A Systematic Review and Meta-analysis of the Effect of Apomorphine in Patients with Parkinson's Disease

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Abstract

Introduction: Regarding a potential relationship between diabetes and the prognostic significance of hyperglycaemia in patients presenting with acute myocardial infarction (AMI), there is still debate. Therefore, we aimed in this study to demonstrate the effect of hyperglycaemia on different outcomes in AMI patients whether they are diabetic or not. **Methods:** Using the following search strategy: 'Diabetes' or 'Diabetic' AND 'Acute myocardial infarction' OR 'AMI' AND 'hyperglycemia' OR 'glucose level', we searched PubMed, Web of Science and Scopus for eligible articles that should undergo the screening process to determine its ability to be included in our study. Using Review Manager version 5.4 software, we conducted the meta-analysis of the included studies by pooling the mean difference (MD) in continuous variables, number and total of dichotomous variables to measure the odds ratio (OR) and generic inverse variance of OR or hazard ratio (HR) as they were reported in the included studies. **Results:** The difference between diabetes and non-diabetes patients regarding blood glucose level was found to be statistically significant with standardised MD of 1.39 (95% confidence interval [CI]: 1.12, 1.66, $P < 0.00001$). Hyperglycaemia in diabetic patients was statistically significantly associated with mortality with HR of 1.92 (95% CI: 1.45, 2.55, $P < 0.00001$) and OR of 1.76 (95% CI: 1.15, 2.7, $P = 0.01$). In non-diabetic patients admitted with AMI, hyperglycaemia was statistically significantly associated with mortality with HR of 1.56 (95% CI: 1.31, 1.86, $P < 0.00001$) and OR of 2.89 (95% CI: 2.47, 3.39, $P < 0.00001$). Moreover, hyperglycaemia in diabetic patients admitted with AMI was statistically significantly associated with occurrence of MACE with HR of 1.9 (95% CI: 1.19, 3.03, $P = 0.007$) and hyperglycaemia in non-diabetic AMI patients was statistically significantly associated with occurrence of MACE with HR of 1.6 (95% CI: 1.15, 2.23, $P = 0.006$). **Conclusion:** Hyperglycaemia in AMI patients is a predictor of worse outcomes including MACE and mortality whether these patients are diabetic or not. Some factors act as predictors for mortality in these patients including older age, higher glucose levels on admission and high Killip class.

Keywords: Acute myocardial infarction, diabetes, glucose, hyperglycaemia

Introduction

As the second most common neurodegenerative illness, Parkinson's disease (PD) affects 1% of people over 60 and reaches 3% in the oldest age groups.[1,2] Intracellular inclusions harbouring aggregates of alpha-synuclein and the gradual death of dopaminergic neurons in the pars compacta of the substantia nigra, which results in striatal dopamine deficiency, are hallmarks of neuropathology. Clinically, PD is defined as having at least one extra cardinal motor characteristic (rigidity or rest tremor) in addition to bradykinesia. The majority of PD patients also have non-motor symptoms (NMSs), which increases the total burden of morbidity associated with

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parkinsonian disease.[2] The first neurodegenerative illness for which very effective therapies were developed was PD. Oral levodopa replacement treatment, which is superior to apomorphine in its magnitude of effect on motor symptoms, remains the gold standard for treating symptoms.[3] Strong dopamine agonist apomorphine has affinity for all subtypes of dopamine receptors. Its anti-parkinsonian action and pharmacological profile are comparable to those of dopamine. Sublingual apomorphine is beneficial for managing severe 'off' phases in Parkinson's disease, offering a non-invasive administration method. In uncontrolled investigations, apomorphine was initially shown to be beneficial for both motor symptoms and non-motor symptoms (NMSs)[2-4] in individuals with advanced Parkinson's disease (PD). These benefits were sustained over time. More recently, its effectiveness in reducing daytime 'off' time has been demonstrated.

The response to levodopa is maintained in the long term, but many patients develop challenging motor complications such as motor fluctuations and dyskinesia as the disease progresses. Apomorphine is now used to treat PD by managing motor problems associated with levodopa. This can be done via continuous subcutaneous mini-pump administration or by intermittent subcutaneous pen injections. As PD advances, motor fluctuations pose increasing challenges. These fluctuations manifest as either predictable end-of-dose motor decline ('wearing-off') or abrupt, unpredictable loss of mobility ('on-off'). While longer-acting dopamine agonists, controlled-release levodopa, catechol-o-methyl transferase inhibitors and amantadine are commonly employed, their efficacy diminishes over time. More invasive options such as subcutaneous apomorphine, intrajejunal levodopa and deep brain stimulation (DBS) are considered as the disease progresses. Subcutaneous apomorphine, administered intermittently during 'off' periods or continuously via infusion during waking hours, proves beneficial, albeit limited by its invasive injection route and associated local tolerability issues. Alternative administration methods, such as intranasal apomorphine, sublingual and rectal routes, have drawbacks such as nasal irritation or delayed onset and lower response. Consequently, managing motor complications remains a significant challenge for patients grappling with fluctuating PD. We review the pharmacological and clinical research on the effectiveness and safety of administering subcutaneous or sublingual film apomorphine to treat motor fluctuations in PD.

Methods

Adhering to the Cochrane Handbook of Systematic Reviews of Interventions at each step[5] and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement's guidelines, we conducted this systematic review and meta-analysis.[6] The protocol of the study with the full details was registered on PROSPERO before conduction of the steps of the systematic review and meta-analysis with registration number (CRD42024558796).

