future opportunities for collaboration between pharma and online patient research entities are briefly discussed.

INTRODUCTION

"Patient centricity" is a timely buzzword in the vernacular of modern medicines research. Now, more than ever, there is an imperative to make safe, effective and tolerable medicines available to those individual patients who are most likely to experience the greatest benefit and the minimum risk. Being ever more patient centric is about partnering more with patients at all stages of the drug development pipeline. Whether the aim is to enhance understanding of disease burden and unmet medical need, improve the design of clinical trials, or appreciate factors underlying drug non-adherence and treatment switching – patients are an absolutely invaluable source of insight. While this has always been the case, there is currently an acceleration of patient-driven research, fuelled by an increasing realisation of the possibilities of social media, online research, and mobile technologies.

PatientsLikeMe is an online patient peer-to-peer learning and research environment founded in 2006 by a family affected by amyotrophic lateral sclerosis (ALS). The website combines the quantified data capture system of a clinical data capture platform (e.g. self reported conditions, treatments, symptoms, side effects, and patient reported outcomes) with elements of a social network (e.g. profile pages, news feeds, message forums, photo sharing). Unlike traditional social networks or health forums there is an emphasis on the sharing of quantified, structured data. So for example data about a medication taken by a patient is not just a story (e.g. "I've had depression for 6 years now and have been on Prozac") but rather is translated into structured data through the use of intuitive questionnaires to yield data that can be analysed and aggregated (e.g. Male, 35 years of age, resident in United Kingdom, diagnosed with Parkinson's disease on 01/04/2009, started fluoxetine (generic) on 03/08/2010 at a dosage of 25mg daily (immediate release)). The primary intent of the site is for patients to connect with one another, learn more about their condition, and take better management of their chronic health conditions. An additional benefit is the potential for research to be conducted quickly on the platform, and through collaborations with academics and life sciences researchers the site has yielded over thirty-five peer-reviewed journal articles.

The following sections describe a pilot collaborative study between AstraZeneca (AZ) and PatientsLikeMe (PLM), focussing on one specific area of patient centricity – drug side effects. The Motivation & Aims section outlines the central hypotheses that this collaboration set out to explore and test, and explains why AZ and PLM chose each other as partners, and why nausea and vomiting as drug side effects was chosen as the research topic. The design and execution of the study is described in the Methods section, and outputs for each key question are presented in the Results section. In the Conclusion section, the successes and challenges of the collaboration are explained. Finally, in the Discussion section, we put the study in a broader context, and take a look to the future.

MOTIVATION & AIMS

WHY AZ AND PLM?

PatientsLikeMe represents the ideal set of capabilities, technologies and expertise with which pharma-based patient-centric research can be pursued. Specifically, it is the combination of the following factors that make PLM unique:

- A first-in-class online patient peer-to-peer environment
- Routine collection of *structured* disease, treatment and lifestyle data, rather than just free text comments
- A large existing, and engaged patient community
- An integrated, flexible and sophisticated eSurveying/ePRO toolset for prospective data collection
- A heritage in producing a steady flow of original medical research publications in peer reviewed journals
- Extensibility: the capability to grow new patient communities in emerging disease areas

From PLM's perspective, AZ make an attractive research partner because:

- A global pharmaceutical company with a broad portfolio of marketed and in-development drugs across therapeutic areas including areas of strength for PLM e.g. mood as well as emergent areas of interest e.g. cancer
- Interested in ways to leverage patient experience into early phases of R&D pipeline
- Deep expertise in patient reported outcomes
- Forward-looking approach to the sharing of datasets with academic partners for maximizing shared value
- Centralized informatics core tasked with supporting innovation and use of big data across the business

WHY STUDY DRUG SIDE EFFECTS?

There are a growing number of studies which report a clear discrepancy between those drug-related events which are recorded by a clinician, and those reported as important by patients [1]. Therefore, it seemed prudent to start in an area where there is already a strong suggestion that becoming more patient centric would be of benefit to the development of new medicines. In order to build on the foundations of existing patients and data within PLM, we decided to pick a specific area of side-effects where there was already a high density of data in the PLM system. Ultimately, we settled on nausea & vomiting (N&V), which is particularly interesting due to the additional factors of (i) poor predictivity of occurrence in humans from pre-clinical studies [2]; and (ii) inadequate characterisation of N&V in clinical trials, from the patients' perspective. In particular, we wanted to explore the concept of the shape of a side-effect. We define "shape" here as the multivariate characterisation of a condition, from the patient perspective. For instance, we may wish to gain insight into whether nausea is more tolerable if it is mild and persistent versus severe and intermittent. These types of insights are often not readily gained based on the data collected in randomised clinical trials.

