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Note

Meeting ~~Commentary-~~commentary~~–~~"Parkinson's disease: From patient to product"

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Abstract

A meeting organised by the Academy of Pharmaceutical Sciences (APSGB) Age-Related Medicines Focus Group took place on the 19th of May 2015, in GlaxoSmithKline Ware, UK [*]. The meeting was the first of a planned series of disease specific meetings organised by APSGB. It was attended by a number of experts involved with the treatment and development of drugs for the older adult, including clinicians, pharmacists, academics, regulators and representatives from industry. The event created the platform to discuss the provision of medicines for the treatment of Parkinson~~'s D~~'s disease (PD) from a pharmaceutical sciences perspective.

~~*KeywordsParkinson's Diseaseolder adultmedicineformulation*~~ *'Medications are something you prescribe: something that gives me my life back' (A PD sufferer)*

Keywords: Parkinson's disease; Older adult; Medicine; Formulation; Dosage form

1 Introduction

PD is a common and slowly progressive neurodegenerative disease neuropathologically characterised by the degeneration of heterogeneous populations of neural cells (mainly dopaminergic neurons). It has no cure. Severe disability or death may be expected in 25% of the patients within 5 years, in 65% of the patients within 10 years and in 80% of the patients within 15 years of onset (EMA PD Guideline, 2012).

Sufferers have a choice of 71 different preparations of their various medicines to alleviate their symptoms and the nature of their illness is that without these drugs, they may not be able to function. To quote one patient addressing the medicine providers 'Medications are something you prescribe: something that gives me my life back'. For the majority of patients on more than one drug, coordinating the different dosing schedules can be challenging and complicated if the

individual is hospitalised and hospital staff are not aware of their different medications or unable to accommodate the dosing schedules. This can have a dramatic effect on the patient, causing incapacitation and making them unrecognisable to their carer ('within 48hours ~~hours~~ he was confused, hallucinating, drowsy and a shell of the man he was' (Parkinson's UK)).

PD is characterised by a range of motor and non-motor symptoms which will differ from patient to patient meaning that the drugs and dose forms need to be tailored to the individual. PD sufferers typically spend almost 75% longer in hospital compared to non-suffering individuals of a similar age. This adds up to more than £20 M additional annual cost to the National Health Service (NHS) (2012/2013 representing 128,513 excess days in hospital (Parkinson~~'s UK)).Parkinson'~~s UK)).

Parkinson's UK is one of the charities representing patients afflicted with the disease. The three priorities from a PD patient's perspective have been identified as better treatments and a cure; taking control of the condition and getting the right services. PD is an individual disease requiring individual approaches for coping with the condition. Parkinson~~'s UK'~~s UK's 'Get it on time' initiative is specifically aimed at raising the awareness of the needs of PD patients and carers. ~~.~~The campaign includes the design of a special washbag that a patient can take into hospital with them to inform hospital ward staff that they need their medication on time. It contains details of their drugs, a checklist to prepare for hospital admission, a card explaining PD to hospital staff and a laminated clock to remind them of the time when the medication needs to be taken.

Over £10 M is projected to be spent on PD drug research over the next 5 years with activities directed towards re-purposing drugs as well as developing novel compounds (Parkinson's UK). The need for more robust clinical trials in the disease has been highlighted as a related issue. ~~Note: The Cure Parkinson'~~the Cure Parkinson's ~~Trust charity is also involved with PD, but they are focussed more on basic research.~~

Parkinson's UK is campaigning to improve the lives of PD sufferers. An example is their lobbying to have the NHS prescribe Duodopa~~e (levodopa / g~~ (levodopa/carbidopa intestinal gel, AbbVie) which is a novel treatment of last resort delivered by a surgically inserted intra-intestinal pump. Individuals refused this medication (by Primary Care Trusts) are left with only palliative or end of life care. Parkinson's UK raised 28 questions in Parliament last year on this subject and 98 MPs signed an Early Day Motion and were asked to write to the Head of the NHS to try and rectify the situation. Another example is Parkinson~~'s UK'~~s UK's initiative to rationalise the calculation of the dose for retigabine patches used to treat PD. (Post meeting note: Shortly after this meeting NHS England announced that they have approved the routine commissioning of Duodopa.)~~.~~

