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Short Communications

Apomorphine titration with and without anti-emetic pretreatment in patients with Parkinson's disease experiencing OFF episodes: A modified Delphi panel

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ABSTRACT

Introduction: In the United States (US), prophylactic treatment with the antiemetic trimethobenzamide has been used before initiating apomorphine therapy. However, US trimethobenzamide stores have been depleted, leaving uncertainty regarding whether antiemetic pretreatment is needed.

Methods: This modified Delphi panel aimed to inform circumstances when apomorphine is initiated without antiemetic pretreatment. During Round 1, a panel of 9 US movement disorder specialists rated the appropriateness of prescribing apomorphine therapy with and without antiemetic pretreatment across 192 patient scenarios and were able to review their scores in relation to other scores. During the Round 2, consensus was defined for each scenario as either strong (>75 % agreement) or moderate (66 % agreement).

Results: There was strong consensus on 118 of 192 scenario's (97 as appropriate and 21 as inappropriate), moderate consensus on 29 scenarios, some agreement on 32 scenarios, and lack of agreement on 13 scenarios. In the absence of an antiemetic, there was strong consensus that titration schedules should be flexible and based on dose response. However, the group only reached moderate consensus on the speed of titration, highlighting the need for more systematic information on this area. In the presence of an antiemetic, panelists considered usual initial dosing and flexible titration to be appropriate in most scenarios except for when the patient is already experiencing dopaminergic adverse events.

Conclusions: Experts generally reached consensus that apomorphine can usually be prescribed without antiemetic pretreatment. Recommendations described here reflect the areas of greatest agreement among a panel of experts based on current available evidence.

1. Introduction

It has long been known that apomorphine can induce nausea and emesis, primarily due to the action of apomorphine on D_2-family dopamine receptors located in the chemoreceptor trigger zone of the brain [1]. Historically, apomorphine was first approved for use in Parkinson's disease (PD) in Europe in the 1990 s. The dopamine antagonist domperidone was recommended for antiemetic prophylaxis when initiating apomorphine because it does not readily cross the blood–brain barrier, thereby minimizing the risk of causing extrapyramidal adverse effects, but effectively treating nausea and vomiting [2]. However, concerns about the use of oral domperidone, including its known cardiotoxicity, have precluded its approval in the US. At the time of US clinical trials [3,4], the use of trimethobenzamide was suggested as a

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substitute for domperidone based on its use at the time in conjunction with chemotherapy, its predominantly peripheral mechanism of action and low incidence of adverse reactions related to PD symptom exacerbation. For these reasons, FDA approval for both subcutaneous and sublingual apomorphine was initially granted with a recommendation in the label to pretreat patients with trimethobenzamide three times a day for three days prior to initiating apomorphine.

Due to a cessation of production by three manufacturers, trimethobenzamide has been unavailable since the summer of 2021 [5] although other sources may become commercially available in the future. Other antiemetics available in the US either worsen motor parkinsonism (e.g., metoclopramide, promethazine and prochlorperazine) or increase the risk of hypotension when used with apomorphine (e.g., ondansetron, granisetron, dolasetron, and palonosetron) and are therefore contraindicated or not recommended. Although studies have shown little clinical benefit of initiating apomorphine with an anti-emetic [6,7], there is limited guidance available on initiating and titrating apomorphine to identify the optimal dose without the use of antiemetic pretreatment.

To help address this issue, we convened a group of US movement disorder specialists to identify circumstances when apomorphine can be initiated to treat OFF episodes without antiemetic pretreatment. This consensus project focused only on the use of apomorphine therapies in the US (intermittent subcutaneous apomorphine injections [8] and sublingual apomorphine [9] are approved medications, and continuous subcutaneous apomorphine infusion [CSAI] is currently under investigation in the US). As domperidone does not have US regulatory approval, the use of domperidone antiemetic pretreatment was not discussed.

