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PERSPECTIVE

Establishing apomorphine treatment in Thailand: understanding the challenges and opportunities of Parkinson's disease management in developing countries

Roongroj Bhidayasiri[a], Onanong Phokaewvarangkul[a], Karn Sakdisornchai[a], Kamolwan Boonpang[a], K. Ray Chaudhuri[b], Jan Parsons[c], Praween Lolekha[d], Parnsiri Chairangsaris[e], Prachaya Srivanitchapoom[f], Sharon Benedierks[g], Pattamon Panyakaew[a], Thanatat Boonmongkol[a], Yuwadee Thongchuam[a], Nitinan Kantachadvanich[a], Saisamorn Phumphid[a], Andrew H. Evans[h], Akravudh Viriyavejakul[i], Apichart Pisarnpong[f], Teus van Laar[j] and Priya Jagota[a]

[a]Chulalongkorn Centre of Excellence for Parkinson's Disease & Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand; [b]The Maurice Wohl Clinical Neuroscience Institute, King's College London and National Parkinson Foundation Centre of Excellence, King's College Hospital, London, UK; [c]The Walton Centre for Neurology and Neurosurgery, Liverpool, UK; [d]Division of Neurology, Department of Medicine, Thammasat University Hospital, Pathumthani, Thailand; [e]Division of Neurology, Department of Medicine, Phra Mongkutklao Hospital, Bangkok, Thailand; [f]Division of Neurology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [g]Stada Pharmaceuticals, Sydney, Australia; [h]Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia; [i]Prasat Neurological Institute, Bangkok, Thailand; [j]Department of Neurology, University of Groningen, Groningen, The Netherlands

ABSTRACT

Introduction: The increasing global burden of Parkinson's disease (PD) poses a particular challenge for developing countries, such as Thailand, when delivering care to a geographically diverse populace with limited resources, often compounded by a lack of expertise in the use of certain PD medications, such as device-aided therapies (DAT).

Areas covered: A panel of local, regional, and international PD experts convened to review the unmet needs of PD in Thailand and share insights into effective delivery of DAT, focusing on experience with apomorphine infusion. Despite its proven efficacy and safety, implementation of apomorphine infusion as a new option was not straightforward. This has prompted a range of health-care professional and patient-focused initiatives, led by the Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders in Bangkok, to help establish a more coordinated approach to PD management throughout the country and ensure patients have access to suitable treatments.

Expert opinion: Overcoming the challenges of education, proficiency, resource capacity and standard of care for PD patients in developing countries requires a coordinated effort both nationally and beyond. The best practices identified in Thailand following the introduction of apomorphine infusion might be helpful for other countries when implementing similar programs.

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Parkinson's disease; apomorphine infusion; motor complications; Thailand; developing countries; device-aided therapy; Parkinson's disease nurse specialists; treatment accessibility; specialist centers

1. Introduction

Thailand is a developing country with an upper-middle-income economy, a diverse population distribution, and limited health-care resources to manage its expanding population of people with Parkinson's disease (PD) [1–3]. There is therefore an urgent need for clear, explicit, evidence-based pathways of care for PD patients, especially in the case of device-aided therapies (DAT), such as apomorphine infusion, to ensure their acceptance, accessibility, and widespread use.

In order to review the unmet therapeutic needs of PD in Thailand and to share insights into how to effectively manage delivery of DAT in this setting, a panel of carefully selected local, regional, and international PD experts were invited to participate in a one-day meeting in May 2019 in Bangkok, Thailand. This took place immediately prior to an Apomorphine Masterclass where all panel members were serving as faculty or expert commentators. Expert Panel included 15 board-certified neurologists with a special interest in PD (12 from Thailand with the rest from UK, the Netherlands, and Australia) as well as 5 PD Specialist Nurses (3 from Thailand and the rest from UK and Australia) and were all invited based on their experience of using apomorphine treatment within Thailand, international experience as clinical trial investigators, or nursing experience in studies related to apomorphine.

Apomorphine infusion was first introduced into Thailand in 2014 which provides a unique opportunity to follow the uptake and use of this therapy by Thai patients and to share experience of its implementation into the PD treatment pathway. In Thailand, apomorphine is available in two formulations – either as an intermittent injection or a continuous infusion – for PD patients with the indication of intractable motor fluctuations who do not adequately respond to optimal oral therapy. This article summarizes the Expert Panel's discussions on the challenges of PD management in developing

CONTACT Roongroj Bhidayasiri rbh@chulapd.org Chulalongkorn Centre of Excellence for Parkinson's Disease and Related Disorders, Chulalongkorn University Hospital, Bangkok 10330, Thailand

Article highlights

- The increasing global burden of Parkinson's disease (PD) represents a significant public health challenge, particularly for developing countries.
- Thailand is an example of a developing country with a diverse population distribution and limited health-care resources to manage this expanding PD population.
- With the projected increase in the number of PD cases, access to device-aided therapies (DAT) will be in greater demand; however, DAT are not available at all centers in Thailand and experience with them is often limited.
- A panel of PD experts convened to review the unmet needs of PD in Thailand and share insights into effective delivery of DAT, focusing on experience with the introduction of apomorphine infusion in Thailand since 2014.
- Led by the Chulalongkorn Centre of Excellence for Parkinson's Disease and Related Disorders in Bangkok, a range of initiatives has now been established both for health-care professionals and patients to improve PD education and to gain experience with apomorphine infusion that can be used as a model for other countries.
- Adoption of apomorphine infusion in Thailand requires a pro-active approach to peer-to-peer education and patient engagement to ensure confident prescribing and persistence with treatment, however, access to therapy with an extremely diverse population will remain an ongoing challenge.
- 'Team' approach to PD care is the ideal scenario for implementing apomorphine infusion in a new environment but the feasibility of this will be dictated by local resources, so capacity building is something that needs to be addressed.
- Increased evidence regarding the efficacy, safety, and cost-effectiveness of apomorphine infusion in Thailand, and in different geographical regions, is of value to help demonstrate for which patients it is suitable and how treatment can be optimized in actual clinical practice, as opposed to a clinical trial setting.

countries focusing on Thailand's experience of the introduction of apomorphine infusion and how it has addressed some of these issues. It is hoped that the challenges and best practices identified along this journey might be used as examples for other countries and regions implementing similar programs.

2. The escalating global burden of PD

Improvements in population health and life expectancy in many areas of the world mean that people are now living longer than ever before, but alongside these benefits comes the challenge of an increase in the burden of chronic diseases. A systematic analysis of data from the Global Burden of Disease Study 2016 found that neurological disorders, including Parkinson's disease (PD), are a leading cause of disability and death worldwide and related to increases in population numbers and longevity [4].

A survey of published studies of the prevalence of PD in the world's 10 most populous nations has reported that the number of individuals with PD over the age of 50 years in these countries is predicted to double from between 4.1 and 4.6 million in 2005 to between 8.7 and 9.3 million by 2030 [3], and to exceed 17 million worldwide by 2040 [5], representing a significant public health challenge. It is recognized that analyses such as this of the combined results from individual studies with inherent methodological differences and other confounding factors have its limitations; however, it is suggested that these figures are probably an underestimate of the true future numbers [6]. In addition to population dynamics, other factors that are thought to contribute to the ongoing rise in PD prevalence, including the decline in smoking rates and exposure to the by-products of industrial expansion [5].

