

Apomorphine subcutaneous titration in Parkinson's disease - the effectiveness and safety of apomorphine challenges: A Literature Review



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Abstract

This review examined the body of evidence to determine the efficacy of an apomorphine challenge. Its primary objective is to identify the dose of the most common adverse events involved with apomorphine challenges. The secondary objective is to determine whether a titration challenge is warranted prior to commencing Apomorphine therapy or an alternate option, such as slow titration, is more efficacious.

Results: The literature review was developed using the Cochrane handbook of systematic reviews. The search yielded 157 results, only 23 were included in the final analysis. Evidence is largely lacking and traditionally anecdotal and based on clinician experience. Studies inadequately control for reporter and rater bias, have small sample sizes; high level evidence is lacking.

Continuous rates range between 2-4mg/hr (Deleu, 2004) and an intermittent dose range between 4mg- 6 mg (Pahwa et al 2007); doses higher than this are likely to induce side effects. QT interval prolongation is linked with both apomorphine and domperidone use and an electrocardiogram (ECG) should be performed prior to commencing both medications.

A positive result for an apomorphine challenge is determined when there is a 20% improvement from baseline score in part III of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS- UPDRS), 30 minutes after a dose is given.

Lastly, review examines a theoretical way to titrate patients using the Tomlinson levodopa conversion.

Introduction

Apomorphine is a specialised therapy for Parkinson's disease, where initiation and titration vary between hospital, health care professional and states. Clinicians perform apomorphine challenges to estimate starting doses and rates for patients. However, there is no literature about the efficacy or accuracy of this practice and how well it helps to predict starting doses or what doses side effects occur. The purpose of this literature review is to analyse the efficacy and safety of performing an apomorphine challenge on a person with Parkinson's disease and whether the process of the challenge is the most efficacious way to determine the starting dose for commencing of apomorphine therapy.

This review will help ensure clinicians are using the best evidence to guide patient care and ensure the best clinical outcomes for patients. Its primary objective is to identify the rates and intermittent doses of the most com-

mon adverse events, involved with apomorphine challenges. The secondary objective is to determine whether this procedure is warranted prior to commencing Apomorphine therapy or if a slow titration is more efficacious.

Methods

This Literature review protocol has been developed in accordance with the process set out in the Cochrane handbook of systematic reviews. As this is a literature review, formal ethics approval was not required.

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Eligibility for materials included in the review include textbooks and journal articles. Editorials, opinion pieces, newspaper articles, materials not based on scientific method, and not written in English were excluded. Studies included randomised controlled trials, observational, cohort and qualitative studies, case studies, systematic reviews and guidelines. The studies had to be specific to people with idiopathic Parkinson's disease and specific to Apomorphine subcutaneous injections, apomorphine therapy, "apomorphine challenge" or "Apomorphine Challenge test".

Types of Participants

Participants in the studies had to be diagnosed with idiopathic Parkinson's disease. Studies were excluded where participants were described as Parkinson's syndrome or atypical Parkinson's disease. No restrictions regarding age, disease stage or sex were applied.

Types of interventions

Types of interventions were specific to subcutaneous apomorphine therapy including continuous infusion and injector pens. Nasal, rectal and oral forms of apomorphine were excluded.

Outcome measures included:

Safety: the types and frequency of adverse events including cardiac arrhythmias, orthostatic hypotension, cardiac arrest, hallucinations, skin nodules, dyskinesia, somnolence, nausea and vomiting. As well as identify apomorphine dose most likely to cause adverse events.

Effectiveness measures: included Hoehn and Yahr score, UPDRS part III and discontinuation rates, ECG, postural blood pressures.

Search Strategy

The review was conducted using published literature from Pub Med/ MEDLINE and CINAHL databases from 1970- 2019. Truncated key words were used to identify key words and synonyms (See appendix 1 for key words). The results were refined using and Boolean operators see appendix 1. Reference lists of relevant articles were searched to identify relevant articles.