Database searching

Using the following search strategy: 'Apomorphine' AND 'Parkinson's disease' OR 'Parkinsonism' AND 'Efficacy' OR 'Safety', we searched PubMed, Web of Science and Scopus for eligible articles that should undergo the screening process to determine its ability to be included in our study.

Screening

After database searching, we removed the duplicates from the resulting articles using EndNote version 7[7] software, and then, we uploaded the remaining articles on Rayyan software[8] to conduct the process of screening. First, four authors who worked independently conducted the screening by title and abstract to see the eligibility for inclusion, and then, they conducted full-text screening of the included articles from the previous step. Any conflicts were referred to a senior author to resolve.

Inclusion and exclusion criteria

The predetermined inclusion and exclusion criteria used for screening were any observational (cohort, cross-sectional or case–control) and randomised controlled trials (RCTs) investigating the effects of apomorphine in PD. Review papers, case reports and pieces written in languages other than English were all disqualified. Narrative reviews, pooled research and duplicate or incompletely detailed publications were also disregarded.

Quality assessment

We used the Cochrane Risk of Bias 2 tool for RCTs[9,10] to check for randomisation process (selection bias), deviation from intended interventions (performance bias), outcome measurement (detection bias), missing outcome data (attrition bias), selection of reported results (reporting bias) and other potential biases. Two independent reviewers decided either low, some concerns or high risk of bias and provided a quote from the study report together with a justification for each judgement. Any conflicts were resolved by discussion with a third reviewer if necessary.

Data extraction

Using Microsoft Excel sheets, four independent authors conducted the process of data extraction to extract the baseline data (study design, country, sample size, groups, age and gender) in addition to the outcomes (change in UPDRS motor score, odds ratio [OR], hazard ratio [HR] of adverse events as nausea, somnolence, headache, dizziness, dyskinesia and neurological side effects of the included studies). Any differences or conflicts were resolved by a senior author.

Statistical analysis

Using Review Manager version 5.4 software,[11,12] we conducted the meta-analysis of the included studies by pooling the mean difference (MD) in continuous variables, number and total of dichotomous variables to measure the OR and generic inverse variance of OR or HR as they were reported in the included studies. The results were considered statistically significant at

$P \leq 0.05$. The used confidence intervals (CIs) were 95%, and the I^2 was used for testing the heterogeneity with the P value for significance.

Sensitivity analysis

Using OpenMetaAnalyst software, we conducted sensitivity analysis using a leave-one-out method to remove the studies that caused heterogeneity in the heterogeneous outcomes.

Results

Database searching and screening

The database searching process yielded a total of 9 articles with 960 duplicates, so a total of 3325 articles entered the title and abstract screening. A total of 2365 articles were excluded, and then, 27 articles were screened by full text to yield a total of 13 articles[13-24] for the meta-analysis. Figure 1 shows the PRISMA flow diagram.

Quality assessment

We used the Cochrane Risk of Bias 2 tool for RCTs[9] to check for randomisation process (selection bias), deviation from intended interventions (performance bias), outcome measurement (detection bias), missing outcome data (attrition bias), selection of reported results (reporting bias) and other potential biases [Figure 2].

Baseline characteristics

All the included 13 articles were RCT studies conducted in different countries including, the USA, Italy, Japan, Germany, France, the United Kingdom and others. Most of the studies compared apomorphine versus placebo. The mean age of the participants ranged from 56.3 years to 72.3 years [Table 1].

Meta-analysis

Change in UPDRS motor score

The analysis of the UPDRS motor score, based on 11 studies with 855 patients, revealed a statistically significant improvement favoring apomorphine (MD = −0.50, 95% CI = [−1.11, 0.11], P = 0.11). Pooled studies were heterogeneous (P = 0.00001; I^2 = 97%). To address the heterogeneity, we applied a random-effects model and conducted a sensitivity analysis by excluding one study at a time. Despite these efforts, the heterogeneity persisted, likely due to methodological discrepancies and variations across the included studies [Figure 3].