3. The impact of increasing PD burden on developing countries

Predictions suggest that the most substantial increases will be seen outside of the Western world, in countries such as China, Indonesia, and India, primarily due to their more rapid population increases, in particular of individuals over 65 years of age [3,5]. Epidemiological studies of PD in small, developing countries are limited. However, it is likely that the number of PD patients will increase in a similar manner to that predicted for India and Indonesia. One project that aims to provide a more accurate insight into the distribution and prevalence of PD in Thailand, and also underlying risk factors, is the Thailand Parkinson's Disease Registry which started collecting data in 2008 [7]. A report of the registry's findings in 2011 identified significant under-reporting of PD and suggested a crude and age-adjusted prevalence of 95.34 and 424.57 cases/100,000 population, respectively, with a significantly higher prevalence in urban versus rural areas [7]. In common with other studies globally, urbanization and, in particular, exposure to pesticides, were identified as possible risk factors for PD in the Thai population [7,8]. The continued use of these agents is therefore likely to contribute to high future number of PD patients around the world.

In developing countries, advances in economic conditions and improvements in health-care provision for PD, such as the establishment of specialist movement disorders centers, may result in an increased knowledge and awareness of the condition, and also in the survival of individuals with PD, which will likely be a contributing factor to the increase in its prevalence in these regions [9]. Many developing countries currently lack the resources and infrastructure to allow the diagnosis and effective treatment of people with PD, and as such represent another, as yet 'unidentified,' population of patients who will also require health-care provision in the near future. As such, Thailand provides a timely example of a currently developing country facing considerable challenges managing PD patients with limited resources and problems of accessibility to a full range of treatment options.

4. Global therapeutic challenges in PD

From the global perspective, while effective strategies are available in many countries for the symptomatic management of PD that allow people to enjoy a good quality of life with their condition, there are still many challenges [10]. Levodopa remains the 'gold standard' PD therapy and for many years research has focused on developing alternative and improved oral medications. However, it is now recognized that gastrointestinal (GI) dysfunction is common in PD and that this can significantly impact oral medication absorption and effectiveness [11,12]. This has highlighted the need for non-oral therapeutic options for PD patients that can bypass the GI route of administration, in order to provide effective resolution of OFF time and control of motor complications [10,13].

Newer oral medications, often with long-acting formulations, have been developed; however, the common limitations of oral/transdermal PD medications – namely absorption and reduced bioavailability, often due to underlying gastrointestinal dysfunction – are still not being fully addressed [13]. In addition, despite progress in our understanding of the underlying pathology of PD, as yet, no neuroprotective or disease-modifying therapy has been identified, and so treatment relies on symptomatic management of both motor and non-motor disease symptoms [14]. PD is a progressive disease and at least 30–50% of PD patients at most PD centers develop motor fluctuations, despite being under care of movement disorder specialists and receiving optimized oral/transdermal medication [15,16]. While this number reflects reports from major academic centers in Western countries, it is also likely that similar number of patients with these debilitating symptoms also occur in developing countries.

The escalating population base of PD and the expected natural history of the condition, progressing from a prodromal stage to early, stable and then unstable stages will necessitate an increasing requirement for long-term treatment of advanced disease using DAT, namely subcutaneous apomorphine infusion, levodopa–carbidopa intestinal gel (LCIG) infusion or deep brain stimulation (DBS) [17–19]. In line with the population dynamics described above, the demand for such therapies is likely to increase in many Asian countries, including Thailand.

With a complex and progressive disease like PD, patients have multiple needs that change over time [20–22]. It has therefore been suggested that the 'ideal' scenario for PD patient care should involve a coordinated multidisciplinary team (MDT) of health-care professionals – including, among others, neurologists, specialist PD nurses, speech and language therapists, and physiotherapists – who can provide their individual, specialist expertise as needed along the patient journey [23–25]. However, achieving this proposed optimal standard of care is often a considerable challenge in less developed countries, like Thailand, particularly due to accessibility issues for patients [26]. While teaching hospitals and specialist centers may be established in these countries, they are generally located in major cities, which creates a significant problem in terms of access for rural or remote populations outside of these urban settings.

While provision of such MDT services may seem like a considerable health-care expense, the efficacy of this approach is currently being explored and has shown some initial promising results regarding patient outcomes [25,27–30]. A retrospective study of over 138,000 PD cases found that specialist neurologist care of PD patients is associated with improvements in some clinical outcomes and also has benefits in terms of survival [31]. Regular neurologist care is also associated with a lower risk of costly hospitalization [32].

5. Current pathways and recent developments in Parkinson's disease management in Thailand

Thailand is currently evolving an effective pathway and standardized protocols for the provision of PD services to its diverse population. The country has a total population of around 67 million people distributed over 77 different provinces; around 64% of citizens live in rural areas [7]. The country is served by a total of 1,384 hospitals which includes 28 regional hospitals (2%), 88 general hospitals (6%), 775 community hospitals (56%), and 321 private hospitals (23%) [33]. However, only around 11% of hospitals have a specialist neurology clinic and the vast majority of PD patients (62%) are treated in the community setting by general practitioners [33].

Thailand currently has five types of oral/transdermal medications available for prescription to PD patients (levodopa/levodopa–carbidopa, dopamine agonists, monoamine oxidase type B [MAOB] inhibitors, catechol-O-methyltransferase [COMT] inhibitors, and anticholinergics) (Table 1) [34]. In addition, subcutaneous apomorphine injection (an intermittent rescue therapy) and two infusion therapies (LCIG or subcutaneous apomorphine infusion) are available, plus surgical treatment options in the form of pallidotomy or DBS [34]. National PD treatment guidelines have been published to aid health-care professionals in the selection of suitable treatments (Figure 1) [35].

Health-care professionals in the PD community in Thailand are supported by two professional societies: The Thai Parkinson's Disease–Movement Disorders Society (Thai PDMDS) and the Neurological Society of Thailand. The Thai PDMDS was founded in 1997 by a group of doctors who were interested in PD and has since expanded to address the personal and social consequences of PD and movement disorders through various educational activities, scientific research, community advocacy, and efforts to increase public knowledge and awareness in both urban and remote communities. They aim to provide ongoing knowledge development opportunities for health-care professionals by holding a regular annual conference on PD and movement disorders. Cooperation and coordination with other major societies and organizations related to PD and movement disorders including both within and outside the country is also encouraged in order to share experiences and best practices. The range of educational materials produced by the Thai PDMDS is aimed at both health-care teams and patients and focuses on easy accessibility.