Data analysis Study Appraisal

Two reviewers independently reviewed the

studies using validated appraisal tools specific to the research design. Disagreements of appraisal were resolved by discussion. Eligible studies were assessed for homogeneity of population, intervention, and validated measurements.

Results were abstracted into a literature matrix by the authors, checked for accuracy, amalgamated and analysed. The extracted information included data on methods, participants, interventions, outcomes and results.

'Summary of findings' tables

Once studies were appraised, the body of evidence was graded using the National Health and Medical Research Council (NHMRC) grades of evidence. The grading was used to make recommendations on apomorphine titrations and intervention efficacy. The key outcomes in 'Summary of findings' table as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Using the Group Reading Assessment and Diagnostic Evaluation (GRADE) approach (Guyatt, 2011), The following was assessed for each outcome: • estimate of the treatment effect; • quantity of supporting evidence; • quality of evidence assessed.

Systematic Review results, discussion and recommendations

Literature search Results

The Literature search yielded: 157 results. When articles were reviewed, only 12 met the inclusion criteria. Review of the reference lists yielded 20 more articles, 9 of which were excluded. 23 final articles included in the final analysis.

Populations, study design, sample sizes and study quality

There were twelve, level 1, literature reviews of Apomorphine (Muguet, Broussolle et al. 1995, Clarke, Davies et al. 2000, Deleu, Hanssens et al. 2004, Factor 2004, Pahwa, Koller et al. 2007, Setter 2008, Perez-Lloret and Rascol 2010, Tomlinson, Stowe et al. 2010, Bhidayasiri, Chaudhuri et al. 2015, Bhidayasiri, Garcia Ruiz et al. 2016, Jenner and Katzenschlager 2016, van Laar and Borgemeester 2016).

Of the twelve literature reviews, only four used the Cochrane guidelines process. (Clarke, Davies et al. 2000, Deleu, Hanssens et al. 2004, Tomlinson, Stowe et al. 2010,

Bhidayasiri, Garcia Ruiz et al. 2016)
There were four level 1, studies which used a randomised controlled, double blind study design (Ostergaard, Werdelin et al. 1995, Pahwa, Koller et al. 2007, Pfeiffer, Gutmann et al. 2007, Katzenschlager, Poewe et al. 2018).

Six, level 3, cohort studies (Frankel, Lees et al. 1990, Colzi, Turner et al. 1998, Pietz, Hagell et al. 1998, Ondo, Hunter et al. 2012, Isaacson, Lew et al. 2016, Sesar, Fernández-Pajarín et al. 2017); two, level 4 expert consensus (Albanese, Bonuccelli et al. 2001, Trenkwalder, Chaudhuri et al. 2015); and one, level 4, case series (Price, Martin et al. 2016).

All studies, except two were specific to the Parkinson's Disease (PD) population while two studies included atypical PD including Progressive supranuclear palsy (PSP), Multiple system atrophy (MSA), Cortico basal syndrome (CBD) and Huntington's (Clarke, Davies et al. 2000, Ondo, Hunter et al. 2012). The cohort and randomised controlled trial (RCT) studies had small sample sizes with a minimum of 19 and maximum of 230 patients. Isaacson, Lew et al. 2016, Sesar, Fernández-Pajarín et al. 2017, Katzenschlager, Poewe et al. 2018; recruited 127, 230 and 128 participants respectively. All had high dropout rates resulting in only 88, 93 and 71 being included in the final analysis respectively.

Research questions

The papers in this literature review did not have study designs or research questions that were appropriate to compare the efficacy and patient outcomes between slow titration and apomorphine challenges. Nor did any of the articles, review the efficacy and safety of performing Apomorphine challenges. However, some of the articles did identify the doses at which adverse events occurred and discussed ways of managing them through a review of literature or referencing literature and RCT data results.

None of the articles included were specific to answering our secondary objective of defining the clinical circumstances where a slow titration may be warranted or more efficacious.

Statistical analysis

A meta-analysis of RCT-studies could not be performed on the cohort and RCT studies due to lack of homogeneity among data.