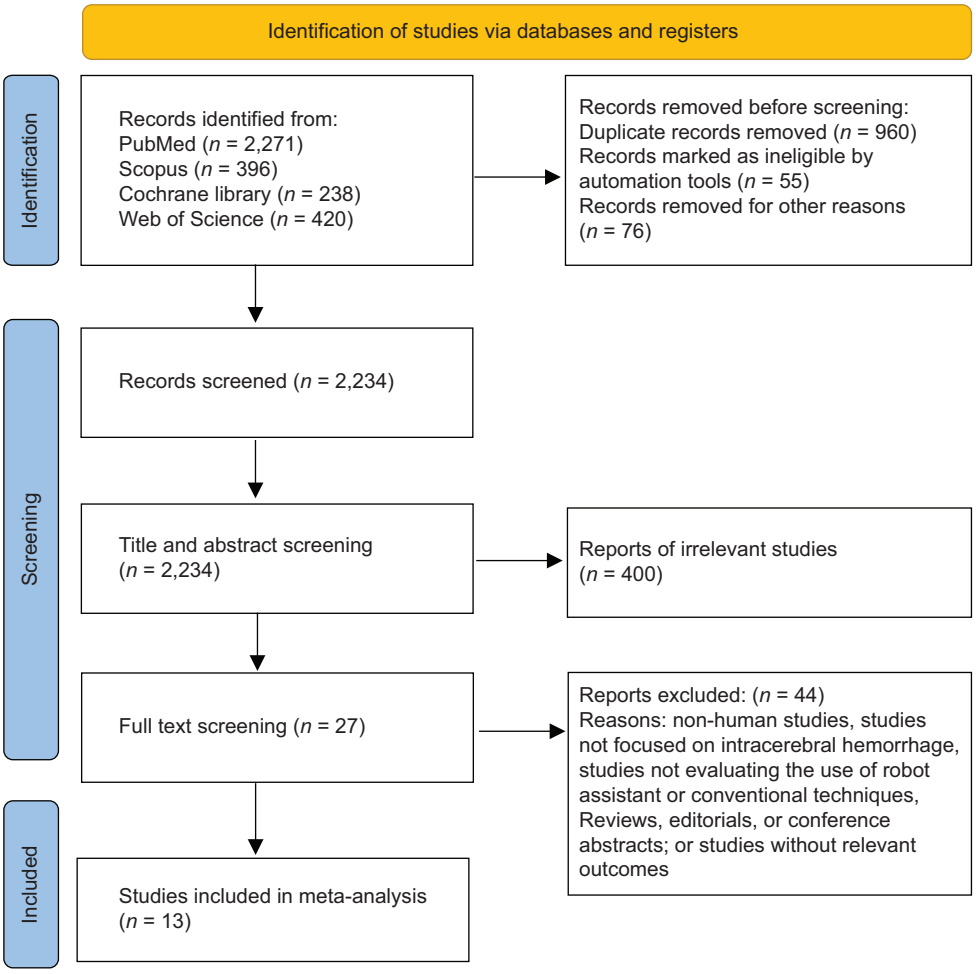

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of included studies

Nausea

Nausea in patients with PD was found to be more statistically significantly associated with apomorphine compared to the placebo group OR of 3.97 (95% CI: 2.12, 7.43, $P = 0.0001$) and heterogeneity measured by $I^2 = 0$, $P = 0.48$ [Figure 4].

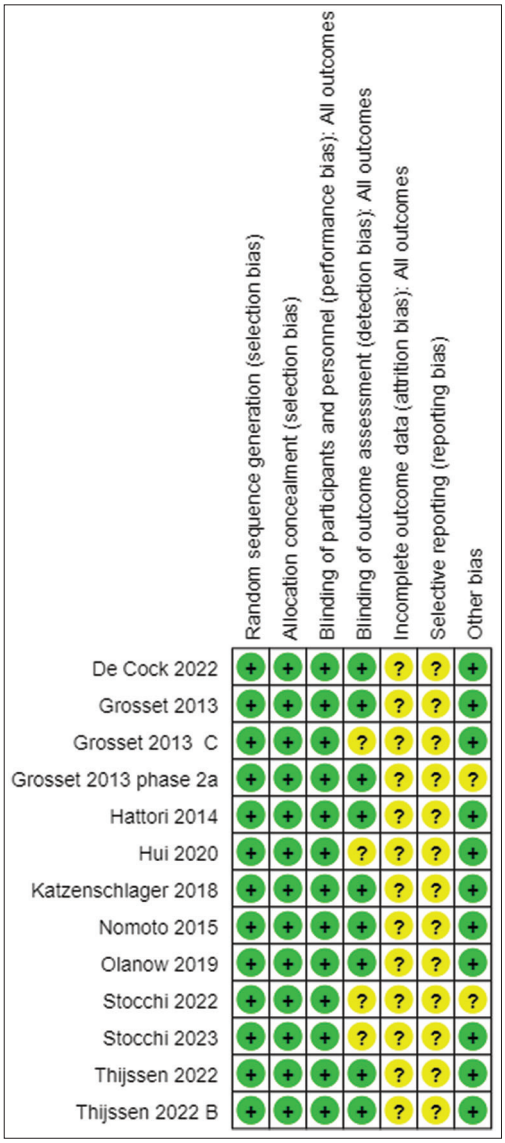

Figure 2: Cochrane ROB 2

Somnolence

Somnolence in patients with PD was found to be more statistically significantly associated with apomorphine compared to the placebo group OR of 6.36 (95% CI: 2.43, 16.62, $P = 0.0002$) and heterogeneity measured by $I^2 = 0$, $P = 0.43$ [Figure 5].

Dizziness

Dizziness in patients with PD was found to be more statistically significantly associated with apomorphine compared to the placebo group OR of 5.40 (95% CI: 1.72, 16.98, $P = 0.004$) and heterogeneity measured by $I^2 = 0$, $P = 0.64$ [Figure 6].

Dyskinesia

Dyskinesia in patients with PD was found to be more statistically significantly associated with apomorphine compared to the placebo group OR of 12.43 (95% CI: 2.30, 67.11, $P = 0.003$) and heterogeneity measured by $I^2 = 0$, $P = 0.82$ [Figure 7].

Headache

Headache in patients with PD was found to be more statistically significantly associated with apomorphine compared to the placebo group OR of 3.20 (95% CI: 1.25, 8.15, $P = 2.44$) and heterogeneity measured by $I^2 = 0$, $P = 0.94$ [Figure 8].

Yawning

Yawning in patients with PD was found to be more statistically significantly associated with apomorphine compared to the placebo group OR of 4.36 (95% CI: 0.66, 28.79, $P = 0.13$) and heterogeneity measured by $I^2 = 0$, $P = 0.97$ [Figure 9].