Of additional interest are the underlying biological mechanisms which lead to nausea, through which different pharmaceutical agents may act, and which may in turn have differing 'shapes'. There are 3 main pathways to N&V:

1. Central Pathway: agents crossing the blood-brain barrier may reach the brainstem emetic control center in the medulla. From here, dysregulation of emetic agonists (e.g. dopamine, acetylcholine, serotonin, histamine) can trigger N&V
2. Vagal Pathway: direct irritation of the gastric mucosa can cause N&V signals to be transmitted via the vagus nerve
3. Vestibular Pathway: related to balance, and transmitted via the vestibulocochlear nerve

STUDY OBJECTIVES

There were two principal objectives to this study:

1. Investigate the feasibility of a future collaborative relationship between AZ and PLM
2. Gain specific patient-centric insights regarding experience of N&V, via a set of shape variables

METHODS

The study was split into three segments. In the first segment, the aim was to analyse N&V side-effect data that was pre-existing in PLM. The second segment involved prospective collection of data, using an online, custom-designed survey instrument. The third and final segment involved analysis of the prospective data, and subsequent reporting of the findings.

RETROSPECTIVE DATA EXTRACTION & ANALYSIS

Patients who are members of PLM, have the facility to continuously record both quantitative and qualitative information about their experiences of their condition, treatment and daily living. In this study, the following retrospective data sets were generated and studied:

1. All drugs which had >50 completed side effect evaluations
2. Top 25 medical conditions, ranked by the number of patients with that primary condition, who also reported N&V, in descending order
3. Top 60 symptoms, ranked by mean severity, in descending order
4. Mean change in symptom severity between patient reports, for the top 5 symptoms by incidence, plus N&V
5. A qualitative data set, based on free text testimonies recorded by patients, that mention N&V

Based on this data, the following additional analyses were performed:

- For the top 8 drug products in PLM according to number of N&V reports, compare the percentage of evaluations citing N&V, with the percentage expected based on the package insert for that product
- Measure the correlation between product label percentage and PLM percentage of N&V side effects

PROSPECTIVE DATA COLLECTION

Data was prospectively collected, via the development and dissemination of an online patient survey. The overall design of the survey was motivated by the following factors:

- Intensity – e.g. mild, moderate, severe
- Vomiting & retching – whether nausea occurred with or without them
- Triggers – e.g. alcohol, medication, food, allergies, pain, stress
- Onset – e.g. start of therapy, on dosing, on dose increase, mornings, night time
- Duration – e.g. minutes, hours, days, most of the day, persistent for weeks
- Frequency – e.g. hourly, daily, weekly, rarely
- Causes – e.g. medical condition, medication, not known
- Amelioration – e.g. eat/don't eat, take anti-emetic(s), sit still after taking medication

The survey was constructed as illustrated in Figure 1. Where the survey used pre-existing patient-reported outcome (PRO) instruments either in whole or part, explicit permission was gained from the licensors, and references for each are provided at the end of this paper [3-10]. In order to enable fast and efficient data collection, the survey was sent to a targeted subset of patients, who met the following criteria:

- Reported a diagnosis of Parkinson's disease, Rheumatoid Arthritis, or Fibromyalgia
- Logged in to PLM at least once in the preceding 90 days