Studies had minor weight due to small sample sizes and high dropouts. Studies appropriately adjusted statistical analysis to account for this.

Measurement tools: sensitivity, specificity, interrater reliability

None of the literature reviews gave enough detail regarding what critical analysis tools were used, nor did they detail the search strategy inclusion and exclusion criteria. Four studies described a detailed search strategy and explained their inclusion/ exclusion criteria (Clarke, Davies et al. 2000, Deleu, Hanssens et al. 2004, Perez-Lloret and Rascol 2010, Tomlinson, Stowe et al. 2010). None of these reviews indicated that two reviewers were used for analysis. Deleu, Hanssens et al. (2004) used a validated means to analyse the strength of the evidence. The review by Clarke, Davies et al. (2000) showed that the meta-analysis tools were validated. The remaining articles by Perez-Lloret and Rascol (2010) and Tomlinson, Stowe et al. (2010) did not identify their critical analysis measures. Pfeiffer, Gutmann et al. (2007) indicated that off symptoms were subjectively measured, increasing risk of measurement bias.

Randomised control trials

The four randomised controlled trials used validated questionnaires and measurements including the MDS-UPDRS, UPDRS, Webster step wise test, vital signs, holter monitor, adverse event (AE) assessment, global dyskinesia scale, ECG & sitting & standing blood pressures.

Katzenschlager, Poewe et al. (2018) used PD diaries, mini-mental state examination (MMSE). Unfortunately, MMSE is not the most appropriate tool for screening cognitive impairment in PD, as it has a low sensitivity for detecting cognitive impairment in PD patients (Mitchell 2013). Further, PD diaries are shown to increase the risk of patient reporter bias and patients are less compliant at reporting events after three days (Hauser, Deckers et al. 2004).

Ostergaard, Werdelin et al. (1995) did not disclose the ECG results making orthostatic hypotension results difficult to correlate with apomorphine doses.

Cohort, expert consensus and case series
Of the six cohort studies (Frankel, Lees et al. 1990, Colzi, Turner et al. 1998, Pietz, Hagell et al. 1998, Ondo, Hunter et al. 2012, Isaac-

son, Lew et al. 2016, Sesar, Fernández-Pajarín et al. 2017), all except (Ondo, 2012) used patient diaries which increase patient bias (Papapetropoulos, 2011). All Cohort studies used UPDRS which is a validated tool that measures motor response. Sesar, Fernández-Pajarín et al. (2017) did not evaluate non-motor symptoms or quality of life and cognitive evaluation was based on UPDRS part 1.

Isaacson, Lew et al. (2016) used UPDRS, 7-day PD diary, clinical global impression scale (CGI-S), EQ-5D-3L, Patient Global Impression of Severity (PGI-S0, Modified Hoehn & Yahr, AE reporting, vital signs measurements, neurological exam & physical examinations.

Ondo, Hunter et al. (2012) used levodopa daily equivalent dose to show total apomorphine doses were similar to the total daily levodopa intake.

Pietz, Hagell et al. (1998) used the obeso dyskinesia rating scale, however this tool is not as well validated as the Abnormal Involuntary Movement scale (AIMS) and the Rush Dyskinesia Rating Scale (Colosimo, C et al. 2010). This case series also used an unvalidated template for collecting standardised

information.

The consensus statement by Albanese, Bonuccelli et al. (2001) does not detail how their consensus statement was reached, increasing risk of investigator bias. Conversely the consensus statement by Trenkwalder, Chaudhuri et al. (2015) uses the Delphi method, using a questionnaire until 80% of investigators reached consensus.

Blinding and randomisation

The four RCT were all randomised and blinded (Ostergaard, Werdelin et al. 1995, Pahwa, Koller et al. 2007, Pfeiffer, Gutmann et al. 2007, Katzenschlager, Poewe et al. 2018). Whilst studies were all randomised and blinded, 2 studies did not have strong randomisation and blinding processes to eliminate bias. Ostergaard, Werdelin et al. (1995) did not have sufficient blinding to eliminate bias. Pahwa, Koller et al. (2007) used a double-blind cross-over design, at visit 1 every patient received a 2mg subcutaneous dose increasing likelihood of unblinding.