In terms of specialist centers in Thailand, the Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders in Bangkok (www.chulapd.org; ChulaPD) is established as the only dedicated tertiary center for PD in the country and has a national network supported via the Thai Red Cross Society [26]. In collaboration with the Ministry of Public Health of Thailand, the Thai National Health Security Office and Bangkok Metropolitan Administration, in 2008 ChulaPD initiated the nationwide PD Registry mentioned previously, one of the aims of which was to evaluate the prevalence of PD in the country [7]. A further research initiative undertaken at ChulaPD to determine the availability of anti-PD medications within the different provinces and regions of Thailand [33]. Questionnaires were sent to Hospital Directors at 1,384 hospitals in all 77 provinces throughout Thailand. The results demonstrated extreme diversity in availability of the five oral/transdermal drug types throughout the country. All 77 provinces have access to oral levodopa and anticholinergics but the availability of dopamine agonists, MAOB and COMT inhibitors is much more variable, with only 17 provinces having availability of all five oral/transdermal anti-PD drug types (Figure 2). Most hospitals where all drug types are available are located in the central region of the country, with only 17% of

Table 1. Availability of anti-parkinsonian medications in Thailand (National Median Drug Price: 5 April 2019, accessed 26 April 2020).

Drug class	Drug generic name	Dosage available	Preparation	Route of administration	Price (THB)	Price ($USD)	Reimbursement
Anticholinergics	Trihexyphenidyl hydrochloride	2 mg	Tab	Oral route	0.21	0.0065	UCS, SSS, OFC
	Trihexyphenidyl hydrochloride	5 mg	Tab	Oral route	0.34	0.010	UCS, SSS, OFC
Levodopa/DDCI	Levodopa + Carbidopa	100 mg + 25 mg	Tab	Oral route	3.85	0.12	UCS, SSS, OFC
	Levodopa + Carbidopa	250 mg + 25 mg	Tab	Oral route	4.17	0.13	UCS, SSS, OFC
	Levodopa + Carbidopa	20 mg + 5 mg per 1 ml	Gel	Intestinal route	4,547.50	140.18	None
	Levodopa + Benserazide hydrochloride	100 mg + 25 mg	Tab (Dispersible tab)	Oral route	7.21	0.22	UCS, SSS, OFC
	Levodopa + Benserazide hydrochloride	200 mg + 50 mg	Tab	Oral route	8.29	0.26	UCS, SSS, OFC
	Levodopa + Benserazide hydrochloride	100 mg + 25 mg	Cap	Oral route	4.15	0.13	UCS, SSS, OFC
	Levodopa + Benserazide hydrochloride	100 mg + 25 mg	Cap (Controlled release cap)	Oral route	6.83	0.21	UCS, SSS, OFC
	Levodopa + Carbidopa + Entacapone	50 mg + 12.5 mg + 200 mg	Tab	Oral route	34.78	1.07	OFC
	Levodopa + Carbidopa + Entacapone	100 mg + 25 mg + 200 mg	Tab	Oral route	36.70	1.13	OFC
	Levodopa + Carbidopa + Entacapone	150 mg + 37.5 mg + 200 mg	Tab	Oral route	38.63	1.19	OFC
	Levodopa + Carbidopa + Entacapone	200 mg + 50 mg + 200 mg	Tab	Oral route	40.55	1.25	OFC
COMT inhibitors	Entacapone	200 mg	Tab	Oral route	32.85	1.01	UCS, SSS, OFC
Dopamine agonists	Apomorphine hydrochloride	10 mg/ml (3 ml per pen)	Pre-filled pen injection	Subcutaneous injection	1,104.28	34.04	OFC
	Apomorphine hydrochloride	10 mg/ml (5 ml per ampule)	Sterile solution	Subcutaneous injection	560.00	17.26	OFC
	Benzatropine mesilate	1 mg/ml (2 ml per vial)	Sterile solution	Intravenous route	250.00	7.71	UCS, SSS, OFC
	Bromocriptine mesilate	2.5 mg	Tab	Oral route	6.46	0.20	UCS, SSS, OFC
	Piribedil	50 mg	Tab (Slow release tab)	Oral route	12.84	0.40	OFC
	Pramipexole hydrochloride	0.125 mg	Tab	Oral route	7.31	0.23	OFC
	Pramipexole hydrochloride	0.25 mg	Tab	Oral route	14.62	0.45	OFC
	Pramipexole hydrochloride	1 mg	Tab	Oral route	50.00	1.54	OFC
	Pramipexole hydrochloride	0.375 mg	Tab (Slow release tab)	Oral route	33.00	1.02	OFC
	Pramipexole hydrochloride	0.75 mg	Tab (Slow release tab)	Oral route	33.00	1.02	OFC
	Pramipexole hydrochloride	1.5 mg	Tab (Slow release tab)	Oral route	100.00	3.08	OFC
	Pramipexole hydrochloride	3 mg	Tab (Slow release tab)	Oral route	100.00	3.08	OFC
	Ropinirole hydrochloride	2 mg	Tab (Prolonged release tab)	Oral route	10.70	0.33	UCS, SSS, OFC
	Ropinirole hydrochloride	4 mg	Tab (Prolonged release tab)	Oral route	21.40	0.66	UCS, SSS, OFC
	Ropinirole hydrochloride	8 mg	Tab (Prolonged release tab)	Oral route	42.80	1.32	UCS, SSS, OFC
	Rotigotine	2 mg/24 hr	Transdermal patch	Transdermal route	128.88	3.97	OFC
	Rotigotine	4 mg/24 hr	Transdermal patch	Transdermal route	143.40	4.42	OFC
	Rotigotine	6 mg/24 hr	Transdermal patch	Transdermal route	166.63	5.14	OFC
	Rotigotine	8 mg/24 hr	Transdermal patch	Transdermal route	204.75	6.31	OFC
MAOB inhibitors	Rasagiline mesylate	1 mg	Tab	Oral route	192.12	5.92	OFC
	Selegiline hydrochloride	5 mg	Tab	Oral route	8.00	0.25	OFC

UCS: Universal Coverage Scheme; SSS: Social Security Scheme; OFC: Governmental or State Enterprise Officer
1 USD = 32.44 THB (Exchange rate on 26 April 2020).