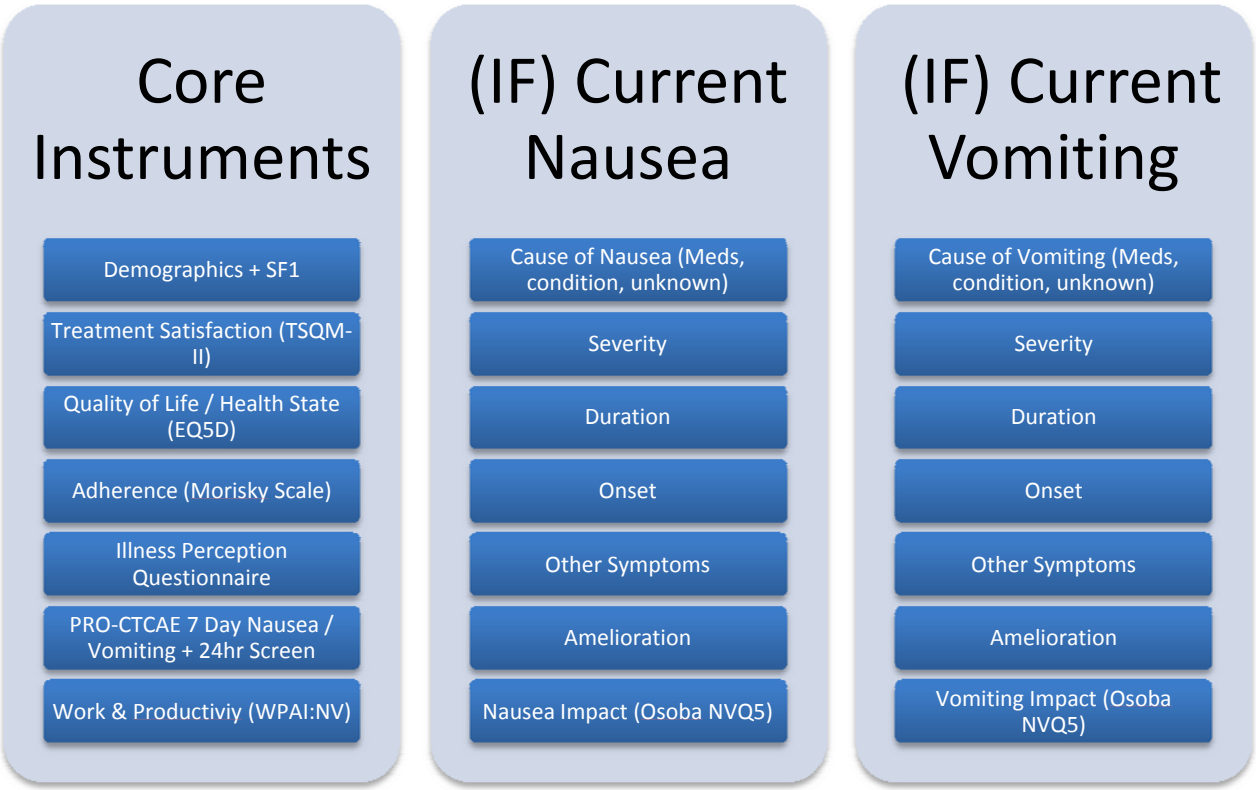

Figure 1: A schematic depicting the construction of the survey used for prospective data collection in the AZ-PLM N&V study. The sections in the middle column were only presented to the respondent if they had reported experience of nausea in the last 24 hours, while those on the right were only presented if the respondent reported vomiting in the same time period.

FINAL DATA ANALYSIS & REPORTING

The prospective data was then analysed, according to a short, pre-written statistical analysis plan. At the core of this plan was the hypothesis that N&V as caused by different vehicles (disease, treatment, unknown) will have statistically different characteristics by: onset, duration, frequency, severity, and amelioration.

Statistical procedures used included the use of simple descriptive statistics and tests for normality. As most data was non-normally distributed, non-parametric between-group analysis was performed using Kruskal-Wallis One-Way ANOVA test and simple Chi-Square tests. All tests were set with alpha at $p<0.05$ (two tailed).

RESULTS

This section is split into two parts: selected results from the retrospective analysis of pre-existing PLM data, and selected results from the analysis of data received from patients in response to a prospective online survey instrument.

RETROSPECTIVE DATA ANALYSIS

A key output from the analysis of pre-existing PLM data on N&V is shown in Figure 2. For all drugs in the data set, we extracted the expected frequency of N&V, as reported in the drug label, and plotted this versus the N&V frequency for the same drug, as reported by patients in PLM. The observed correlation as measured by Pearson's R is moderate at 0.62. Two particularly discordant drugs are specifically labelled in the figure. For each we hypothesise as to why they may be so:

- Tacrolimus: Data on this immunosuppressant prescribed to prevent post-organ transplant rejection comes from patients in two different states. The label data comes from the first few weeks or months post the transplant operation, whereas data from PLM comes from patients who have been stable on the drug for months or years.

- Carbidopa-Levodopa: Label data for carbidopa-levodopa (Sinemet) is likely to draw upon older trials with low doses and co-medication. PLM users might be on particularly high doses of the drug in combination with dopamine agonists and dopamine metabolism inhibitors.

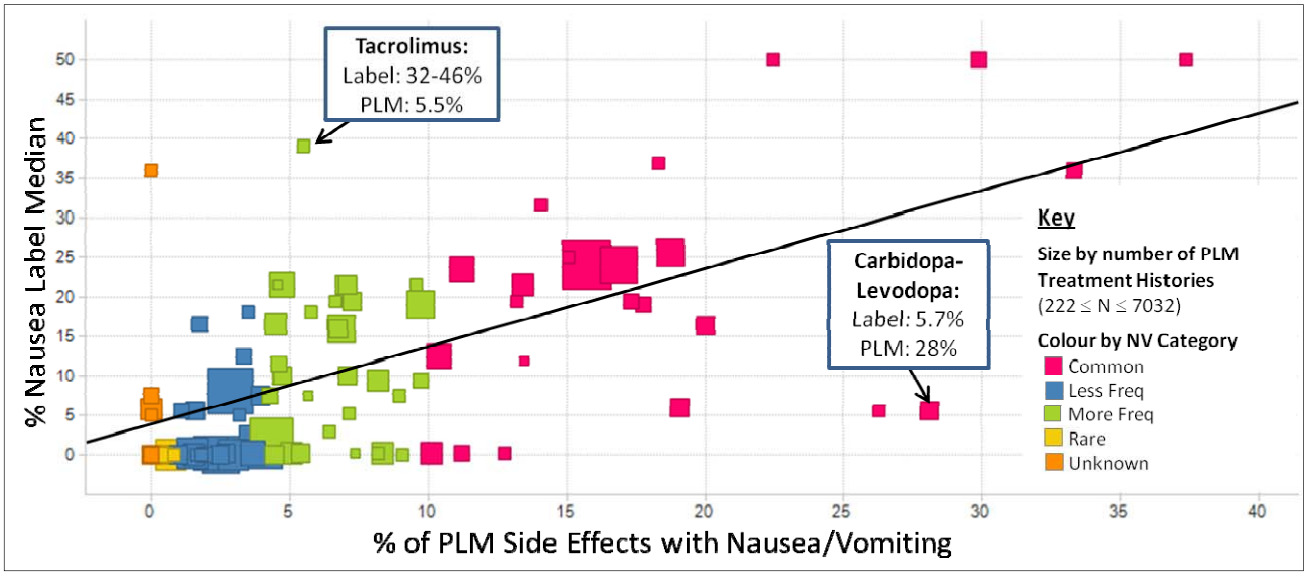

Figure 2: A scatter plot showing the expected percentage of patients likely to experience nausea as taken from drug labels, versus the percentage of patients reporting nausea/vomiting for the same drug in PLM. The size of the boxes is proportional to the number of PLM treatment histories considered, while colour indicates reporting frequency in PLM. A moderate correlation is seen between PLM and drug label side effect frequency data, where R= 0.62. The straight line indicates the outcome of a linear regression analysis on the data.