2. Methods

We used the RAND/UCLA modified Delphi panel method, which systematically and quantitively combines expert opinion and the latest clinical evidence [10]. Nine panel members (consisting of movement disorder experts based in university, academic, and private clinical practices) were chosen based on their extensive clinical and research experience of using apomorphine for the management of OFF episodes in the US; all panel members had been investigators in US-based apomorphine clinical trials and all have been using apomorphine in clinical practice since the first US approval in 2004. Panelists represented centers from across the US, including those that treat rural populations. Modified Delphi panels do not involve human subjects as defined by 45 CFR Part 46 and therefore do not require Institutional Review Board approval. The panel sponsors (Sunovion and Supernus) did not provide any input on panelist selection, study design, methods, or interpretation of results.

Panel members reviewed a broad summary of current clinical evidence, including clinical trials of intermittent subcutaneous apomorphine [3], sublingual apomorphine [4], CSAI [11], as well as studies reporting on the initiation of apomorphine with and without prior antiemetic therapy [6,7,12]. Taking the literature into account and based on their own clinical experience, panelists rated the appropriateness of prescribing apomorphine therapy with and without antiemetic pretreatment across 192 patient scenarios (prepared by the panel steering committee SHI, RP, and KEL) prior to a panel meeting. Panelists discussed these ratings during a moderated face-to-face discussion in June 2022, then rated the same scenarios a second time via email before reconvening to discuss the final recommendations.

Each scenario was defined by permutations of the following clinical

Table 1
Strength of consensus. ***Key:*** *Panelists rated the appropriateness of prescribing on a scale of 1 (highly inappropriate, risks outweigh the benefits) through 5 (not sure,* e.g. *due to inadequate data or experience OR risks and balances appear balanced) to 9 (highly appropriate, benefits outweigh the risks). Data are median [range] scores. Green is strong consensus (>75 % agreement as appropriate), red is strong consensus (>75 % agreement as inappropriate), light green is moderate consensus (66 % agreement as appropriate), pink is moderate consensus (66 % agreement as inappropriate), light grey is some agreement (50–65 % agreement), and dark grey is no agreement (<50 % agreement) reached. *rated as uncertain because of lack of data or the risks and benefits seem balanced.*