Both these activities highlight Parkinson~~'s UK'~~s UK's drive to provide PD education, training, networking opportunities, to ensure that patients are engaged such that the services available suit them and to equip Parkinson's professionals to influence the services available. The recently launched 'Excellence Network' is an innovative linkage between PD professionals, people living with the condition and Parkinson's UK to help achieve these aims (http://www.parkinsons.org.uk/professionals/about-excellence-network). There are 23 regional working groups including neurologists and geriatricians and 7 cross-~~-~~themed areas covering Education, Technology, and Evidence-based Practice etc. Work by Parkinson's UK identified 10 research priorities related to PD. High among these was the cause and prevention of falls in PD patients and the development of once a day formulations. They are also active in getting 'John~~'s Campaign'~~s Campaign' (which is working towards the right of carers to stay with people with dementia in hospital) extended to Parkinson's patients.

In the Q&A that followed the presentation a question was asked as to whether it would be better to have hospitals which focussed on PD. The number of PD patients is relatively low (127,000 compared to 3.8 million individuals with diabetes for example) which would make this difficult. A PD ward in one hospital was great for the patients on the ward but not so good for others when the ward was full. In addition specific wards work well for some diseases (e.g. Stroke) but the benefits are less clear for diseases such as PD which is much harder to clearly diagnose.

2 Non-~~Motor S~~motor symptoms in PD

When people think of PD they usually think of the motor related symptoms (~~dyskinesia~~ bradykinesia ~~—~~—characterised by involuntary movements) as these are most highly visible, however the non-motor symptoms (NMS) are often ~~typically~~ the ones which have the most negative effect on the sufferer. All of the body's neurotransmitters, e.g. dopamine, acetylcholine, noradrenaline and serotonin are implicated in NMS and deficiency in these neurotransmitters to varying degrees can cause a range of symptoms. Espay and LeWitt (2014), in a paper relating to norepinephrine (noradrenaline) deficiency in PD, suggests that early recognition of the various clinical manifestations associated with its deficiency, which may precede development of motor symptoms, could provide a window of opportunity for early neuroprotective interventions. Typically 80% of the dopaminergic neurons are lost by the time an individual is diagnosed hence the importance of picking up the early symptoms as soon as possible. However the early symptoms are~~n~~' not always obvious. For example one PD patient had complained about being able to smell burnt rubber before being diagnosed. Others have disturbed sleep (fighting things in their dreams) or mood changes (including changes to their voice). All of these are not obvious signs of PD.

Obsessive compulsive disorders can also be a sign, linked to the dopamine signalling pathway. These might include an obsessive interest in sex, or in shopping or in gambling. Particularly distressing is a symptom characterised by freezing in doorways as this can make individuals stop going out to save their embarrassment when the symptom occurs when entering or exiting a door in a busy situation for example getting on or off an underground train.

Pont-Sunyer et al. (2015) have reported four clusters of NMS in PD patients: rapid eye movement sleep behaviour disorder symptoms-constipation, cognition-related, mood-related, and sensory-~~-~~/other NMS cluster. Interestingly the various non-motor symptoms appeared with more prevalence at different times before the onset of motor symptoms. Thus anhedonia (inability to experience pleasure), apathy, memory complaints, and inattention occurred more frequently during the 2-year premotor period. Those reported more frequently in the 2- to 10-year premotor period were smell loss, mood disturbances, taste loss, excessive sweating, fatigue, and pain. Constipation, dream-enacting behaviour, excessive daytime

sleepiness, and postprandial fullness were frequently perceived more than 10 years before motor symptoms (Pont-Sunyer et al., 2015).