PROSPECTIVE DATA ANALYSIS

We invited 3,170 patients, of whom 1,727 (54%) opened the invitation message and 472 (15%) completed the survey in a two week window. An overview of their demographic and high-level medical characteristics is shown in Figure 3. The responder population is predominantly female, which is consistent with PLM's overall demographic. It is also dominated by patients whose primary medical condition is fibromyalgia, Parkinson's Disease or rheumatoid arthritis. This is to be expected, since there are relatively few cancer patients in PLM, and given the treatment profile of those three conditions:

Condition	Typical Treatment in PLM	Expected Nauseogenicity
Fibromyalgia	Milnacipran	SNRI drug, therefore increased levels of serotonin could cause N&V via the Central Pathway
Parkinson's Disease	Ropinirole Carbidopa-Levodopa	Dopamine agonists/precursors, therefore increased levels of dopamine could cause N&V via the Central Pathway
Rheumatoid Arthritis	Methotrexate	Chemotherapy, therefore expected to cause N&V via direct irritation of the gastric mucosa – the Vagal Pathway

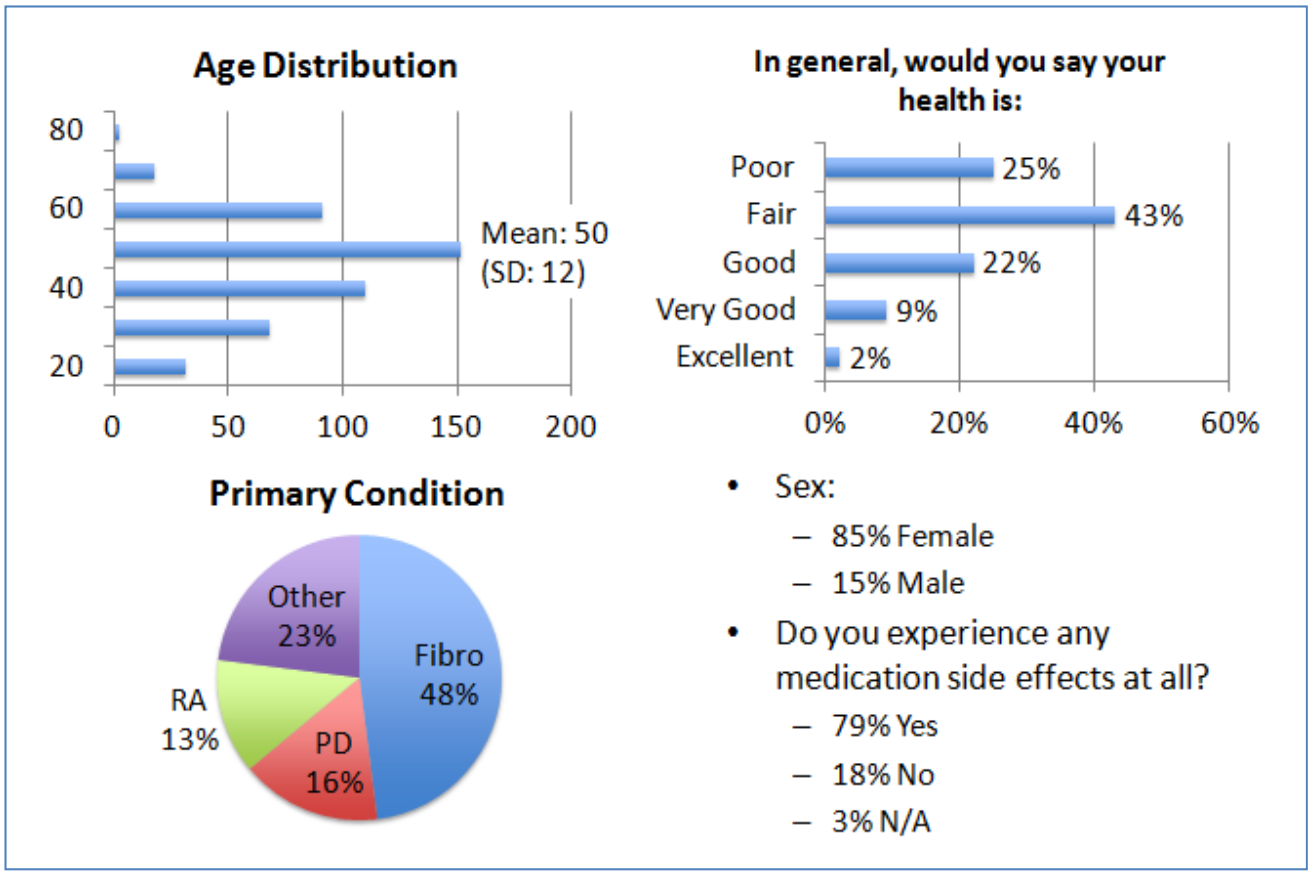

Figure 3: High-level demographic and medical characteristics of the AZ-PLM N&V study responder population. N=472. Fibro = Fibromyalgia; PD = Parkinson's Disease; RA = Rheumatoid Arthritis.