			With antiemetic pretreatment						Without antiemetic pretreatment					
Currently:			i. Usual initial dose (per PI)	ii. Lower initial dose	iii. Usual titration, after each dose (per PI)	iv. Slower titration, increase after 2-3 days or doses	v. Slow titration, increase after 4-7 days or doses	vi. Flexible, based on response	i. Usual initial dose (per PI)	ii. Lower initial dose	iii. Usual titration, after each dose (per PI)	iv. Slower titration, increase after 2-3 day or doses	v. Slow titration, increase after 4-7 days or doses	vi. Flexible, based on response
DA	Experiencing nausea	N	9 (8-9)	8 (2-9)	9 (1-9)	4 (2-9)	3 (1-8)	9 (7-9)	8 (7-9)	9 (5-9)	7 (2-8)	7 (5-9)	7 (5-9)	9 (7-9)
		Y	2 (1-3)	8 (6-9)	2 (1-5)	7 (6-9)	8 (6-9)	9 (8-9)	1 (1-3)	7 (5-9)	1 (1-3)	7 (5-8)	8 (6-9)	9 (6-9)
	Experiencing symptomatic NOH	N	9 (1-9)	8 (2-9)	8 (5-9)	5 (2-9)	3 (1-8)	9 (7-9)	8 (1-9)	5 (3-9)	5 (5-9)	6 (3-9)	5 (2-8)	9 (6-9)
		Y	2 (1-8)	9 (5-9)	1 (1-3)	5 (5-8)	8 (6-9)	9 (6-9)	1 (1-3)	9 (5-9)	1 (1-3)	7 (3-8)	8 (6-9)	9 (6-9)
	Experiencing asymptomatic NOH	N	9 (8-9)	8 (2-8)	8 (5-9)	5 (2-9)	3 (1-8)	8 (7-9)	8 (7-9)	8 (4-8)	8 (4-9)	6 (2-9)	5 (1-8)	9 (7-9)
		Y	2 (1-7)	7 (5-9)	3 (2-7)	6 (6-9)	6 (4-8)	9 (7-9)	2 (1-6)	8 (6-9)	3 (2-5)	6 (6-8)	7 (6-9)	9 (7-9)
	Experiencing somnolence	N	9 (8-9)	8 (2-8)	9 (5-9)	5 (2-9)	3 (1-8)	9 (7-9)	8 (7-9)	8 (3-8)	8 (4-9)	6 (3-9)	5 (2-8)	9 (7-9)
		Y	4 (1-6)	9 (7-9)	2 (1-6)	7 (5-9)	8 (6-9)	9 (7-9)	3 (1-6)	8 (7-9)	2 (1-6)	7 (6-9)	8 (6-9)	9 (7-9)
Not on DA	Experiencing nausea	N	8 (7-9)	8 (2-9)	7 (3-9)	8 (3-9)	5 (2-8)	9 (7-9)	7 (4-9)	8 (4-9)	5 (4-7)*	7 (5-9)	7 (5-8)	9 (7-9)
		Y	2 (1-2)	8 (6-9)	2 (1-5)	7 (5-9)	8 (6-9)	9 (7-9)	1 (1-2)	9 (6-9)	1 (1-2)	7 (5-9)	8 (5-9)	9 (7-9)
	Experiencing symptomatic NOH	N	9 (7-9)	8 (3-9)	8 (5-9)	7 (3-9)	4 (2-8)	8 (7-9)	8 (4-9)	8 (4-9)	7 (4-9)	7 (5-9)	6 (4-8)	9 (7-9)
		Y	2 (1-4)	9 (6-9)	2 (1-3)	7 (4-8)	7 (5-9)	9 (6-9)	1 (1-4)	9 (6-9)	1 (1-3)	7 (4-8)	8 (5-9)	9 (7-9)
	Experiencing asymptomatic NOH	N	8 (8-9)	8 (2-9)	8 (5-9)	7 (2-9)	5 (1-8)	8 (7-9)	8 (4-9)	8 (3-9)	7 (4-9)	7 (2-9)	6 (1-8)	9 (7-9)
		Y	3 (1-7)	6 (5-9)	3 (2-7)	6 (6-9)	7 (6-9)	9 (7-9)	3 (1-6)	9 (6-9)	3 (1-5)	7 (5-9)	7 (5-8)	9 (7-9)
	Experiencing somnolence	N	9 (7-9)	8 (3-9)	7 (5-9)	6 (3-9)	5 (2-8)	9 (7-9)	8 (4-9)	8 (3-9)	7 (4-9)	7 (3-9)	7 (2-9)	9 (7-9)
		Y	3 (1-6)	9 (7-9)	2 (1-5)	8 (5-9)	8 (6-9)	9 (7-9)	3 (1-6)	9 (7-9)	2 (1-5)	7 (5-9)	8 (6-9)	9 (7-9)

characteristics: use of antiemetic pretreatment, initiation dose, current dopamine agonist use, current or prior dopaminergic adverse effects (e.g. nausea, neurogenic orthostatic hypotension [NOH], and somnolence), and titration frequency (Table 1). Panelists rated the appropriateness of prescribing on a scale of 1 (highly inappropriate, risks outweigh the benefits) through 5 (not sure, e.g. due to inadequate data or experience OR risks and balances appear balanced) to 9 (highly appropriate, benefits outweigh the risks). When rating the scenarios, panelists were asked to consider the best clinical choice for these patients based on available evidence and their clinical experience with these and other medications. The scenario's assumed patients previously had a robust response to PD medications, were willing and able to take non-oral medications, were able to be reasonably compliant with treatment protocols and had none of the contraindications listed in the prescribing information for either apomorphine treatment.