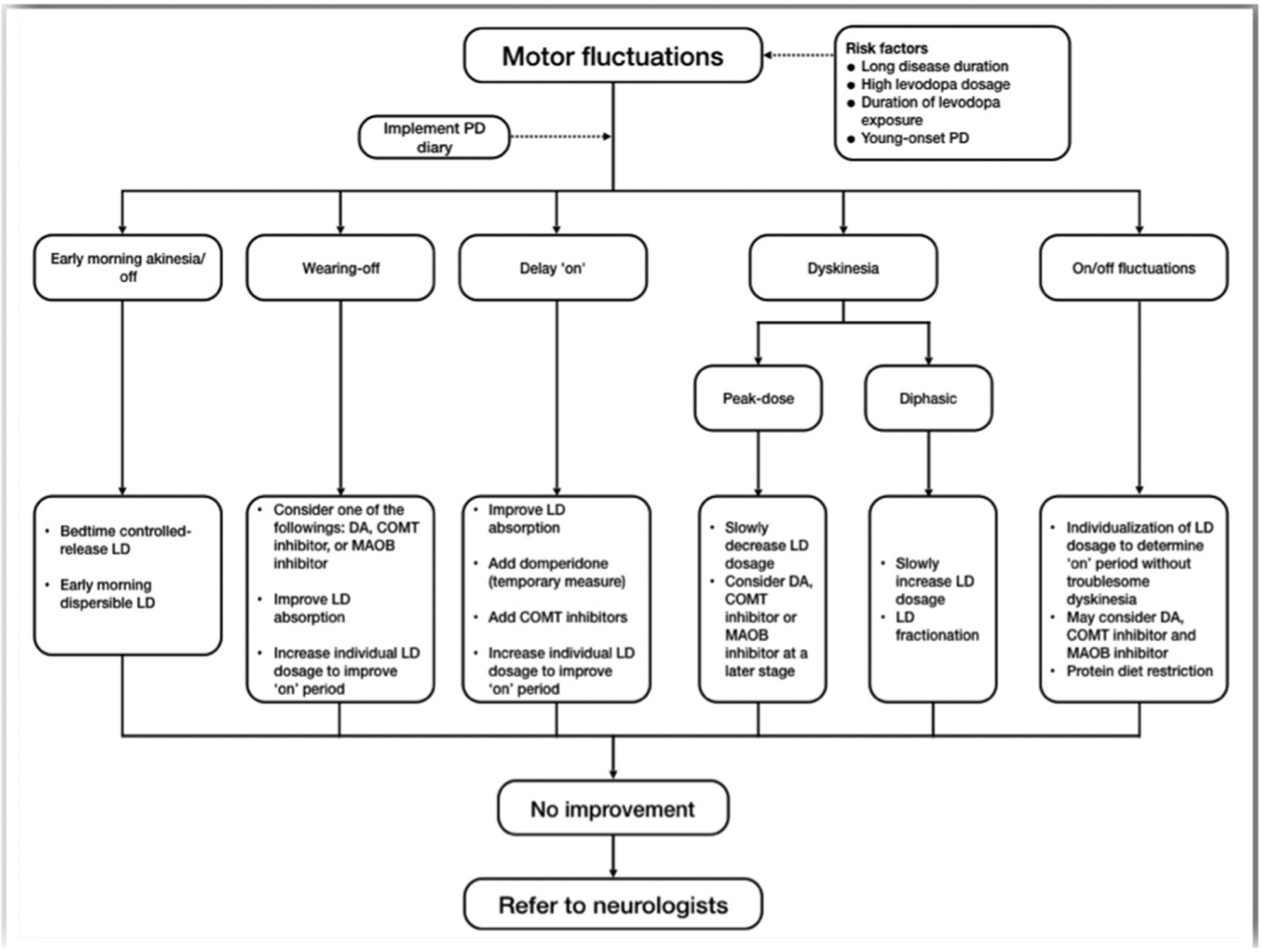

Figure 1. Overview of the PD treatment guidelines in Thailand.

hospitals in the south and 8% of hospitals in the north and northeast of the country having complete availability of anti-PD drugs in their hospital drug lists. Most hospitals with complete lists of all available anti-parkinsonian medications are usually University teaching hospitals, main regional hospitals for referrals, and major general hospitals in large cities in Thailand.

It is apparent from these data that despite considerable progress in Thailand in recent years, there are still significant unmet needs in PD and its treatment [36]. As noted, these include the wide variation in the availability of the standard oral/transdermal PD medication in different provinces and regions of Thailand meaning that many PD patients may not receive the best therapy to meet their particular needs [33]. Added to this, there is often limited availability of DAT, and the experience of how best to use them, in many centers. Most PD patients in Thailand are treated by general practitioners or internists, rather than neurologists or movement disorders specialists, who may not have the knowledge or skills to determine the most appropriate diagnosis and treatment for PD patients [7,36]. Even those who have access to specialists may be faced with long waiting lists and also significant challenges related to travel to these centers, as most patients do not live in urban areas [7].

6. Device-aided PD therapies in Thailand – the introduction of apomorphine infusion

All three DAT – apomorphine infusion, LCIG, and DBS – are available in Thailand as treatment options for suitable patients but, as mentioned, not all are accessible to patients at every center [36,37]. Most are limited to University Hospitals; uptake at other centers is limited by the lack of training opportunities for health-care professionals to gain experience in their use, and due to challenges in terms of reimbursement. DAT have a valuable role to play in the PD treatment paradigm when patients develop persistent motor fluctuations that can no longer be adequately controlled by optimized oral/transdermal medication, so their wider availability would be of considerable benefit to PD patients [38].

f the three DAT options available, continuous subcutaneous apomorphine infusion is the least invasive, and is also easily reversible, while the other two options require surgery [18,38]. Apomorphine has been used in clinical practice for many years around the world and has proved to be effective and well tolerated for the management of motor fluctuations and dyskinesias in a range of open-label studies [39–42]. Due to its name,