Figure 4 gives a sense of the data density of N&V incidents, and specifically those perceived to be caused by a medication. The pie chart displays the distribution of responses to a question regarding how many times patients had experienced N&V in the last 7 days, and the sample flow diagram illustrates the breakdown of causes of N&V. Within the two primary causes of N&V, a further breakdown of which specific medications and conditions is shown in Figure 5.

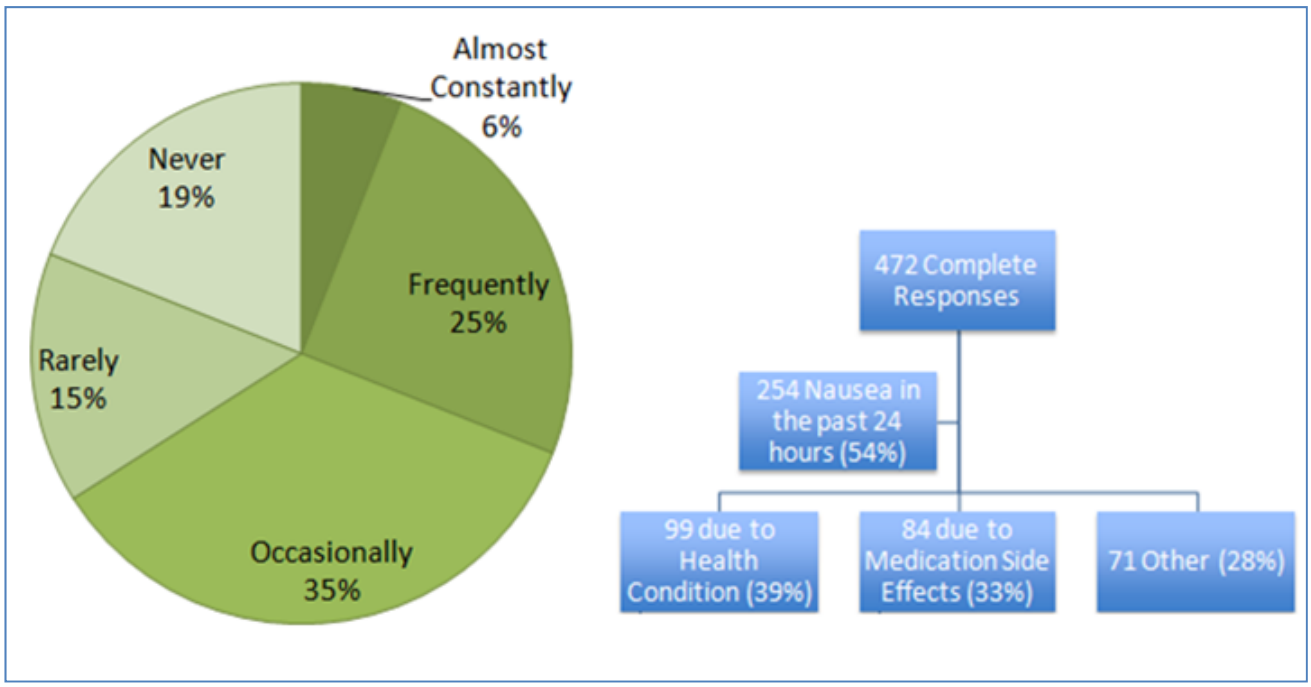

Figure 4: Data density of N&V instances among the responder population. The pie chart represents frequency within the last 7days. The flow chart illustrates perceived cause of the N&V.

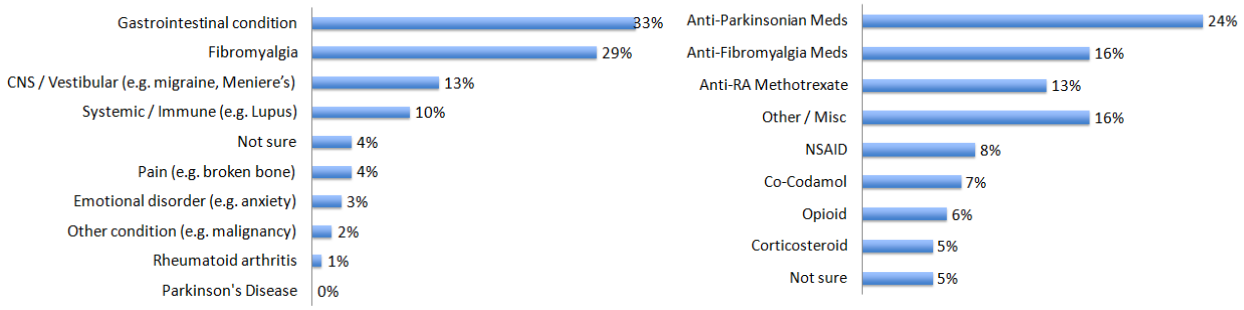

Figure 5: Breakdown of specific conditions (medications) perceived to be causing N&V, among the responder population, shown in the left (right) figure. For conditions N=99, and for medications, N=84.