Discussion

The current study showed that the change in UPDRS motor scores was significantly improved in the apomorphine group compared to the placebo group. Our included studies assessed different routes of apomorphine administration, including subcutaneous and sublingual methods. A study by

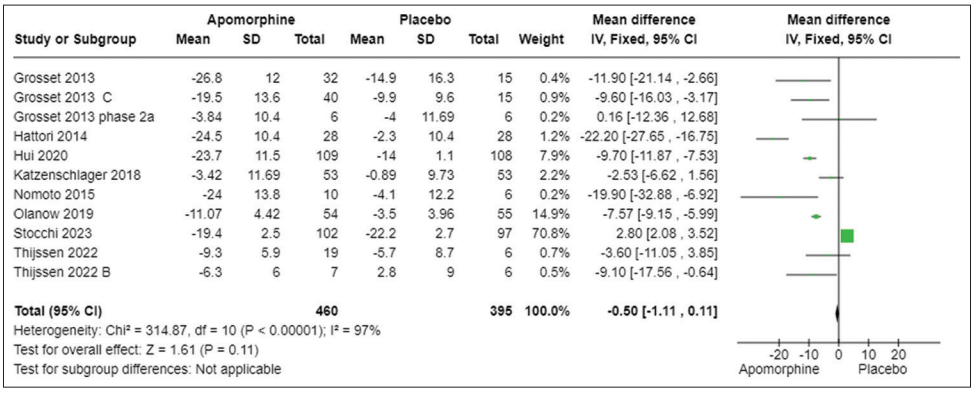

Figure 3: Analysis showing change in UPDRS motor score. CI: Confidence interval

Table 1: Summary and baseline characteristics of the included studies

Study ID	Design	Country	Group 1	Group 2	Apomorphine dose and route of administration	Sample size		Age		Male	
						Group 1	Group 2	Group 1	Group 2	Group 1, *n* (%)	Group 2, *n* (%)
De Cock, 2022	RCT 'cross-over study'	France	Placebo->apomorphine	Apomorphine->placebo	SC apomorphine (up to 5 mg/h)	21	25	62.95 (11)	64.13 (7.3)	13 (65)	14 (56)
Inhaled apomorphine/ placebo. Respirable doses (drug predicted to reach the lung), ascending through 1.5, 2.3, 3.0 and 4.0 mg	32	UK	Inhaled apomorphine	Placebo			15	61.3	59.1	81.3	80.0
Grosset, 2013 phase 2a	RCT	UK	Inhaled apomorphine	Placebo	Three escalating single doses of inhaled apomorphine (0.2, 0.5 and 0.8 mg fine particle dose)	6	6	61.0 (7.1)	56.3 (10.1)	5 (83.3)	5 (83.3)
Grosset, 2013 phase 3	RCT	UK	Apomorphine	Placebo	Three escalating fine particle doses of 1.5, 2.5, 3.5 and 4.5 mg	40	15	65.6 (7.7)	65.8 (5.7)	20 (50.0)	8 (53.3)
Hattori, 2014	RCT 'Cross over study'	Japan	Placebo->apomorphine	Apomorphine->placebo	Apomorphine hydrochloride 10 mg/mL	15	13	64.3 (10.9)	58.5 (9.9)	7 (46.7)	8 (61.5)
Hui, 2020	RCT 'open label'	Canada	Apomorphine	-	Apomorphine sublingual film 10 mg	141	-	63.5 (8.8)	-	89 (63.1)	-
Katzenschlager, 2018	RCT	UK	Apomorphine	Placebo	Apomorphine infusion (mean final dose 4.68 mg/h)	53	53	63·6 (9·3)	63·0 (8·3)	34 (64)	32 (60)
Nomoto, 2015	RCT	Japan	SC apomorphine	Placebo	SC apomorphine. The maintenance dose of apomorphine (1–6 mg per dose)	10	6	57.7 (11.4)	58.8 (5.3)	4 (40.0)	1 (16.7)
Olanow, 2019	RCT	Multicentre study (32 in the USA and 1 in Canada)	Apomorphine	Placebo	Apomorphine sublingual film (10–35 mg)	54	55	62·9 (9·79)	62·5 (8·12)	37 (69)	31 (56)
Stocchi, 2022	RCT	Multicentre study (13 clinical sites in Italy and the United States)	Apomorphine 'cross-over study'	-	Apomorphine sublingual film	40		63.7 (8.68)		26 (65.0)	
Stocchi, 2023	RCT	Multicentre study (13 clinical sites in Italy and the United States)	Apomorphine 'cross-over study'	-	Apomorphine sublingual film	112		64.4 (8.8)		78 (69.6)	
Thijssen, 2022	RCT	The Netherlands	Apomorphine	Placebo	SC apomorphine (2, 3, 4 mg)	26	9	64.2 (9.2)	63.3 (6.3)	19 (73)	4 (44)
Thijssen, 2022 B	RCT	The Netherlands	Apomorphine	placebo	2 mg SC apomorphine	8	4	39 (34.85)	39 (42.59)	3 (37.5)	2 (50)