Loss of sense of smell, constipation and depression can also all be red flags ahead of the onset of PD with motor symptoms. Six related phenotypes have been identified and bio-markers exist for some of these (e.g. fatigue and pain specific phenotypes).

The use of dopaminergic drugs (levodopa-/carbidopa) to treat the motor symptoms of PD can cause NMS (such as anxiety and-/or pain) on withdrawal with no respite on administration of anti-anxiety or analgesic drugs.

NMS in patients with PD havehas a significant impact on their quality of life and are suffered by over 97% of individuals. The impact can be assessed by the use of a self-completed questionnaire (NMSQuest) (Chaudhuri and Sauerbier, 2015) which has 30 questions. Other questionnaires are available including the PDQ8 and PDQ39 with 8 and 39 questions, respectively, NMS Scale, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale MDS-UPDRS (Martinez-Martin et al., 2015) and new scales are under development. Typically PD sufferers have >8 NMS regardless of ethnicity.

More than 45% of non-drug treated PD patients (i.e. those without motor symptoms) have NMS. Patients may not report these, indeed they may not appreciate they are part of their PD. Clinical trials for PD still focus primarily on the motor-symptoms and not on the NMS.

A major issue with research into drugs to treat NMS in PD patients is the difficulty in getting payer organisations to accept the need for specific treatment of these symptoms i.e. there are already anti-anxiety and analgesic products (the fact that these do not treat these symptoms in PD patients is ignored). NMS phenotyping could help direct the right medicines to those who most need them. A NICE PD guideline is due to be published in 2017 and will include discussion of NMS.

3 Development of drug products for PD patients

A proportion of PD patients (32%) suffer dysphagia (difficulty swallowing) and this can be exacerbated if they are administered anti-muscarinic drugs (not common for idiopathic PD) which can cause dry-mouth symptoms. PD patients can be taking >-9 tablets per day and as mentioned previously adherence to their medicine is critical as missing a dose can have an almost immediate effect.

There are different types of dysphagia linked to issues with saliva production: the inability to form a bolus in the mouth, issues with the muscles involved in swallowing and the risk of aspiration. These issues can lead to dosage forms being manipulated to facilitate swallowing including the crushing of tablets. This can have a number of undesirable consequences depending on the nature of the drug and formulation including: stability issues, altered release characteristics, local irritation effects (to the patient and crusher), failure to reach the desired site of action, failure to deliver the correct dose and taste problems. A further consideration is the legal implications of changing the dosage form.

These consequences were studied in a care home setting by Wright (2002) and the problem remains very relevant. Viewed simplistically provision of a liquid version of the dosage form would appear to be the answer and indeed this was the view of nurses. However studies at the University of Hertfordshire consisting of in-depth PD patient interviews revealed a strong preference for solid oral dosage forms (tablets or capsules) with patches, buccal formulations, and dispersible tablets all also scoring more highly than liquids (Lefteri, 2015).

When asked what their ideal preparation would look like PD patients wanted a product which was dosed once daily, was self-administered, non-invasive and worked!

In a second phase to the study, PD patients (with a low incidence of dysphagia) were asked to evaluate a variety of mocked up placebo dosage forms and formulations. The oral route scored most highly with tablets, not larger than 6-–8 mm being preferred. Liquids again scored poorly with concerns over the ability to take the dose due to dexterity issues, general concerns over swallowing a liquid (perhaps due to inhalation risks) and issues about what to do if the dose or part of it was dropped (you can simply pick up a tablet). PD patients were similarly not keen on the various liquid dispensing systems (pouches, mixing systems etc.) and felt that they were being treated like children when given liquid formulations.

Transdermal formulations rated most highly of the non-orals (particularly if the patient was suffering from dysphagia) including sprays (arm or upper part of leg rated highest in terms of dosing areas). Roll-ons were also liked although it is difficult to see how the correct dose would be guaranteed. Interestingly research by UCB identified a preference for large transdermal patches over small ones (Hakes, 2015).