Confounders

None of the studies have eliminated bias completely see table below.

Article Number	Type of Bias Found
(Pfeiffer, Gutmann et al. 2007) RCT	Measurement bias, Funding bias
(Pahwa, Koller et al. 2007) RCT	Sampling bias, Participant/ rater bias, Funding bias
(Katzenschlager, Poewe et al. 2018) RCT	Funding bias
(Ostergaard, Werdelin et al. 1995) RCT	Sample bias, Blinding bias
(Ondo, Hunter et al. 2012) Cohort	blinding, sample bias, reporter, patient bias,
(Colzi, Turner et al. 1998) Cohort	Sample, Measurement, Unblinded, No randomisation
(Sesar, Fernández-Pajarín et al. 2017) Cohort	Attrition bias, Measurement bias, Unblinded, No randomisation
(Isaacson, Lew et al. 2016) Cohort	Funding, Unblinded, No randomisation
(Pietz, Hagell et al. 1998) Cohort	Measurement bias, Sample bias, Unblinded, No randomisation
(Muguet, Broussolle et al. 1995)	Measurement, reporter, search strategy, design

Article Number	Type of Bias Found
(Setter 2008)	Measurement, reporter, search strategy design
(Perez-Lloret and Rascol 2010)	Measurement, reporter, search strategy design
(Factor 2004)	Measurement, reporter, search strategy design
(van Laar and Borgemeester 2016)	Measurement, reporter, search strategy design
(Bhidayasiri, Garcia Ruiz et al. 2016)	Not systematic, excluded studies or inclusion criteria, did not explain risks of bias or study design, nil meta-analysis, reporter, publication, selection bias, omitted bias, statistical and observer
(Deleu, Hanssens et al. 2004)	Rater bias,
(Clarke, Davies et al. 2000)	Reporter bias - unable to tell if reviewed independently.
(Tomlinson, Stowe et al. 2010)	Rater bias,
(Bhidayasiri, Chaudhuri et al. 2015)	Rater, measurement, reporter, search strategy, design
(Price, Martin et al. 2016)	Nil blinding, selection bias, reporter bias, study design, no control of confounders, nil blinding, nil standardised collection tools, nil statistical analysis
(Albanese, Bonuccelli et al. 2001)	Not systematic, no thorough literature search methods mentioned, did not list excluded studies or inclusion criteria, did not explain risks of bias or study design, nil metanalysis, high risk of reporter, publication, selection bias, omitted bias,
(Trenkwalder, Chaudhuri et al. 2015)	Rater, reporter, funded, measurement, sample, design, blinding,
(Jenner and Katzenschlager 2016)	Rater, measurement, reporter, sample, design, blinding, funding

Discussion

This literature review highlights the lack of evidence that apomorphine challenges accurately predict the initiation or continuing doses for apomorphine therapy. The review shows that most studies regarding the use of apomorphine challenge in initiating and titrating this therapy is anecdotal and based on clinician experience. Studies inadequately controlled for reporter and rater bias, have small sample sizes and high-level evidence is currently lacking. This review found that performing an apomorphine challenge does not equate to that patient staying on that dose and often further titration to correct the dose is required for months after performing the challenge.

An apomorphine challenge needs to be structured around the drug's pharmacokinetics and patient safety parameters; in particular, ensuring cardiac arrhythmias are screened and controlled for. It's noteworthy that there are no qualitative studies that investigate the patient's experience of the apomorphine challenge and how this experience impacts on the patient's confidence in commencing and continuing the therapy. It's also interesting to note that 1 in ten people commenced on apomorphine usually discontinue within the first year (Sesar. 2017). Commonly cited reasons for discontinuing include lack of drug efficacy at relieving symptoms but also include high rates of orthostatic hypotension, nausea, skin nodules and hallucinations (Sesar. 2017). What studies don't comment on is whether discontinuation rates are higher when patients are not in regular contact with a Parkinson's specialist nurse or movement disorder specialist and how the types of support impact discontinuation rates.