SC: Subcutaneous, RCT: Randomised controlled trial

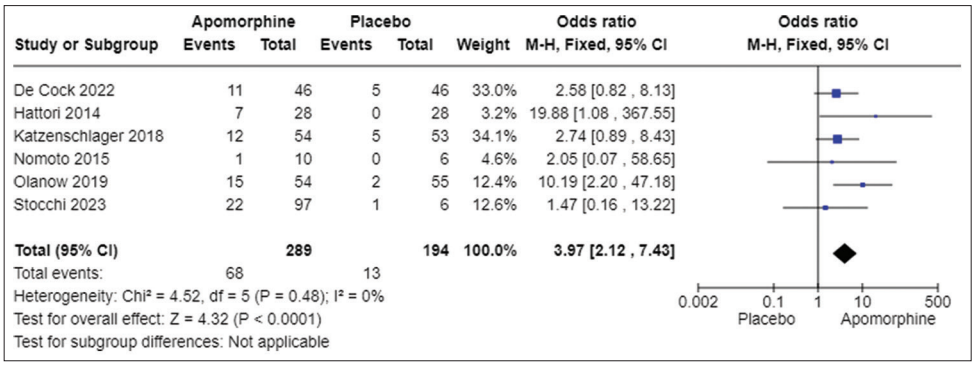

Figure 4: Analysis showing nausea. CI: Confidence interval

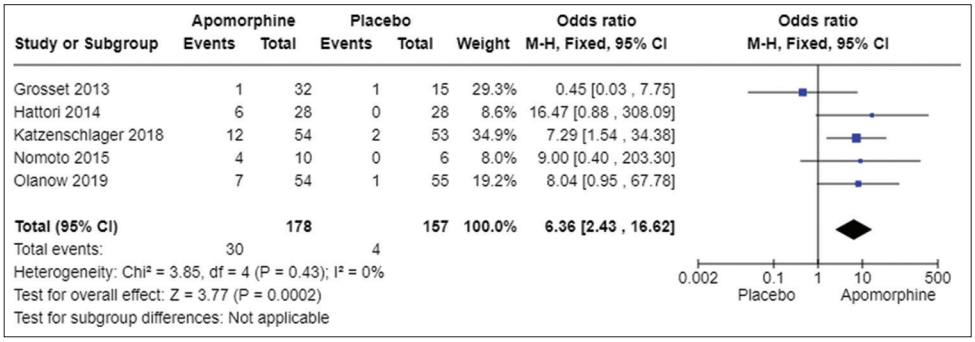

Figure 5: Analysis showing somnolence. CI: Confidence interval

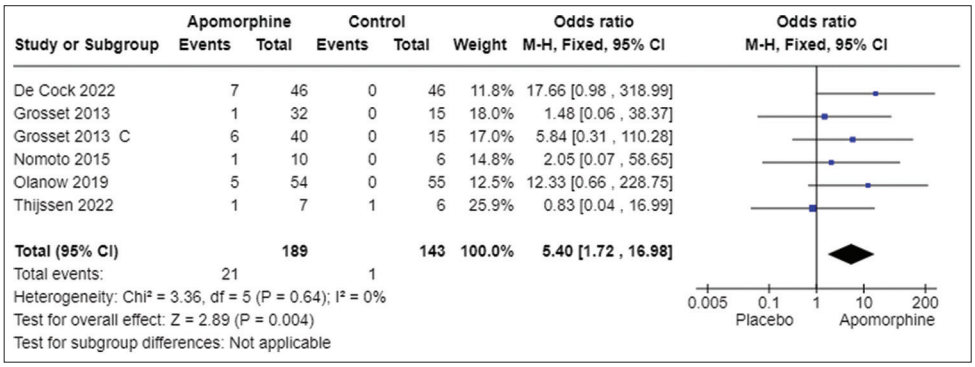

Figure 6: Analysis showing dizziness. CI: Confidence interval

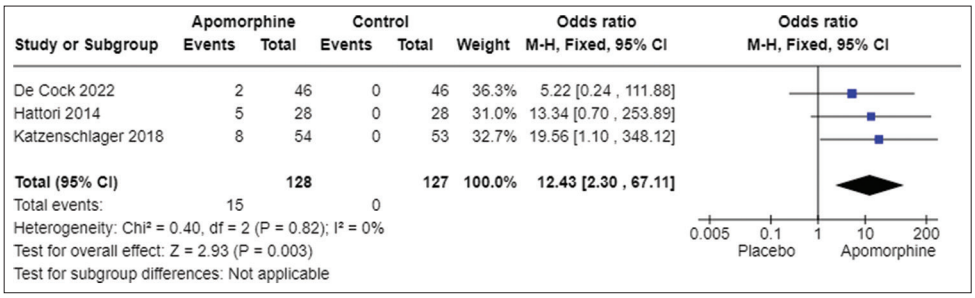

Figure 7: Analysis showing dyskinesia. CI: Confidence interval

Carbone *et al*.[25] demonstrated that continuous subcutaneous apomorphine infusion (CSAI) is one of the mainstays of treatment for severe Parkinson's disease (PD), alongside deep brain stimulation (DBS) and levodopa/carbidopa intestinal gel (LCIG) infusions.[26,27] In contrast to oral medications, infusion therapies target continual dopaminergic activation and are predicated on continuous drug administration. Stimulating the striatal dopamine receptor continuously can prevent or