Next, the influence of medication class on the various N&V shape variables was calculated. Figure 6, Figure 7, Figure 8 and Figure 9 show the outcome for whether medication class affects duration, severity, onset or potential for amelioration. A statistically significant effect was observed for duration and onset, but not severity or amelioration. It should be noted that at this stage of the analysis, the numbers of patients are low relative to the overall sample: N=13 for fibromyalgia; N=19 for Parkinson's disease; N=11 for RA. This is partly because the data was additionally filtered to keep only patients who experienced N/V in the 24 hours prior to completing the survey, in order to limit recall, and therefore inaccuracies in the data. Figure 10 shows how, rather than occurring in isolation, N&V is often concurrent with a complex mixture of other symptoms, which may also vary by medication.

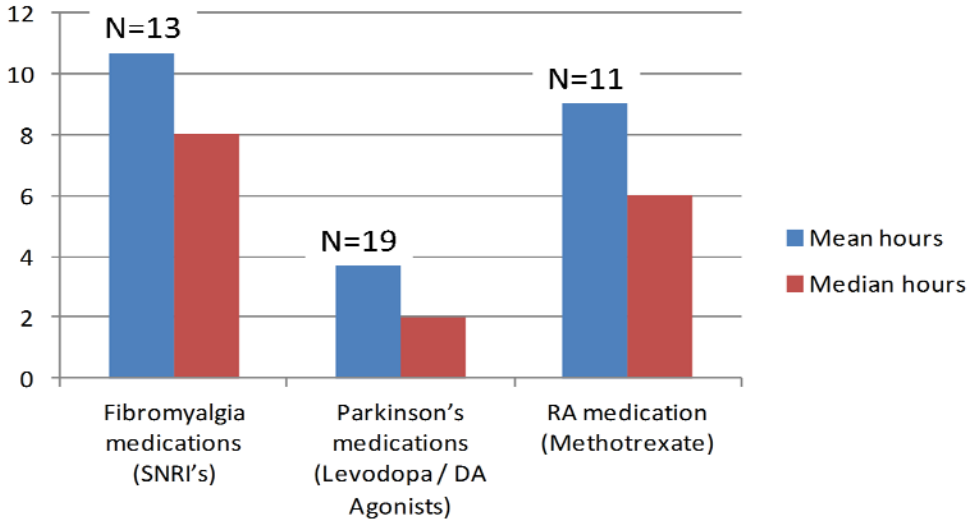

Figure 6: Distribution of patient response to questions about the duration of N&V. The answers were split by disease (Fibromyalgia, PD or RA). The patient population used for this analysis was those reporting experience of N&V in the 24 hours preceding completion of the survey. Chi-square statistics were calculated to test for any difference from uniformity of response. In this case: Kruskal-Wallis Chi Square (2 df) = 8.448, p=0.015.

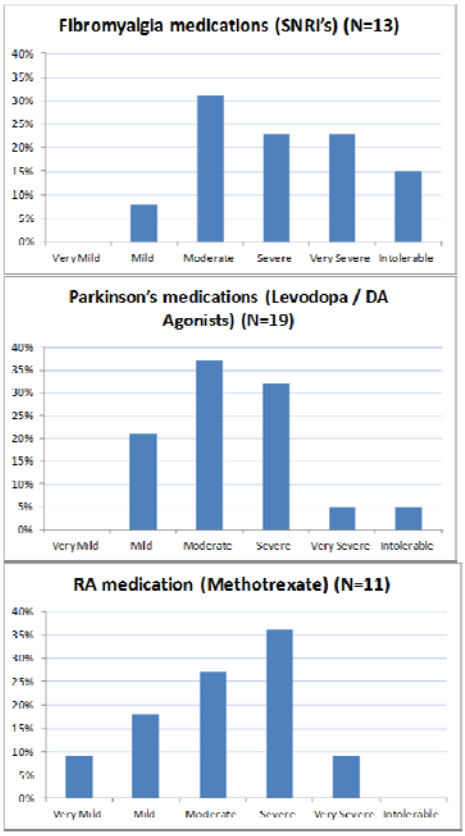

Figure 7: Distribution of patient response to questions about the severity of N&V. The answers were split by disease (Fibromyalgia, PD or RA). The patient population used for this analysis was those reporting experience of N&V in the 24 hours preceding completion of the survey. Chi-square statistics were calculated to test for any difference from uniformity of response. In this case: Chi-Square (df 10) = 8.724, p=0.558 (n.s.).