This literature review highlights that most patients have a continuous flow rate between 2-4mg/hr (Deleu, 2004). During pharmacodynamic studies, 60% of patients achieved a clinically significant improvement (20%) with subcutaneous apomorphine 2mg, which increased to 75% after subcutaneous apomorphine 4mg (Deleu, 2004). Similar results were produced by Ondo (2012); who showed patients who are on continuous doses higher than this are more likely to experience side effects, which may encourage therapy discontinuation.

This review also found that nausea is more likely a complication when patients are on intermittent apomorphine rather than continuous apomorphine, which is likely due to a down regulation of medullary dopamine re-

ceptor sensitivity with continuous dopaminergic stimulation (Bhidayasiri, Garcia Ruiz et al. 2016). Domperidone is superior to trimethobenzamide for preventing nausea for people with PD. Of note, trimethobenzamide is not available for use in Australia (Bhidayasiri, Garcia Ruiz et al. 2016). Nausea symptoms tend to reduce after a week of being on apomorphine therapy (Bhidayasiri, Garcia Ruiz et al. 2016), unless a patient is on less than four intermittent injections per day, where nausea is likely to persist (Bhidayasiri, Garcia Ruiz et al. 2016). Theoretically, domperidone could be discontinued one week post commencement of apomorphine infusion, if there have been no problems with nausea to that point. Studies indicate that a positive result for an apomorphine challenge is when MDS-UPDRS part III improves by 20% from baseline (Albanese, Bonuccelli et al. 2001, Deleu, Hanssens et al. 2004). This is usually achieved at doses between 2-4 mg, negating the need to continue the challenge to higher doses beyond the 20% MDS-UPDRS score improvement (Deleu et al. 2004).

It is not uncommon for clinicians to give doses greater than 7mg during an apomorphine challenge (Ondo et al. 2012). However, given that most side effects occur when patients are given >4mg, it's questionable whether doses higher than 5mg are really necessary within the challenge structure. In the past apomorphine challenges have been used to help diagnose those who may have an undifferentiated diagnosis such as PSP, MSA or CBS (Muguet, Broussolle et al. 1995). However, The NICE guidelines from 2018 state that apomorphine challenges are not useful as diagnostic tools (NICE, 2018), showing that apomorphine challenges need not exceed 5mg as other diagnostic tools, such as fluorodopa pet scans, are more accurate for diagnosing atypical parkinsonism syndromes (Brown et al., 1999).

While cardiac arrest is extremely uncommon (Attanasio, Capria et al. 1990, Muguet, Broussolle et al. 1995), it is still a risk and therefore all first apomorphine doses should be given in a clinical setting and a bed should be allocated to the patient, to help manage the patient in situations where orthostatic hypotension or cardiac arrest occur.

QT interval prolongation is linked with both apomorphine and domperidone use (Trenkwalder, Chaudhuri et al. 2015). It's interesting to note that within the apomorphine challenge structure most ECGs are performed before commencing apomorphine, but not before commencing domperidone.

Further studies are required to determine whether domperidone is more likely to induce QT prolongation than apomorphine and whether an ECG is necessary both prior to commencing domperidone and the apomorphine challenge.

Lastly, Tomlinson (2010) investigates the levodopa equivalent dose (LED) conversion formulae which can be used to compare the dose intensities of different PD treatment regimens. Tomlinson's conversion formulae help to convert different doses of antiparkinsonian medications into a standard levodopa dose equivalent helping clinicians convert oral medications into an apomorphine equivalent and calculate the average dose a person would require each hour to maintain motor control.

Tomlinson calculated the arithmetic mean and mode for each drug (Tomlinson, 2010). A limitation of this review is the paucity of direct randomized comparisons between different agents. Therefore, Tomlinson's LED estimates are approximations and not absolute. Tomlinson (2010) states that their review must be seen as a consensus document rather than a quantitative data synthesis.