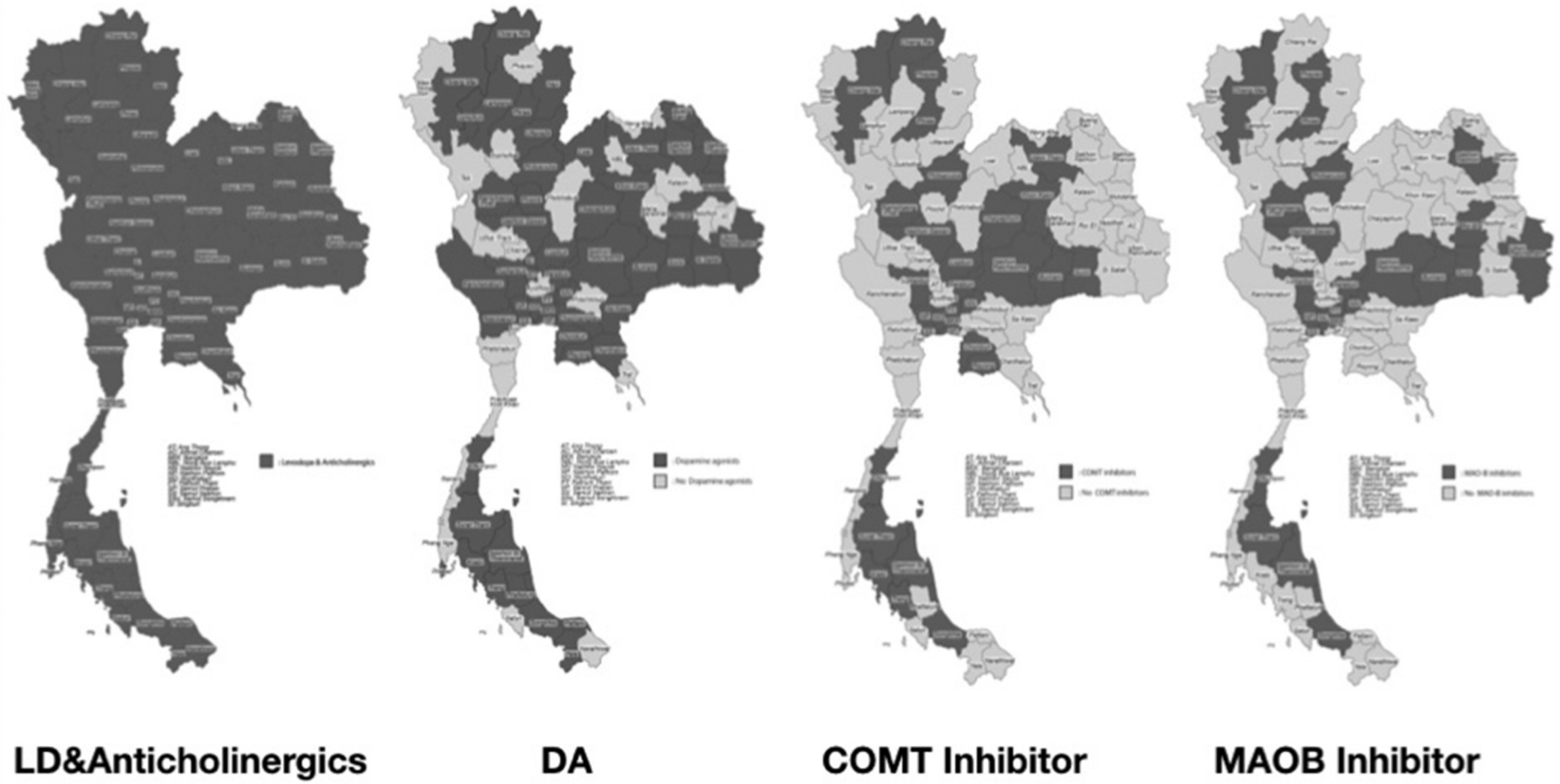

Figure 2. Availability of different PD medication types in Thailand.

COMT, catechol-O-methyltransferase; DA, dopamine agonist; LD, levodopa; MAOB, monoamine oxidase B.

a common misperception is that 'apomorphine' has similar effects to 'morphine' but both clinicians and patients alike should be made aware that, unlike morphine, apomorphine has no narcotic properties [43,44]. While there is no formal study documenting this misconception in Thailand, it was raised by Thai Experts Panel members as a common issue in their clinical practice experience.

Treatment with apomorphine infusion has been shown to allow patients to reduce their intake of oral therapy, thus minimizing the overall PD medication burden [44,45]. As a result, apomorphine infusion is included as a treatment option for PD patients with motor fluctuations in the International Parkinson and Movement Disorder Society evidence-based medicine review [46]. More recently, Level 1 evidence of the efficacy and safety of apomorphine infusion have been provided by the TOLEDO study, the first prospective, randomized, double-blind, placebo-controlled trial of the product. Results of TOLEDO confirmed that treatment of PD patients who are experiencing persistent motor fluctuations despite receiving optimized oral/transdermal medication with apomorphine infusion leads to a significant improvement in OFF time with a corresponding improvement in good ON time [45].

6.1. Suitable candidates for apomorphine infusion

Clinical experience and controlled clinical trial evidence demonstrate that apomorphine infusion can be a useful treatment option in suitable patients, when repeated adjustments to oral medications no longer provide adequate motor control and their quality of life is being adversely affected [47]. Subcutaneous delivery means that it avoids the GI route [11,13]. In addition, continuous dopaminergic stimulation, or CDS, which apomorphine infusion and other continuous drug delivery (CDD) therapies aim to provide, is thought to achieve a more physiological stimulation of postsynaptic neurons than that seen with intermittently administered oral therapies [47–49].

Once patients become refractory to oral/transdermal medication, the decision as to which DAT, or CDD, therapy to use is an individual one and should be decided in a consultation between the health-care provider and the patient, taking their personal circumstances and preferences into account. No head-to-head comparative studies have been undertaken on the three available CDD therapies, however, to aid clinicians in the choice of treatment, expert consensus guidelines and reviews of available evidence have been produced which summarize what patients are best suited to each option [50–52]. Suitable candidates for apomorphine infusion therapy are summarized in Table 2 [39]. Often, DAT are not considered until late-stage disease when in fact they can be of substantial benefit earlier in the disease course. In the UK, guidelines produced by the National Institute for Health and Care Excellence (NICE) position apomorphine as part of 'best medical therapy' alongside oral/transdermal treatments and before considering surgical options, such as LCIG or DBS [53].

Table 2. Suitable candidates for treatment with apomorphine infusion [40].

Suitable candidates for apomorphine infusion
Patients with motor complications (particularly motor fluctuations with frequent and prolonged OFF periods) who do not obtain adequate control despite optimized oral/transdermal treatment
Patients who do not wish to receive DBS or do not fulfill the selection criteria for that surgical procedure
Those in whom rescue doses of apomorphine intermittent injection are effective but are either required more than 5 to 6 times per day or are associated with peak effect dyskinesia (note: patients do not have to be treated previously with apomorphine injection to be suitable for apomorphine infusion)
Patients who have swallowing difficulties that may interfere with their ability to adhere to an oral medication regimen
Patients who experience gastrointestinal problems such as delayed gastric emptying (gastroparesis), which can impact the delivery or oral medications to the small intestine and therefore limit their clinical efficacy

6.2. Starting patients on apomorphine infusion

In common with other DAT for PD, starting patients on apomorphine infusion therapy is usually undertaken in a hospital setting; however, the initiation procedure can be on either an in-patient or out-patient day-case basis (as is done at ChulaPD), depending on the facilities available [39,40]. When apomorphine infusion was first introduced, in-patient initiation was usually undertaken. Over time, as experience has been gained with a greater number of cases, the practice is now to initiate apomorphine infusion as a PD day-case in order to offer convenience to patients and their families. Moreover, day-care setting provides an opportunity for health-care professionals to provide education related to apomorphine and train patients and carers on certain techniques related to the device and injection [54]. However, in-patient initiation is still considered the norm in some countries depending on the local set-up and availabilities of resources.

Although apomorphine infusion is recognized as an effective therapy to reduce OFF time and increase 'good' ON time [39,50], for some neurologists the perceived complexities surrounding the selection of suitable patients, the subcutaneous route of administration, and the device itself may be barriers to using this approach [55]. A recent survey amongst Thai neurological medical professionals identified several misconceptions in their general knowledge of apomorphine therapy, practical skills, understanding of how to manage adverse events, and ability to troubleshoot issues (personal communication with Dr. Phokaewvarangkul). The five most common misconceptions concerned dyskinesia from intermittent apomorphine injection, the suitable concentration of apomorphine dilutions, continuation of previous oral dopamine agonists during titration periods, and possible `side effects of apomorphine. This highlights the importance of continuing medical education, particularly the need for mandatory PD-specific training among neurologists.

Therefore, practical guidance for clinicians and PD nurses on effective delivery of apomorphine therapy has been published and include recommendations for pre-treatment patient assessment, the use of anti-emetic medication, titration to optimal dose, reduction of oral PD medications, and follow-up of patients [40,56,57]. The challenge for health-care providers in Thailand is how to implement effective apomorphine services in a range of different centers where resources are limited, and for patients, it is gaining access to this therapy now that it is an option available to them.