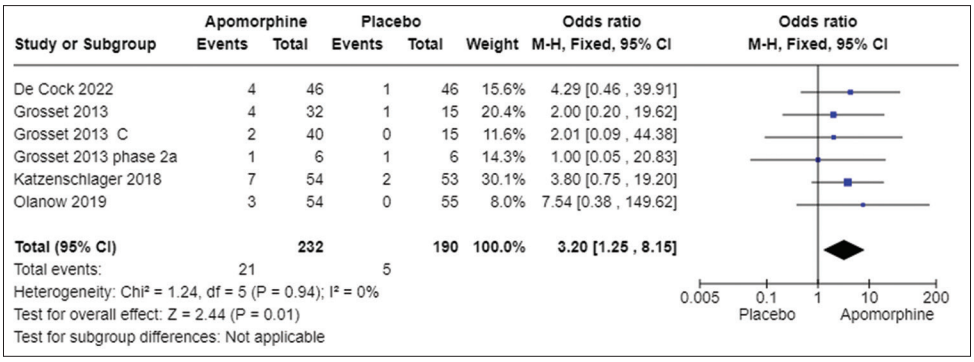

Figure 8: Analysis showing headache. CI: Confidence interval

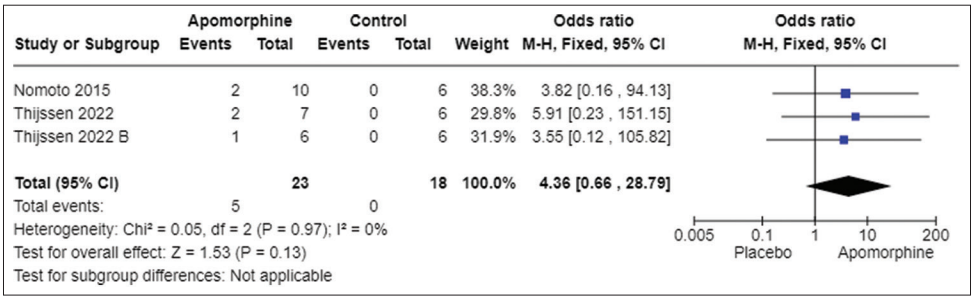

Figure 9: Analysis showing yawning. CI: Confidence interval

lessen drug-induced dyskinesias in addition to reducing response oscillations. In contrast to sporadic apomorphine injections, randomised placebo-controlled trials evaluating the effectiveness of CSAI were notably lacking until recently. The effectiveness of CSAI as monotherapy or in conjunction with levodopa has been repeatedly documented in a number of uncontrolled open-label trials,[28-30] with an average 'of' time reduction of 59.3% and a reduction in dyskinesia severity of 32.4%.[31] Consistent with these findings, a prospective investigation verified a significant decrease in the occurrence and intensity of dyskinesias among PD patients receiving CSAI.[21] Improvements in dyskinesia typically correspond with a reduction in oral medicine, suggesting that the reduction in dyskinesia is greatest in individuals who can rely on CSAI as a monotherapy.[21,32] Antiemetics, such as trimethobenzamide or domperidone, can be temporarily administered as a prophylactic measure to decrease nausea and vomiting in reaction to apomorphine.[33] At the initiation of apomorphine treatment, patients are more likely to experience nausea, vomiting, and hypotension with intermittent subcutaneous apomorphine compared to continuous subcutaneous apomorphine infusion (CSAI).[29] The most frequent adverse responses are cutaneous and subcutaneous, which include bruising, subcutaneous nodules and, in rare cases, necrosis or abscess development at injection or infusion sites. Nausea and somnolence are the next most common adverse reactions. According to histology, subcutaneous nodules appear as infiltrates that include lymphocytes, histiocytes, eosinophils and pigments that resemble melanin. In chronic cases, there may also be fibrosis.[34,35] Even while these skin responses are often moderate, in rare instances, necrosis and abscess may result in treatment withdrawal. By practicing good skin cleanliness, switching up the injection location and using fresh needles for every injection, this danger can be decreased. Adverse responses involving the skin and subcutaneous layers included bruises, subcutaneous nodules, and in rare cases, necrosis or abscess formation. Based on controlled trials, the adverse event profile of intermittent subcutaneous apomorphine injections is typically mild to moderate. The APO202 trial found that the incidence of adverse events was nearly equal in the apomorphine and placebo groups (89% vs. 85%) and that the majority of the occurrences were classified as treatment-emergent adverse events. Only yawning (40%) and somnolence (35%) were recorded in the apomorphine group.

Dyskinesias were recorded as an adverse event in 35% of patients treated with apomorphine and in 11% of the placebo group. Thirty per cent of patients taking apomorphine reported experiencing nausea during the trial's inpatient phase; in contrast, this was essentially never the case during the outpatient period that followed.

Apomorphine has traditionally been administered subcutaneously to patients with PD, either as a continuous infusion or as sporadic pen injections. Although this approach has shown to be effective, one of the most frequent side effects is skin irritation, which can make therapy more difficult or cause withdrawal.

Due to needle anxiety, this delivery may also provide difficulties for certain individuals; for others, bradykinesia and tremor may make the pen injection difficult to utilise in treating an acute 'of' phase. Apomorphine's exceptional effectiveness

is hampered by the absence of an 'easier' and less intrusive administration method. As a result, several other delivery methods have been tried, and several are now undergoing clinical research.

The feasibility of oral apomorphine is hindered by the molecule's extensive first-pass hepatic metabolism.[36] Nevertheless, recent studies in animal models of PD have explored the administration of apomorphine and its prodrug (dipalmitoyl apomorphine) through oral lipid-based formulations. Although still in the pre-clinical phase, this formulation shows promise for achieving sustained dopaminergic stimulation due to its controlled drug release.[37] Sublingual formulations of apomorphine have been considered a practical alternative to subcutaneous administration for many years.[38-40] Requiring no needles, causing minimal discomfort and being easily administered, a sublingual formulation proves advantageous even during severe 'off' phases. An innovative sublingual apomorphine formulation, represented by a bilayer two-film strip containing apomorphine (APL-130277), has demonstrated consistent efficacy in alleviating 'off' periods across various clinical trials.