During the initial discussion, panelists were invited to share their own ratings and the rationale for that rating, focused particularly on scenarios for which there was disagreement. Results were aggregated, and in the first round, each scenario was rated as having strong consensus (>75 % panelists agreed), some agreement (50–75 % agreement) or no agreement (<50 % agreement). At the end of the first round, panelists were able to review their ratings in relation to the other panelist scores (minimum, maximum and median scores).

For the second round, consensus was defined for each scenario as either strong (>75 % agreement) or moderate (66 % agreement). We also noted the scenarios for where there was some agreement (>50–65 % agreement) and those for which the experts did not agree (<50 % agreement). Scenarios for which there was consensus were further classified as 'appropriate' if they had a median rating of 7–9, 'inappropriate' if the median was 1–3, and 'uncertain' if the median rating was 4–6. Ratings at this stage were considered to represent the group consensus, and panelists reviewed and commented on the summary before it was finalized for this report.

3. Results

At the end of the second round there was reasonable consensus on the options for initiating apomorphine with and without anti-emetics. There was strong consensus on 118 of 192 scenario's (97 as appropriate and 21 as inappropriate), moderate consensus on 29 scenarios, some agreement on 32 scenarios and lack of agreement on 13 scenarios (Table 1). Results for Round 1 are shown in **Supplementary Table S1**.

In the presence of an antiemetic, panelists considered the recommended schedules for initial dosing and flexible titration (e.g. with intermittent subcutaneous administration start at 1–2 mg [0.1–0.2 mL], and if insufficient effect is observed, increase by 1–2 mg [0.1–0.2 mL] at the next OFF episode or every few days as tolerated [8]) to be appropriate in most scenarios except for when the patient was already experiencing dopaminergic adverse events, when they considered usual dosing to be inappropriate. When patients were receiving an antiemetic, key areas for contention were related to the need for slower titration schemes, where panelists either did not agree or thought there is insufficient information on this issue. While panelists regarded the benefits of slower titration (increase after 2–3 or 4–7 days) as equivocal for patients already on a dopamine agonist, there was a tendency for more panelists to regard slower titration schemes as appropriate for patients naïve to dopamine agonist therapy.

In the absence of an antiemetic, there was strong consensus that titration schedules should be flexible and based on dose response. Although panelists agreed that starting apomorphine at the usual initial dose (2 mg [0.2 mL] intermittent subcutaneous apomorphine or 10 mg sublingual apomorphine) is inappropriate for patients experiencing dopaminergic side effects of nausea and symptomatic NOH, there was only moderate agreement on starting at lower initial apomorphine doses. Once again, the main area for contention was related to the need for slower titration schemes, where panelists were either equivocal or uncertain about the benefits of a slower titration where the apomorphine dose is increased after 2–3 days/doses and more likely to support an even slower titration where titration interval is set after 4–7 days/doses.

4. Discussion

Apomorphine is utilized for treatment of OFF episodes worldwide. However, since trimethobenzamide is now unavailable in the US and domperidone is not an FDA-approved therapy, treating clinicians do not have an antiemetic option when apomorphine therapy is initiated. Using a modified Delphi method, experts generally agreed that apomorphine can be prescribed without antiemetic pretreatment. However, the group only reached moderate consensus on the speed of titration, highlighting the need for more systematic information in this area.

While only moderate consensus was reached on the speed of titration for patients initiating apomorphine with an antiemetic, there was consensus that without an antiemetic to initiate a low dose and employ a slow titration schedule, with increases after 4–7 days (vs. dose increases at the next OFF episode). This 'start low and go slow' is already common practice for available oral and transdermal D2-family predominant dopamine agonists. Indeed, oral and transdermal agents are typically initiated with a 4–6-week titration schedule. Conversely, the development of apomorphine used a faster titration that was facilitated in Europe by domperidone to improve tolerability [13].