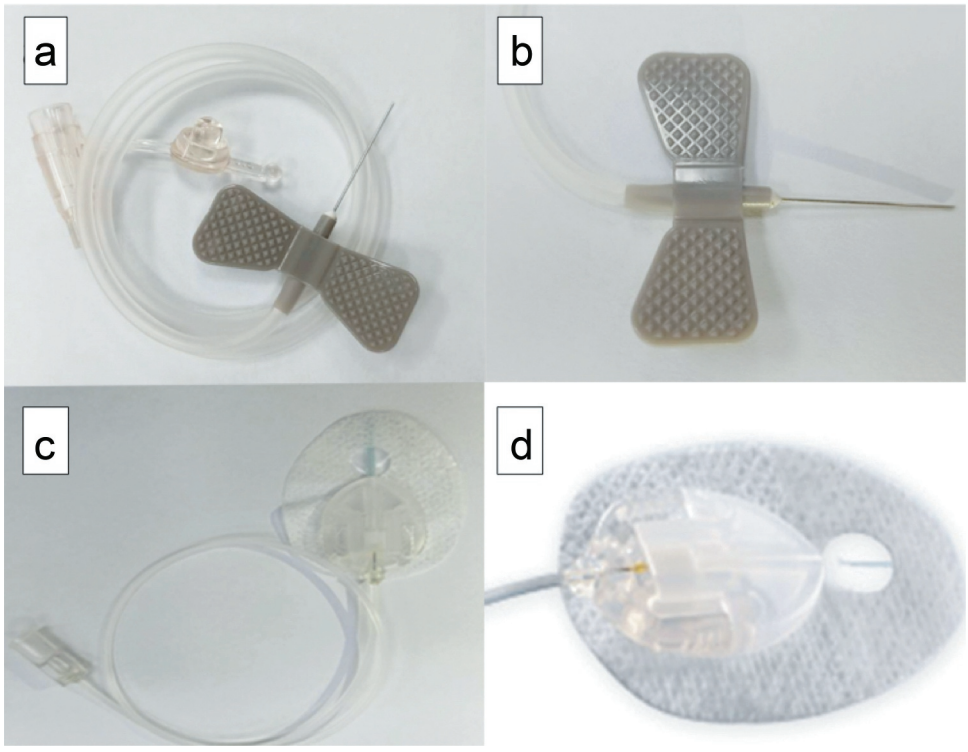

Figure 3. Comparison of the butterfly and Neria infusion sets: (a) butterfly infusion set, (b) close-up of stainless-steel needle, (c) Neria infusion set, (d) close-up of Neria needle.

6.3. Adverse events related to apomorphine infusion

The potential for adverse events is often cited as a barrier to the use of apomorphine infusion. One important reason for this is probably a perception of difficulty in managing the infusion, including management of its adverse events. In a long-term retrospective study involving 166 PD patients with apomorphine infusion, only one in 10 patients discontinued because of secondary side effects [58]. In the TOLEDO study, apomorphine infusion was shown to be well tolerated and most adverse events, although found to be common (93%), were mild-to-moderate in intensity, ranging from skin nodules (44%), nausea (22%), and somnolence (22%) with no deaths occurred during the study [45]. Severe adverse events were noted in 6% of patients, including severe hypotension, intermittent confusion, and severe cellulitis. Although adverse events may develop, they are mostly manageable if patients, caregivers, and nurses work as a team to actively manage them as early as possible [59]. For example, good injection practice can potentially minimize nodule formation [60].

6.4. Persistence with therapy

One of the benefits of apomorphine infusion is that it is minimally invasive however a downside of this is that it is easy for patients to discontinue treatment if they experience or perceive difficulties [55,61,62]. To get the full benefits of apomorphine therapy, patients should adhere to treatment over the long term [63]. Many of the issues that arise when starting apomorphine infusion treatment, such as skin problems at the injection site, often result in patients stopping therapy unnecessarily, when in fact they are easily manageable. Successful long-term continuation of patients on apomorphine infusion therapy has been shown to benefit from a MDT approach, including regular patient follow-up and assessment, and prompt resolution of any queries and concerns that arise [64].

A study undertaken to evaluate reasons for discontinuation of apomorphine therapy at specialist centers in Spain and Thailand revealed that the type of needle used for infusion may also have a role to play [55]. Experience in Thailand, where all patients use standard winged infusion set with a stainless-steel cannula, shows that the presence of this steel cannula throughout the period of infusion can potentially cause patient's discomfort at the injection site. This is in contrast to the softer Neria needles – not currently available in Thailand – where the stainless-steel guide is only used during needle insertion and therefore may be more acceptable to patients (Figure 3).

Although unproven, there may be differences in response to apomorphine infusion therapy between Caucasian subjects and Asian subjects, not only in terms of clinical effect also in terms of possible side effects, such as skin tolerability. Similar adverse events related to infusion sets/catheters have also been observed in diabetic patients with continuous subcutaneous insulin infusion [65]. Therefore, neurologists should be extra-cautious for possible increased dermatological adverse events in certain subgroups of PD patients with coexisted disorders, such as diabetes mellitus, for apomorphine infusion. Geographical location may also have a role to play here with warmer climates increasing the likelihood of skin reactions; however, this is hypothetical and as yet unproven. This

highlights the need for a truly 'personalized' approach to PD management taking into account all the individual patient's characteristics [66]. It also demonstrates the importance of educating patients about strategies to ensure optimal injection technique and good skin hygiene [54,56,60]. According to the expert consensus, the recommendations for the management of common skin reaction (skin nodules) could include rotation of the choice of infusion sites, use of Teflon needles, adjusting delivery through the skin at an optimal angle (45–-90°), choosing a lower concentration, massaging the infusion site, applying ultrasound treatment, and use of silicone gel dressings [39].

6.5. Challenges with the introduction of apomorphine infusion

Despite its proven utility as a valuable PD treatment, implementation of apomorphine infusion as a new treatment option in Thailand was not straightforward, and there were many challenges along the way. Studies have shown that within Thailand there are often considerable gaps in the knowledge of not only patients but also health-care professionals about PD and its treatment [67,68]. Both groups were found to have certain misconceptions about the disease, its course and prognosis, and appropriate treatment, highlighting the need for both professional and community education. Added to this, in the case of apomorphine infusion, the lack of availability of specialists with experience in its use, and also training centers where this knowledge could be shared, was an issue for widespread uptake. This meant that, initially at least, access for patients was restricted to those who were referred to specialist centers and could travel to them for treatment.

Currently, apomorphine is not listed as an essential drug in the Thai FDA guidelines, and is therefore not universally available to all Thai patients. Apomorphine infusion treatment is only reimbursed in major academic centers in Thailand when patients are under care of movement disorders specialists and have the availability of supporting team. However, it should be noted that while DAT, such as apomorphine infusion should be universally accessible, they should not in fact be universally prescribed to every PD patient, only to those who fulfill the suitability criteria. It is therefore critical for successful treatment with apomorphine infusion that a care pathway is in place such that suitable patients are selected and referred on to centers with experience in delivering apomorphine therapy. Treatment can then be initiated and patients followed-up in a joint care plan between local physicians and movement disorders neurologists. The greatest benefits of this treatment are fully realized when suitable patients are carefully selected under the care of specialists. In addition, the long-term success of apomorphine infusion is also best when the patient has the availability of a supportive health-care team and good family or carer network [55,62].