Opinion on the buccal route was mixed. Sprays were difficult to administer (particularly compared to a transdermal spray although a mouthpiece of some kind could help) and films were difficult to manipulate being too small and flimsy.

Preferences were influenced by whether the PD patient had another illness (for example asthmatics rated inhaled sprays more highly as they had experience of these) and PD patients whose disease was more advanced were generally more accepting of a range of treatments.

It should be noted that some of the dosage form preferences are linked to the strong desire to self-administer and would not necessarily be as much of an issue for a care provider.

Development of modified release formulations of PD drugs to achieve the preferred oral once-a-day dosing regimen can lead to large dosage forms and problems with swallowing. A possible NMS in PD patients is anosmia (loss of sense

of smell) which needs to be considered when developing costly and perhaps unnecessary taste-masked formulations. Tilt-tabs, a tablet shape developed by GSK consisting of a six-sided tablet with a pointed fulcrum which prevents it sitting flat on a surface, may have value to facilitate handling in PD patients but such shapes are difficult to manufacture and have somewhat gone out of fashion. The new advanced method in producing tablets of different shapes using 3-D printers could be a promising solution to this (Goyanes et al., 2015).

Before the PD patient takes their medication they need to extract it from the pack and more user-friendly pack designs can be of value but can increase the cost of the product and need to be balanced with the requirements for child-proofing. One consideration is rather than making the pack physically difficult to access, is to make it easy but somewhat tedious to access (e.g. multiple layers of packaging) and rely on the fact that children get easily bored and would give up before they get access to the medicine. A further potential approach is to use a two-part device (i.e. bottle and key for example); however, this has its own limitations (loss of the key!). The fundamental requirement when developing childproof packs is one of risk mitigation rather than complete avoidance.

The dispersible tablet formulation is an attractive one for PD patients and caters for a range of different physiological constraints as it provides the option of swallowing the tablet 'as is' or dispersing it in water.

In regards of age-appropriate formulation development for older adults, the meeting also heard about the development of a taste-masked oral suspension multi-use product suited to such patients. The formulation of this product used the shear thinning properties of hydroxypropyl cellulose as suspending agent to facilitate re-suspension, an ion-exchange resin to achieve taste masking and methyl/propyl parabens as preservatives to prevent microbial growth on storage. The potential impact of taste masking on bioavailability was reported. One of the considerations in developing this product was an acceptable mouth feel of the suspension. To ensure patient acceptability it was important to optimise the particle size of the ion-exchange resin. A particle size of >~~=~~ 150 microns gave a gritty mouth-feel, >~~90~~ 90 microns was still noticeable but <60 microns had a good mouthfeel.

Balda Medical offer a dispensing device mMTS (mechanical mini-tablet system) which fits a normal tablet bottle and can be programmed to manually dispense different numbers of (mini) tablets which makes it an attractive option for a PD patient who might struggle to swallow large tablets and manually count small tablets. Versions of the dispenser device can also notify the patient if they have missed a dose and prevent them taking multiple doses. An earlier study on using mini-tablets accompanied by a dose dispenser revealed that this could also offer the potential to improve dose flexibility and offer individualised dosing to meet the treatment needs of PD patients (Bredenberg et al., 2003).

4 New approaches in the treatment of PD

As previously indicated, the motor-symptoms of PD can currently be treated quite well ~~–~~ the problem comes when trying to treat the NMS.

Levodopa is the gold standard from treating the motor-symptoms. However, it has a short half-life and patients with late stage PD may need to take this medication up to 7 times a day. This has the consequence of creating fluctuating blood levels which when they fall below therapeutic levels cause 'off-times' with the consequent effect on the symptoms (patient may be rendered immobile or suffer debilitating motor fluctuations). Note: ~~O~~one of the impacts of this is that adherence to their medication is often less of an issue in PD patients as the consequences of missing a dose are so dire (there is a rapid clinical impact to missing a dose that reminds both patient and carer).