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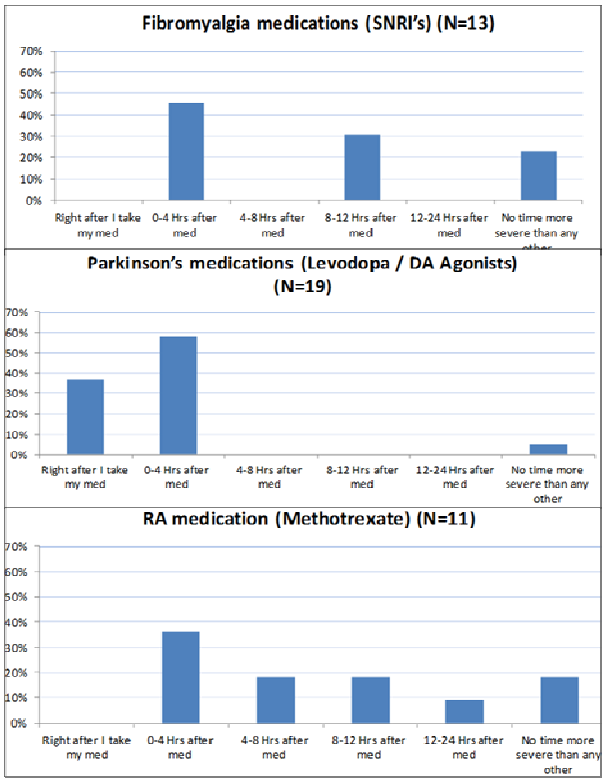

Figure 8: Distribution of patient response to questions about the onset of N&V. The answers were split by disease (Fibromyalgia, PD or RA). The patient population used for this analysis was those reporting experience of N&V in the 24 hours preceding completion of the survey. Chi-square statistics were calculated to test for any difference from uniformity of response. In this case: Chi-Square (df 10) = 25.630, p=0.004**.

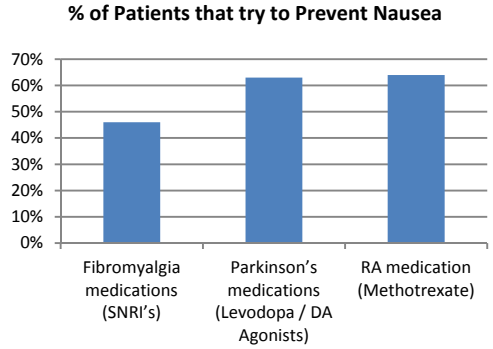

Figure 9: Distribution of patient response to questions about the amelioration of N&V. The answers were split by disease (Fibromyalgia, PD or RA). The patient population used for this analysis was those reporting experience of N&V in the 24 hours preceding completion of the survey. Chi-square statistics were calculated to test for any difference from uniformity of response. In this case: Chi Square (2 df) = 1.101, p=0.577.

	Dizziness	Lightheaded	Feeling hot	Feeling cold	Stomach pain	Bloating	Diarrhea	Constipation	Heartburn	Burping	Palpitations	Headaches	Migraine	None of the above
FM Meds (N=13)	31%	54%	31%	39%	46%	31%	31%	23%	23%	31%	15%	31%	31%	15%
PD Meds (N=19)	20%	35%	10%	5%	30%	0%	5%	20%	5%	15%	10%	20%	0%	20%
RA Meds (N=11)	36%	55%	27%	27%	46%	36%	27%	9%	18%	9%	27%	64%	0%	0%

Figure 10: Symptoms co-occurring with N&V, by medication type. FM = Fibromyalgia; PD = Parkinson's Disease; RA = Rheumatoid Arthritis.

Finally, PCA was conducted, using all variables in the survey as a starting point. After some pruning of variables with significant missing data, 46 variables remained and the consequent scatter plot of patients against the first two principal components is shown in Figure 11.