While initial clinical trials that established the efficacy and safety of apomorphine treatment employed the use of antiemetics during apomorphine initiation and titration, subsequent trials have not supported the need for antiemetic pretreatment [14]. In a Japanese trial, investigators considered there was no clear evidence showing the necessity of antiemetic pretreatment when initiating apomorphine and as a result, prophylactic antiemetic use was prohibited in their study unless the patient had already been receiving antiemetic treatment prior to study initiation [7]. This study of intermittent subcutaneous apomorphine used a slow dosing strategy with patients starting treatment at 1 mg and increased doses in 1 mg increments. Notably 77 % of 'antiemetic naïve' patients were able to start apomorphine treatment without reporting gastrointestinal upset [7].

The consensus developed in this study aligns with and augments prior clinical trial experience demonstrating the efficacy and safety of apomorphine treatment without antiemetic pretreatment [6,7,12]. We used the RAND/UCLA modified Delphi panel method in this study. This method has been used extensively to develop quality measures and clinical guidance in a variety of areas and has recently been updated to allow for virtual meetings [10]. The method does have limitations. Firstly, the method requires panelists to respond considering their personal experience/judgment on the proposed statements: the conclusions provided in this report are based therefore on the opinions of a panel with differences in experience, practice settings and patient populations. Due to the cessation of trimethobenzamide manufacture, some of the experts had more experience than others with using a slow titration scheme for their apomorphine patients. Further, panelists rated all three apomorphine treatments as a class. These ratings cannot speak to differences between individual medications. Indeed, CSAI is an investigational drug in the USA and experience with this formulation required the panelist to be a study investigator.

In summary, we used a rigorous and comprehensive method to develop guidance on initiating apomorphine treatment and titration to optimal dose. Recommendations described here reflect the areas of greatest agreement among a panel of experts based on current available evidence. These recommendations can successfully guide clinicians in the appropriate use of apomorphine treatments for patients with OFF episodes.

CRediT authorship contribution statement

Stuart H. Isaacson: Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Data curation. **Richard Dewey:** Writing – review & editing, Investigation. **Robert A. Hauser:** Writing – review & editing, Investigation. **Daniel Kremens:** Writing – review & editing, Investigation. **Rajeev Kumar:** Writing – review & editing, Investigation. **Mark Lew:** Writing – review & editing, Investigation. **William Ondo:** Writing – review & editing, Investigation. **Fernando Pagan:** Writing – review & editing, Investigation. **Kelly E. Lyons:** Writing – review & editing, Supervision, Data curation. **Rajesh Pahwa:** Writing – review & editing, Investigation.

Declaration of competing interest

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

Stuart H. Isaacson reports honoraria for CME, consultant, research grants, and/or promotional speaker on behalf of AbbVie, Acadia, Acorda, Adamas, Addex, Affiris, Alexva, Allergan, Amarantus, Amneal, Aptinyx, Axial, Axovant, Benevolent, Biogen, Britannia, Cadent, Cala, Cerecor, Cerevel, Cipla, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Impel, Intec Pharma, Ipsen, Jazz, Kyowa, Lundbeck, Merz, Michael J. Fox Foundation, Mitsubishi Tanabe, Neuralys, Neurocrine, NeuroDerm, Parkinson Study Group, Pharma2B, Prilenia, Promentis, Revance, Roche, Sanofi, Sunovion, Sun Pharma, Supernus, Teva, Theravance, UCB, Zambon. Richard B. Dewey, Jr., reports consulting fees from Amneal Pharmaceuticals and grant support from NINDS and the Jean Walter Center for Movement Disorders. Robert A. 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Author contributions

SHI conceived the Delphi panel and wrote the first draft of the manuscript. KEL provided project oversight. SHI, RD, RAH, DK, RK, ML, WO, FP, and RP participated in the Delphi panel and all authors provided critical review of the manuscript including a discussion of their own clinical experience. All authors approved the final manuscript as submitted.

Data sharing statement

All available data are contained within this short report.

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Appendix A. Supplementary data

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