Various companies are developing or have recently received approval for different formulations and dosage forms of the well-established levodopa~~/~~carbidopa combination including immediate and delayed release beads in a capsule (Impax) and liquid trans-dermal formulations including a patch pump for moderate PD and a belt pump for more severe cases (NeuroDerm). Other companies are developing other PD drugs including a sub-lingual thin strip for delivery of apomorphine (Cynapsus) and a dry powder inhaled version of levodopa (Civitas).

Surgical approaches to the treatment of (late stage) PD include deep brain stimulation (high cost and not suited to all PD patients) and the Duodopa~~®~~ (AbbVie) delivery device (see above).

Glial cell-derived neurotrophic factor (GDNF) is a natural 'growth-factor' protein produced in the brain which supports the survival of many different types of brain cells including those lost to PD. The compound is being assessed in Phase 2 trials, funded by Parkinson~~'~~s UK, by infusion using catheters directly into the brain.

~~A~~Alpha-synuclein is a presynaptic neuronal protein found in brain tissue that is linked genetically and neuropathologically to PD (Stefanis, 2012). While the role of the protein in normal cellular functioning is unclear, it may be associated with the stability of cellular membranes and~~/~~or their turnover. However the protein is a key component of protein aggregates known as Lewy bodies which characterise PD. Hence pharmacological approaches to reduce the levels of the protein are under investigation include alpha-synuclein antibodies and vaccines (the latter being studied in trials funded by the Michael J. Fox Foundation).

Until the mechanism responsible for dopaminergic cell loss is identified PD research will always be somewhat restricted. As it stands there is no current pharmacotherapy that has been shown to delay disease progression.

5 Clinical investigation of medicinal products in the treatment of PD~~– –~~ a regulatory perspective

PD is relatively rare in individuals under 65 and increases thereafter with age (the incidence is 0.6% at 65~~–69 and 3.5% at 85~~ –69 and 3.5% at 85–89) and hence the EMA Geriatric Medicines Strategy (2011) is relevant. This has two principles:

- Medicines used by older patients must be of high quality, appropriately researched and evaluated: safety and efficacy studies in the relevant population… for use in a geriatric population. In other words 'evidence based medicine'. See also ICHE7 'Studies in support of special populations: geriatrics'.
- Improve the availability of information on the use of medicines for older people, thereby helping informed prescription.

The need for further action in this area is highlighted in a paper by Cerreta et al. (2012) which reports the increased use of cardiovascular (CV)~~CV~~ drugs by age but the lower inclusion of older adults in trials for these drugs. The EU Clinical Trial Regulation 536/2014 Article 6 emphasises that the clinical trial must represent the population to be treated and Annex 1 paragraph 17 point (y) states that regulatory submissions must include 'a justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or under-represented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria'.

Achieving this objective can be challenging when the desire in the clinical trial is to reduce the degree of variability.

The EMA is taking the following actions in the geriatric medicines area:

~~○~~• CHMP/PRAC/SAWP~~/~~ (Committee for Medicinal Products for Human Use/Pharmacovigilance Risk Assessment Committee/Scientific Advice Working Party)—Sponsors nominated to coordinate actions across the product lifecycle.

• Dedicated Geriatric Expert Group (GEG) which links to the Scientific Advice Working Party (SAWP)~~○~~.

• Assessment report modification, strengthening the risk management template.

~~○~~• Geriatrician on the SAWP~~○~~.

• Development of an elderly Good Pharmacovigilance Practices (GVP) module~~○~~.

• Issue of a concept paper on the need for a reflection paper on quality aspects of medicines for older people (formulation and packaging considerations)~~○~~.