7. Meeting the challenges of Parkinson's disease care in Thailand

The challenges identified during the introduction of apomorphine infusion into Thailand and the desire to implement a more coordinated and inclusive approach to PD treatment in the country as a whole, have prompted a range of initiatives, led by ChulaPD. It is recognized that providing continuing educational programs are one means to address the challenge of knowledge gaps identified in clinicians [69]. Clinician education and training programs have been established at ChulaPD over the last 12 years which focus on developing new PD specialists through fellowship training and PD specialist nurse training.

These initiatives include a two-year Movement Disorders Fellowship Program, developed on the defined curriculum of Chulalongkorn University (www.chulapd.org). The fellowship emphasizes clinical training and the care of movement disorders patients during the first year, then focuses on training in a selected research discipline during the second year. Since 2007, a total of 11 PD specialists and 4 current fellows have graduated from the program. In addition, an elective fellowship training course in Movement Disorders for oversea neurologists has been initiated from which there are now two graduated fellows from Myanmar and one current fellow from Vietnam. Joint collaborative research is also ongoing with centers in Europe, Asia, and North America.

Recognizing the need to enhance the ability and capacity of neurologists and primary care physicians in underserved regions to treat patients with movement disorders, a collaborative MDS Center-to-Center Movement Disorders Training Program has been established between an expert center (Mentor Center) and a center in an underserved region (Mentee Center). This program includes access to many types of online materials, regular teleconferences, and face-to-face visits that all help to provide the higher education and skills needed to promote growth at centers in underserved regions. Over the long term, it is hoped that the program may result in some institutions developing their own specialist Movement Disorders Center. The types of training programs and initiatives described above will likely result in more and better qualified PD specialists in the region, expanding the availability of skilled personnel who can subsequently form a multidisciplinary team and deliver DAT, including apomorphine infusion in more developing countries in the Asian region.

For PD specialist nurses, ChulaPD is committed to develop training programs that provide them with the specialist experience, knowledge, and skills in PD and Movement Disorders, allowing them to fulfill their vital role in giving expert care to patients. A PD nurse training course of up to 3 months is available for local and international registry nurses. In addition, ChulaPD holds an annual, 2-day, PD nurse conference to enhance and update nursing skills and knowledge about PD which is attended by over 250 delegates. The ChulaPD team also holds regular international and national congress events, including an Apomorphine Masterclass in May 2019 and the Chulalongkorn 2019 International Forum, allowing experts in the field of PD and apomorphine infusion therapy to share their knowledge with practicing clinicians in Thailand [23].

Focusing on generating information and data for apomorphine use in Thailand, ChulaPD has also set up a specific apomorphine registry and is undertaking and publishing research related to apomorphine use since its introduction in

the country [70]. Online education training materials about apomorphine infusion designed for neurologists, PD nurses, and other medical professionals interested in its use treatment of PD have been developed in a joint collaborative project by ChulaPD and the Thai PDMDS which includes a dedicated webpage and mobile platform. The Thai PDMDS also hosts online materials about apomorphine infusion on their website. In addition, an online education and training resource has been developed by ChulaPD and Chulalongkorn University and entitled Chulalongkorn Massive Open Online Courseware project (Chula MOOC). This comprises real-time education and is aimed at general practitioners, residents, and other medical professionals interested in learning about PD and other common movement disorders.

It is hoped that the successful introduction of apomorphine infusion in Thailand can serve as a model for introducing this treatment, or other new therapy, into developing countries in Asia and other world regions.

8. Progressing the development of PD care provision in Asia

While Thailand has all three DAT available within the healthcare system (although not necessarily accessible to all patients) – apomorphine infusion, LCIG, and DBS – neighboring countries in the Southeast Asian region, such as Lao-PDR, Cambodia, and Myanmar, have no or limited access to prescribe these treatments. Asia is not alone: many regions throughout the world are underserved in terms of the education, proficiency, resource capacity, and standard of care available for the provision of care to people with PD [71–73]. To overcome this requires a coordinated effort within the Asian region, and more widely.

8.1. Center-to-center programs

One initiative that is a first step toward tackling some of these issues is the 'center-to-center' program initiated in Thailand. This has the objective of raising the educational standard in underserved areas in the Asian region. The initial collaboration between Thailand and Laos will be undertaken in three phases: (1) identifying target physicians for education, (2) classifying the fundamental requirements of these clinicians and then providing academic programs to fit their needs, and (3) evaluating the impact of the program to inform future initiatives. Ultimately, the 'center-to-center' program offers the higher education and skills needed to promote growth in PD services at centers in underserved regions such as Laos.

8.2. Developing a team approach

As previously discussed, it is generally believed that an MDT approach is key to providing individualized PD care, and while theoretically, it may seem like the ideal solution, robust evidence to support it is limited. It is important to establish how this 'ideal' scenario can be matched to the 'reality' of real-world demands and limited resources, and whether it is even feasible in some settings. Studies have been undertaken to explore the effectiveness of an integrated MDT approach compared with usual care, but results are equivocal [24,74,75]. The results of one non-randomized, study suggested that in fact an MDT approach delivers only small benefits to PD patients which disappear after correction for baseline disease severity [27]. However, a randomized, controlled trial found that UPDRS scores and some quality of life parameters significantly improved with MDT care [25], indicating that further research is needed to confirm these findings. Overall, these results suggest that a range of approaches is needed, particularly in resource-restricted regions to achieve substantial health benefits for PD patients, but where feasible, an MDT approach is beneficial.

A key member of any MDT is the PD nurse specialist. Reports and ongoing studies from around the world have recognized the value of this service and the positive impact it can have on the provision of care for patients with PD [29,54,74,76–78]. They are often the key point of contact for patients and their families and caregivers, providing education, support, a link with the clinician, and advice on treatments, in particular with device-aided therapies where communication and ongoing support are vital to their success. ChulaPD now has an established, experienced and well-coordinated PD nurse service which underpins the MDT and can provide not only clinic support but also undertake home visits and telephone consultations.

While an MDT approach is ideal, it is impractical to institute this routinely in developing countries where resources are limited. Although not a full 'MDT,' it can still be possible to implement a team approach, consisting of core people, including neurologists and nurses with experience of using apomorphine infusion. In addition, candidate selection is crucial since those who engage with their treatment and have good and knowledgeable carers are likely to do well. Whatever the composition of the team, a structured and practical approach is needed including processes for pre-assessment, initiation, treatment adjustment, and follow-up. The center-to-center programs described above allow experienced centers to share these practices with new service development teams.

8.3. Patient and carer education and engagement

Patient engagement is considered one of the key factors in treatment success in PD [23,79]. As mentioned previously, a survey of Asian PD patients identified significant knowledge gaps in three key areas evaluated diagnosis, therapeutic options, and disease course [67,80]. It is therefore important that patients who have either inaccurate or insufficient disease-related knowledge are identified quickly and provided with educational interventions to improve their understanding of the disease and the treatment they are receiving. A survey of PD patients in the USA found that care by PD specialists, rather than general neurologists, and provision of education about PD and its treatment, either in the clinic or through support groups, enhanced satisfaction, and perception of health-care quality [81].