The Tomlinson levodopa conversion chart offers a theoretical way to titrate patients by calculating the apomorphine equivalent dose. However, a straight conversion of levodopa to apomorphine, where dose would be higher than 4mg are likely to induce side effects as shown by Ondo (Et al 2014). A sensible approach is to convert the oral parkinsonian medications that are being down titrated as apomorphine is up titrated.

Conclusion and Recommendations for Practice

This review found there is a lack of evidence that apomorphine challenges accurately predict the initiation or continuing doses for apomorphine therapy. Adverse events predict the maximum rate or dose a patient can tolerate and further studies are required to determine whether domperidone is more likely to induce QT prolongation than apomorphine and whether an ECG is necessary both prior to commencing domperidone and the apomorphine challenge. On this basis, we conclude that further research and investigatory studies are required to determine the above recommendations and in particular defining the clinical circumstances where a slow titration may be warranted or more efficacious. Based on this literature review the investigators make several recommendations for practice

based on the literature review findings: Domperidone can be used 2-3 days before apo challenge to control nausea. Grade A (Bhidayasiri, Garcia Ruiz et al. 2016, Deleu, Hanssens et al. 2004)

There is one study where domperidone was administered as one initial 10mg initial dose pre apomorphine challenge and when requested thereafter, with only a minimal number of patients having problems with nausea. Therefore, it may be useful for some patient to only have domperidone on initiation of apomorphine challenge and as requested; grade D (Bhidayasiri, Garcia Ruiz et al. 2016). Domperidone is most useful for intermittent apomorphine injections. Can be discontinued after 3–6-week post apomorphine initiation but will vary depended on patient reactions and should be regularly reviewed; Grade D. (Deleu, Hanssens et al. 2004)

Patients who do not experience nausea on oral dopamine agonists are less likely to experience nausea with apomorphine, therefore could have an initial dose of domperidone for the apomorphine challenge. Grade D (Bhidayasiri, Garcia Ruiz et al. 2016) Apomorphine flow rates more than 4mg/hr are likely to induce side effects. Grade C (Deleu, 2004, Pahwa et al 2007)

An apomorphine challenge should only be continued until the part III of the MDS-UPDRS shows a 20% improvement and should be stopped if side effects are experienced i.e., orthostatic hypotension, nausea, arrhythmia, hallucinations. Grade C (Albanese, Bonuccelli et al. 2001, Deleu, Hanssens et al. 2004)

When commencing an apomorphine infusion, 50% of the maximum cumulative dose reached in the apomorphine challenge should be used as the continuous infusion hourly flow rate. Grade C (Deleu, 2004, Pahwa et al 2007)

The order to down titrating antiparkinsonian medications are dopamine agonists, monoamine oxidase type B (MAO-Bs), COMT-Inhibitor, amantadine, levodopa. Grade C (Trenkwalder, Chaudhuri et al. 2015). The Tomlinson conversion can be used to assist in calculating the levodopa equivalent of the ceased antiparkinsonian medications and help determine the apomorphine dose which will fill in the gaps. Grade B (Tomlinson. 2010).

Appendix 1

Key search words: "Apomorphine", "Apomorphine Challenge" "Apomorphine challenge test" "Apomorphine titration", "24-hour continuous apomorphine therapy", "Safety and Efficacy of Apomorphine, "intermittent subcutaneous apomorphine injection", "Apomorphine rescue dose".

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The poster features a dark blue vertical bar on the left containing the ANNA logo (a circular emblem with 'ANNA' in the center and 'AUSTRALASIAN NEUROSCIENCE NURSES' ASSOCIATION' around the perimeter) and the text 'Australasian Neuroscience Nurses' Association' and 'SHINING A LIGHT ON NEUROSCIENCE NURSING'. The right side of the poster has a background image of a lighthouse on a rocky island with turquoise water. Overlaid on this image is the text '2023 CONFERENCE' in large white letters, and at the bottom, '9-10 November, Esplanade Hotel Fremantle by Rydges, Perth WA' in white text.

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