Previous studies[16,41,42] have shown that inhaled apomorphine significantly improved UPDRS-III scores compared to placebo. These results validate the conclusions drawn from our research. In addition, apomorphine inhalation increased the likelihood of both 'wearing off' and 'sudden off' events ending earlier than placebo. Thijssen *et al*.[23] conducted a study evaluating the breath-actuated oral inhalation device, AZ-009, which utilises Staccato technology.[43,44] Upon inhalation, this device thermally generates fine aerosol particles of apomorphine, facilitating rapid delivery to the deep lungs and subsequent systemic absorption. Our findings demonstrate the efficacy of apomorphine in improving motor function across various routes of administration. However, the observed adverse events range from mild to severe. We propose conducting more targeted RCTs to precisely identify and characterise these adverse events. Additionally, further evaluation of apomorphine's impact on neurological and cognitive aspects is recommended to enhance our understanding of its usage and provide more accurate insights.uent systemic exposure.

A significant strength of our systematic review and meta-analysis lies in its exclusive focus on RCTs, enabling a thorough comparison of apomorphine efficacy through various routes of administration. Nevertheless, it is important to acknowledge the potential limitation arising from variations in drug dosage among the included studies. Consequently, we advocate for further trials to elucidate the optimal dosage and follow-up period, enhancing the precision and applicability of future findings.

Conclusion

The effectiveness of apomorphine is evident in individuals with PD, as it enhances the UPDRS motor score. The range of adverse events associated with its use spans from mild to moderate. It is advisable to conduct additional assessments of the effects of apomorphine on neurological and cognitive aspects. This will contribute to a more comprehensive understanding of its utilisation and yield more precise insights into its impact on these aspects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna) 2017;124:901-5.
2. Poewe WH, Lees AJ, Stern GM. Low-dose L-dopa therapy in Parkinson's disease: A 6-year follow-up study. Neurology 1986;36:1528-30.
3. Kempster PA, Frankel JP, Stern GM, Lees AJ. Comparison of motor response to apomorphine and levodopa in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:1004-7.
4. Sweet RD, McDowell FH. Five years' treatment of Parkinson's disease with levodopa. Therapeutic results and survival of 100 patients. Ann Intern Med 1975;83:456-63.
5. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al*, (editors). Cochrane handbook for systematic reviews of interventions version 6.5. Cochrane, 2024. Available from www.training.cochrane.org/handbook. [Last updated on 2024 Aug]. [Last accessed on 2024 Nov 22].
6. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010;8:336-41.
7. Eapen BR. EndNote 7.0. Indian J Dermatol Venereol Leprol 2006;72:165-6.
8. Rayyan.Available from: https://rayyan.ai/. [Last accessed on 2024 Nov 22].
9. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
10. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, *et al.* The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. Nat Med 2021;27:1954-60.
11. Maisano F, Torracca L, Oppizzi M, Stefano PL, D'Addario G, La Canna G, *et al.* The edge-to-edge technique: A simplified method to correct mitral insufficiency. Eur J Cardiothorac Surg 1998;13:240-5.
12. Palau P, Amiguet M, Domínguez E, Sastre C, Mollar A, Seller J, *et al.* Short-term effects of dapagliflozin on maximal functional capacity in heart failure with reduced ejection fraction (DAPA-VO(2)): A randomized clinical trial. Eur J Heart Fail 2022;24:1816-26.
13. De Cock VC, Dodet P, Leu-Semenescu S, Aerts C, Castelnovo G, Abril B, *et al.* Safety and efficacy of subcutaneous night-time only apomorphine infusion to treat insomnia in patients with Parkinson's disease (APOMORPHEE): A multicentre, randomised, controlled, double-blind crossover study. Lancet Neurol 2022;21:428-37.
14. Grosset KA, Malek N, Morgan F, Grosset DG. Inhaled dry powder apomorphine (VR040) for off periods in Parkinson's disease: An in-clinic double-blind dose ranging study. Acta Neurol Scand 2013;128:166-71.
15. Grosset KA, Malek N, Morgan F, Grosset DG. Phase IIa randomized double-blind, placebo-controlled study of inhaled apomorphine as acute challenge for rescuing 'off' periods in patients with established Parkinson's disease. Eur J Neurol 2013;20:1445-50.
16. Grosset KA, Malek N, Morgan F, Grosset DG. Inhaled apomorphine in patients with 'on-off' fluctuations: A randomized, double-blind, placebo-controlled, clinic and home based, parallel-group study. J Parkinsons Dis 2013;3:31-7.
17. Hattori N, Nomoto M, 6500-004 Study Group. Sustained efficacy of apomorphine in Japanese patients with advanced Parkinson's disease. Parkinsonism Relat Disord 2014;20:819-23.