It is well recognized that PD imposes a substantial burden on those who care for the person with PD [82,83]. Families and carers often play a critical role in helping with or administering

medication and providing practical support, and their role becomes even more burdensome if the person with PD experiences nighttime symptoms which cause sleep disturbances for both parties involved. It is important that the carers' mental health status is considered as part of the overall package of PD care and suitable interventions suggested where they are warranted [82,84]. Recognizing this important dynamic, at ChulaPD, patients are involved in various group activities, including art therapy and physiotherapy, and participate, along with their carers, to share their experiences at the Chulalongkorn 2019 International Forum.

9. Conclusion

Although the World Medical Assembly endorses and promotes patient autonomy and access to good quality medical care without discrimination according to the Declaration of Lisbon on patients' rights in 1984 [85], there are notable challenges in providing equitable health care in developing countries with aging populations, which further highlights the health-care inadequacy in underdeveloped countries. All PD patients should have the right to access appropriate and effective treatments for their condition and, while they all have the same underlying disease, how specific symptoms affect each person differs. Each individual patient, therefore, represents a unique challenge to the clinician in terms of matching their specific symptom profile with available therapeutic options to ensure successful resolution of symptoms. This is particularly true for a device-aided therapy like apomorphine infusion. What has been demonstrated from the experience in Thailand is that while delivering apomorphine infusion therapy is doable, a tailored approach is needed to identify suitable candidates based on input from a team of core health-care personnel experienced in the use of apomorphine therapy. The model used in Thailand demonstrates a learning curve since the introduction of apomorphine infusion in 2014 and could be considered as a learning opportunity or a shared best practice experience for those countries aiming to deliver this service.

10. Expert opinion

PD patients in developing countries, in common with those in more developed countries, deserve to be offered the best evidence-based treatments available for their particular symptoms [85]. This article has highlighted the challenges faced in developing countries regarding access to and implementation of available therapies, particularly DAT which are perceived as more complex to administer and manage. Lessons from the learning curve experienced by Thailand when introducing apomorphine infusion demonstrate the need for greater coordination and collaboration both within and between countries, importantly sharing best practice and expertise at a national and international level in order to improve knowledge levels of both patients and health-care professionals to give them confidence to use these therapies. Importantly, there is often a reluctance amongst health-care professionals to prescribe DAT – a factor not limited to developing countries – in some cases due to lack of expertise of using the therapy, but also due to the fact that they are seen as labor-intensive for the health-care team. While to a degree that is true it also highlights the need for clear guidelines and streamlined processes to help identify those patients who are suitable candidates and a priority for specialized treatment like apomorphine infusion, as well as guidelines for initiation and follow-up to facilitate this process and ensure the best outcomes from the therapy. Patients' long-term well-being and optimal outcomes should be at the forefront of prescribing decisions and in suitable patients DAT, such as apomorphine infusion, can be a beneficial choice that actually gives a better overall quality of life than multiple oral medications, particularly if the patient has gastrointestinal issues, as is common in PD.

Adoption of apomorphine infusion in Thailand has required a pro-active approach to peer-to-peer education and patient engagement to ensure confident prescribing and persistence with treatment, however, access to therapy with an extremely diverse population will remain an ongoing challenge. As discussed, a 'team' approach to PD care is the ideal scenario but the feasibility of this will be dictated by local resources, so capacity building is something that needs to be addressed.

Knowledge gaps amongst both physicians and patients can be a potential barrier to treatment update, in particular, misconceptions about DAT amongst patients. Asian patients tend to believe that needing to take non-oral PD treatment implies that their disease is very advanced or terminal and can not be controlled by simple oral medications. Also, wearing devices may stigmatize patients.

Continual generation of evidence regarding the efficacy, safety, and cost-effectiveness of apomorphine infusion in Thailand, and in different geographical regions, is of value to help demonstrate for which patients it is suitable and how treatment can be optimized in actual clinical practice, as opposed to a clinical trial setting. In this regard, the first apomorphine treatment registry was established in Thailand in 2015 led by ChulaPD to allow prospective data collection of patients treated with apomorphine intermittent injection or continuous infusion. This comprehensive database will allow ongoing standardized evaluation of treatment efficacy, patient outcomes, and cost-effectiveness that will help inform patient care pathways, health-care policy, and future research.

Education on PD and available therapies, particularly when new treatments are introduced, needs to be prioritized at a local and national level across developing countries and built into health-care professional training. Skills training at a peer-to-peer level or 'masterclass' events that allow sharing of experiences with DAT, such as apomorphine infusion, are invaluable not only for competence building but also to demystify that such therapies are 'too complex' to prescribe, which is depriving patients of a potentially effective therapy and a good quality of life.

Improved apomorphine delivery methods or formulations are likely to lessen patient's burden whilst enjoying the efficacy of this therapy [86]. New, smaller, and more discreet pumps are being developed alongside softer needle sets that allow easier handling by non-healthcare professionals, such as carers.

With the rise in digital health technologies, it is likely that advances in telemedicine will allow remote monitoring and consultation of patients in rural areas who may struggle to access specialist centers [87,88]. Video links may also allow for

teaching opportunities for between specialist centers and regional hospitals.

Data suggest there will be more PD patients in the future, but at the same time, our knowledge of the underlying disease has increased and we have a wider range of therapeutic options for patients. So, the challenge for health-care professionals is to match the right patient to the right treatment at the right time – ensuring they receive individualized therapy to resolve their motor symptoms promptly and without delay as their disease progresses.

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R Chaudhuri has worked on advisory boards for AbbVie, UCB, Pfizer, Jazz Pharma, GKC, Bial, Cynapsus, Novartis, Lobsor, Stada, Medtronic, Zambon, Profile, Sunovion, Roche, Therevance, Scion. Honoraria for lectures: AbbVie, Britannia, UCB, Mundipharma, Zambon, Novartis, Boehringer Ingelheim, Neuroderm, Sunovion. Grants (Investigator Initiated): Britannia Pharmaceuticals, AbbVie, UCB, GKC, Bial, Academic grants: EU, IMI EU, Horizon 2020, Parkinson's UK, NIHR, PDNMG, EU (Horizon 2020), Kirby Laing Foundation, NPF, MRC. P Lolekha has received honoraria/lecture fees from Abbott, Allergan, Berlin Pharm, BL Hua, Boehringer-Ingelheim, Eisai, GlaxoSmithKline, Novartis, and Siam Pharmaceutical; he has received research funding from Thammasat University. J Parsons is employed by Britannia Pharmaceuticals Ltd, UK. S Benedierks is employed by STADA Pharmaceuticals Australia Pty Ltd. A has received reimbursement of travel expenses to scientific meetings or honoraria for lecturing or consultancy from UCB, Seqirus, Theravance, Teva, Abbott, AbbVie, Stada, Allergan, Ipsen, and Merz. He holds shares in CSL Australia and Global Kinetics Corporation. T van Laar has received speaker fees from Britannia Pharmaceuticals and AbbVie. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

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