• Proposal for the development of points to consider for baseline characterisation of frailty status (due for release for consultation in 3rd quarter 2015). This will reflect on the fact that chronological age (ICH E7) alone is a poor predictor of adverse events. In some ways the very old (>95) are not appropriate for inclusion in clinical trials because to have survived to this age they must have had good genes, benefited from good nutrition etc. and therefore are~~n'~~ not necessarily representative of older adults. Classification of individuals by frailty will need to take into account the following:

~~○Their physical state (the Short Physical Performance Battery (SPPB) test appears to be a good way of assessing this)○~~• (For interpretation of the references to colour in the text, the reader is referred to the web version of this article.)

• Their cognitive state (a revision to the guideline on developing products for Alzheimer~~'s is planned)○~~'s is planned).

• Their nutritional state (whether they are malnourished due to a poor diet, whether they have dysphagia, or are obese etc.)~~○~~.

• Their co-morbities (there is interest in the epidemiology of PD and how it relates to other illnesses).

The EMA hosted a dose finding workshop in December 2014 and issued a report on this in April 2015 (EMA, 2015). The workshop concluded in respect of medicines for older adults:

- That it was hard to perform a ~~P~~pharmacodynamic/PK analysis due to the insufficient numbers of the very old in studies.
- That the impact of the decline in creatinine clearance in the elderly could be assessed by the inclusion of younger patients with renal issues in clinical trials.
- That it was important to use the individual~~'~~s frailty rather than chronological age when including older adults in trials so the population studied reflects the population of use.
- That it was useful to use PBPK/Pharmacodynamic mechanistic approaches.
- That it was important to identify groups of individuals who were at greatest risk of under or over dosing (with the example being given of an elderly woman of small build who was being treated with multiple concomitant medications).
- That identification of the lowest effective dose is key to improving the tolerability of medicines in the elderly. Consider trial designs that incorporate dose titration.

Better data on older adults in clinical trials can be achieved by:

- Increased attention to unjustified exclusion criteria – it may be appropriate to include (rather than the default exclusion) patients with comorbidities who are on other medications.
- Encouraging clinical trial designs which are older person-friendly to avoid unintentional exclusion (i.e. less complicated designs reducing the burden of assessments etc.).
- Having an early dialogue with the Regulatory Agency is essential (particularly with respect to 'challenging the exclusion criteria', potential drug–drug interactions and study design.

The EMA have published guidance (2012) on the clinical investigation of medicinal products in the treatment of Parkinson's disease. This makes recommendations for the conduct of clinical trials in PD. These are particularly difficult due to the slow progressive course of the disease, the heterogeneity of symptoms and their change in severity over the course of a day related to the time of medication, co-morbidities and co-medications. Clinical trials may need to last >5 years depending on the stage of PD that the drug is designed to address.

During a Q&A session the presenters were asked whether the regulation of medicines for older adults might follow a similar route to that for paediatric products with the requirement for Paediatric Investigation Ppaediatric investigation plans (PIPS) and incentives to develop such products. It was pointed out that the largest consumers of medicines were older adults and hence there was already a strong market driven incentive for pharma companies to develop such products.

A further question asked whether the innovator company would have to demonstrate a patient- centric design approach for their products (i.e. was their product user friendly?). This would typically be assessed during the clinical trial as any difficulty taking the product could negatively impact the trial outcome. However, what has to be considered is the fact that the clinical trial can be a tightly controlled environment which doesn' not reflect how the product might be used in the 'real world'. For this reason as products become more complicated there is an increased need for handling studies and clear patient instruction leaflets (package inserts).

In conclusion, PD is a debilitating neurodegenerative disease with no known cure. While medication for the motor symptoms dramatically improves the lives of sufferers, there are many opportunities to improve the treatments. The NMS of PD are less easily diagnosed and treated and can have an equally devastating impact. While there are a number of initiatives underway and guidelines in development, there remains much to do and the pharmaceutical scientist can play an important role to simplify the dosing schedules, target treatments directly to the brain and make medicines more suited to the PD patients' needs and capabilities.

Uncited referencesEMA (2012), EMA (2015).AcknowledgementAcknowledgements

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