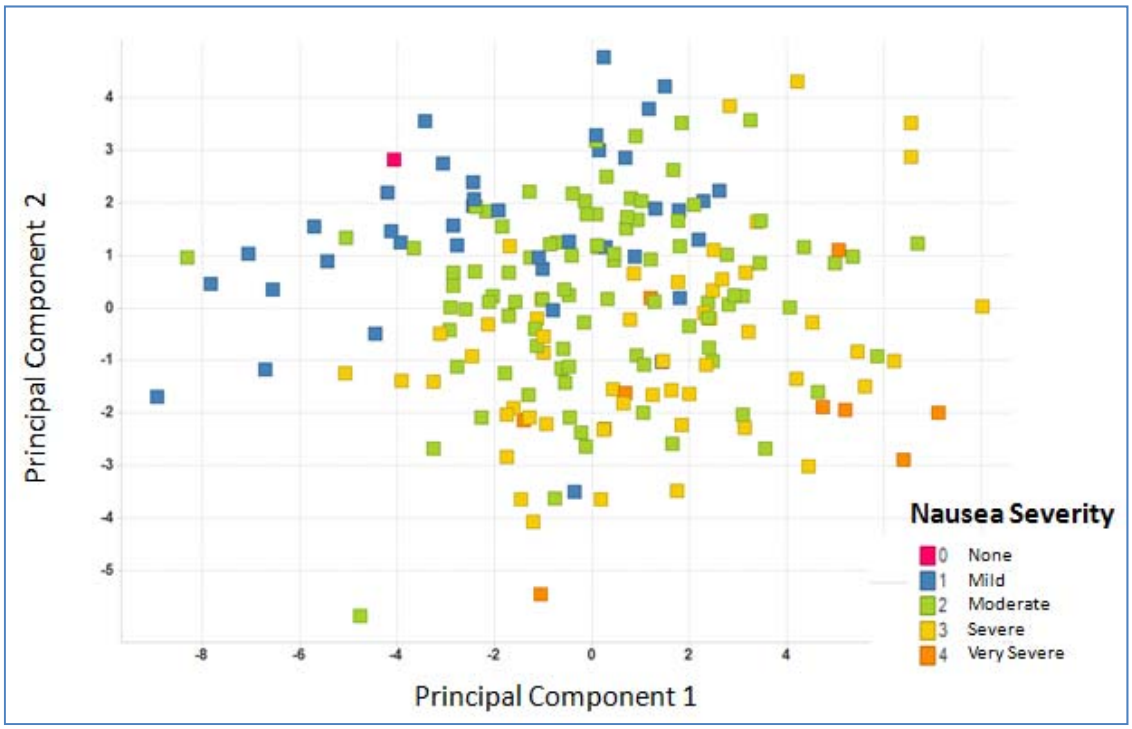

Figure 11: The result of a PCA analysis on 46 key variables from the AZ-PLM N&V study prospective data set. Some separation of patients reporting differing severities of N&V can be observed.

CONCLUSIONS

This pilot study showed that productive and meaningful patient-centric collaboration between AZ and PLM is possible. In particular, the following factors made this so:

- Co-location: significant time spent face-to-face during the study planning, execution and analysis phases
- Flexible use of experts: achieving a balance between a small core team, and a large extended set of reference experts, used transiently
- Data sharing: ensuring that all study data that could be shared with both parties, was shared
- Transparency with patients: the PLM patients contributing information to the study were fully informed as to the goals of the study and therefore how their data was to be used
- Mutual benefit: establishing up-front the key reasons why it would make sense to work together on a specific scientific question. This then naturally leads to a high level of shared commitment towards those common goals

The retrospective analysis of pre-existing PLM data, appears to reinforce the hypothesis that direct-from-patient data collection does not always agree with results as measured via other means, and therefore offers an important alternative lens through which to study drug side effects (as discussed in [1]).

Our preliminary findings on the 'shape' of N&V in relation to medication usage are the following. For those patients who attributed N&V to medication side effects for fibromyalgia, Parkinson's disease or rheumatoid arthritis, the below table describes whether different patterns were seen across the three diseases:

N&V Shape Variable	Different Pattern Across FM/PD/RA?
Duration	YES
Severity	NO
Onset	YES
Other symptoms	MAYBE
Amelioration	NO

Furthermore, one can infer some typical N&V shapes for each disease by extracting the modal values from each group on the parameters of interest:

Indication of treatment	Duration of N&V	Onset of N&V	Co-Occurring Symptoms
Fibromyalgia	8 hours a day	Hours after taking it	Lightheaded, Stomach Pain (15% none)
Parkinson's Disease	2 hours a day	Immediately after taking it	Lightheaded, Stomach Pain (20% none)
Rheumatoid Arthritis	6 hours a day	Heterogeneous	Headaches, Lightheaded (0% none)

Therefore, even with the limited patient numbers in this study, we believe it is a promising route to study the patient-centric aspects of medication side-effects and overall drug tolerability. However, due to the low numbers of patients in each disease area (Parkinsons', Fibromyalgia, Rheumatoid Arthitis), we would recommend that these findings be validated in a larger sample.

DISCUSSION

The AZ-PLM N&V study was the first study of its kind to be conducted between a pharmaceutical company and a peer-to-peer online patient-centric research platform. It's overall importance will be seen in the coming years, when we predict that those discovering, developing & marketing medications will begin to realise the full potential of achieving a genuine triangulation between: (i) clinician-recorded data; (ii) patient-generated information; (iii) background knowledge of disease and drug class. At the same time, it is prudent to be mindful of some of the main limitations of patient-centric information collection:

- The patient is not (usually) medically trained, and therefore will not have the same level of scientific understanding of disease and treatment as a clinician
- Recall and subjective bias may affect the quality of the data set
- There can be potential for responder bias – i.e. the subset of patients that opts to complete the survey are not as representative of the overall population as they could be

Regarding future directions, there are a number of promising areas where such a collaboration could evolve in the future:

- Building new patient populations in PLM (e.g. in certain cancers)
- PRO development – the PLM platform is an excellent way to get rapid patient feedback on new instruments
- PRO bridging – e.g. understanding how/whether disease-specific instruments can be mapped to the EQ5D
- Gaining a deeper understanding of medication (non-)adherence
- Patient-centric side-effect profiling, leading to an enhanced understanding of drug tolerability
- Overall improvement of health outcomes, via peer-to-peer disease management

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