18. Hui JS, Fox SH, Neeson W, Bhargava P, Pappert E, Blum D, *et al.* Open-label titration of apomorphine sublingual film in patients with Parkinson's disease and "OFF" episodes. Parkinsonism Relat Disord 2020;79:110-6.
19. Olanow CW, Factor SA, Espay AJ, Hauser RA, Shill HA, Isaacson S, *et al.* Apomorphine sublingual film for off episodes in Parkinson's disease: A randomised, double-blind, placebo-controlled phase 3 study. Lancet Neurol 2020;19:135-44.
20. Nomoto M, Kubo S, Nagai M, Yamada T, Tamaoka A, Tsuboi Y, *et al*. A randomized controlled trial of subcutaneous apomorphine for Parkinson disease: A repeat dose and pharmacokinetic study. Clin Neuropharmacol 2015;38:241-7.
21. Katzenschlager R, Hughes A, Evans A, Manson AJ, Hoffman M, Swinn L, *et al.* Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: A prospective study using single-dose challenges. Mov Disord 2005;20:151-7.
22. Stocchi F, Peckham EL, De Pandis MF, Sciarappa K, Kleiman R, Agbo F, *et al*. A randomized thorough QT study of apomorphine sublingual film in patients with Parkinson's disease. Clin Pharmacol Drug Dev 2022;11:1068-77.
23. Thijssen E, den Heijer JM, Puibert D, van Brummelen EM, Naranda T, Groeneveld GJ. Safety and pharmacokinetics of multiple dosing with inhalable apomorphine (AZ-009), and its efficacy in a randomized crossover study in Parkinson's disease patients. Parkinsonism Relat Disord 2022;97:84-90.
24. Thijssen E, den Heijer J, Puibert D, Moss L, Lei M, Hasegawa D, *et al*. A randomized trial assessing the safety, pharmacokinetics, and efficacy during morning off of AZ-009. Mov Disord 2022;37:790-8.
25. Carbone F, Djamshidian A, Seppi K, Poewe W. Apomorphine for Parkinson's disease: Efficacy and safety of current and new formulations. CNS Drugs 2019;33:905-18.
26. Antonini A. New routes of dopaminergic drug delivery in patients with Parkinson's disease. Lancet Neurol 2020;19:105-6.
27. Antonini A, Jenner P. Apomorphine infusion in advanced Parkinson disease. Nat Rev Neurol 2018;14:693-4.
28. Sesar Á, Fernández-Pajarín G, Ares B, Relova JL, Arán E, Rivas MT, *et al.* Continuous subcutaneous apomorphine in advanced Parkinson's disease patients treated with deep brain stimulation. J Neurol 2019;266:659-66.
29. Pietz K, Hagell P, Odin P. Subcutaneous apomorphine in late stage Parkinson's disease: A long term follow up. J Neurol Neurosurg Psychiatry 1998;65:709-16.
30. Borgemeester RW, Drent M, van Laar T. Motor and non-motor outcomes of continuous apomorphine infusion in 125 Parkinson's disease patients. Parkinsonism Relat Disord 2016;23:17-22.
31. Todorova A, Chaudhuri KR. Subcutaneous, intranasal and transdermal dopamine agonists in the management of Parkinson's disease. In: Galvez-Jimenez N, Fernandez HH, Espay AJ, Fox SH, editors. Parkinson's Disease. 1st ed. Cambridge University Press; 2016. p. 48-62. Available from: https://www.cambridge.org/core/product/identifier/9781107284210%23CT-bp-6/type/book_part. [Last accessed on 2024 Mar 01].
32. Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: Long-term follow-up study of 64 patients. Mov Disord 2002;17:1235-41.
33. Corsini GU, Del Zompo M, Gessa GL, Mangoni A. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. Lancet 1979;1:954-6.
34. Loewe R, Püspök-Schwarz M, Petzelbauer P. Apomorphine hyperpigmentation. Hautarzt 2003;54:58-63.
35. Acland KM, Churchyard A, Fletcher CL, Turner K, Lees A, Dowd PM. Panniculitis in association with apomorphine infusion. Br J Dermatol 1998;138:480-2.
36. Nicolle E, Pollak P, Serre-Debeauvais F, Richard P, Gervason CL, Broussolle E, *et al.* Pharmacokinetics of apomorphine in parkinsonian patients. Fundam Clin Pharmacol 1993;7:245-52.
37. Borkar N, Andersson DR, Yang M, Müllertz A, Holm R, Mu H. Efficacy of oral lipid-based formulations of apomorphine and its diester in a Parkinson's disease rat model. J Pharm Pharmacol 2017;69:1110-5.
38. Argiolas A, Hedlund H. The pharmacology and clinical pharmacokinetics of apomorphine SL. BJU Int 2001;88 Suppl 3:18-21.
39. Isaacson S, Pappert E, Dzyngel B, BIlbault T, Argo A. Safety of sublingual apomorphine (APL-130277) for the treatment of OFF episodes in patients with Parkinson's disease (P2.337). Neurology 2016;86 Suppl 16:P2.337.
40. Lees AJ, Montastruc JL, Turjanski N, Rascol O, Kleedorfer B, Peyro Saint-Paul H, *et al.* Sublingual apomorphine and Parkinson's disease. J Neurol Neurosurg Psychiatry 1989;52:1440.
41. Kapoor R, Turjanski N, Frankel J, Kleedorfer B, Lees A, Stern G, *et al.* Intranasal apomorphine: A new treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:1015.
42. Ondo W, Hunter C, Almaguer M, Jankovic J. A novel sublingual apomorphine treatment for patients with fluctuating Parkinson's disease. Mov Disord 1999;14:664-8.
43. Rabinowitz JD, Lloyd PM, Munzar P, Myers DJ, Cross S, Damani R, *et al.* Ultra-fast absorption of amorphous pure drug aerosols via deep lung inhalation. J Pharm Sci 2006;95:2438-51.
44. Rabinowitz JD, Wensley M, Lloyd P, Myers D, Shen W, Lu A, *et al.* Fast onset medications through thermally generated aerosols. J Pharmacol Exp Ther 2004;309:769-75.