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REVIEW ARTICLE

The Many Faces of Apomorphine: Lessons from the Past and Challenges for the Future

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Abstract Apomorphine is now recognized as the oldest antiparkinsonian drug on the market. Though still underused, it is increasingly prescribed in Europe for patients with advanced Parkinson's disease (PD) with motor fluctuations. However, its history is far from being limited to movement disorders. This paper traces the history of apomorphine, from its earliest empirical use, to its synthesis, pharmacological development, and numerous indications in human and veterinary medicine, in light of its most recent uses and newest challenges. From shamanic rituals in ancient Egypt and Mesoamerica, to the treatment of erectile dysfunction, from being discarded as a pharmacological tool to becoming an essential antiparkinsonian drug, the path of apomorphine in the therapeutic armamentarium has been tortuous and punctuated by setbacks and groundbreaking discoveries. Throughout history, three main clinical indications stood out: emetic (gastric emptying, respiratory disorders, aversive conditioning), sedative (mental disorders, clinical anesthesia, alcoholism), and antiparkinsonian (fluctuations). New indications may arise in the future, both in PD (palliative care, nonmotor symptoms, withdrawal of oral dopaminergic medication), and outside PD, with promising work in neuroprotection or addiction.

Key Points

Apomorphine has a long and tortuous path in the therapeutic armamentarium, with numerous indications in human and veterinary medicine.

The controversy that apomorphine aroused among clinicians in the past (and in some ways, continues among neurologists) can be explained by the lack of controlled studies and its affiliation to morphine.

There are three main indications for apomorphine: emetic, sedative, and antiparkinsonian.

This old drug needs to be reconsidered by clinicians and will benefit from current galenic and technical advances, both in Parkinson's disease and in other indications.

1 Introduction

Apomorphine is recognized as the oldest antiparkinsonian drug and is increasingly prescribed across Europe [1–3]. It is currently used by subcutaneous injection, as needed (pen) or continuously (continuous subcutaneous apomorphine infusion or CSAI), to treat motor fluctuations in patients with advanced Parkinson's disease (PD) [4]. If apomorphine was first synthesized in the middle of the 19th century, its history goes back much further. This old drug has followed a tortuous path in and out of the armamentarium, shaped by a blend of mystical beliefs and stereotypes, and punctuated by setbacks and groundbreaking

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discoveries (Table 1). In this article, we trace the rich and eventful history of apomorphine, bringing to light some of the forgotten names associated with it. There is a copious literature on apomorphine, but much of it consists of uncontrolled studies and case reports. We therefore adopted a descriptive and categorizing approach, reporting the essential archival literature on apomorphine published between 1845 and January 2018, and discussing it in light of contemporary issues. We undertook a nonsystematic database (MEDLINE, NCBI, PubMed, Google Scholar, JSTOR, BnF Gallica and the Internet Archive) search for French and English articles with the terms 'apomorphine', 'apomorphia,' and 'sulfomorphide' (Fig. 1). This analysis was supplemented with pragmatic searches using references and authors' names found in these articles.

Three main indications stood out from all the rest: emetic, antiparkinsonian, and sedative. It was quite astonishing to see the amount of controversy that apomorphine aroused among clinicians in the past and, in some ways, continues among neurologists.

2 Waterlilies and Aporphine Alkaloids: An Insight into Empirical Pharmacology

Though apomorphine is known as a synthetic product, anthropologists, ethnobotanists and pharmacologists have tracked down an early use of it in ancient civilizations, with striking cross-cultural similarities in *Nymphaea* cults between Mesoamerica and Egypt, where mind-altering plants were part of the religious and healing systems [5, 6].

The blue waterlily, *Nymphaea caerulea* Savigny, grows in the still waters of northern and central Africa [5]. An Osirian emblem [5, 6] by virtue of its natural cycle, and a

Table 1 Landmarks in the modern history of apomorphine

Date	Author(s)	Discovery
1845	Arppe (Finland)	First synthesis of apomorphine (morphine + sulfuric acid)
1848	Laurent & Gerhardt (France)	Apomorphine is named *sulfomorphide*
1851	Anderson (Scotland)	Apomorphine synthesized from codeine (+ sulfuric acid)
1869	Matthiessen and Wright (England)	*Apomorphia* synthesis (morphine + hydrochloric acid)
1869	Gee (England)	Emetic, stereotypogenic, sedative and excitatory properties (experiments on dogs and humans)
1869	Hare (England)	Treatment of alcoholism
1870	Pierce (England)	Beneficial on choreic movements in humans
1871	Siebert (Estonia)	Pharmacological study (humans, dogs, cats, frogs, rabbits)
1874	Harnack (Estonia)	Pharmacological study (mammals and frogs)
1884	Weill (France)	Apomorphine first suggested as a treatment for several motor disorders: chorea, shaking, and Parkinson's disease
1899	Douglas (USA)	Powerful sedative properties (alcoholism)
1902	Pschorr et al. (Germany)	Apomorphine structure is elucidated
1923	Amsler (Austria)	Involvement of the striatum in apomorphine's action
1935	Anderson (Canada)	Used in the treatment of *paralysis agitans*
1951	Schwab et al. (USA)	Short-lived but marked improvement in Parkinson's disease
1965	Ernst et al. (The Netherlands)	Structure similar to dopamine (rats and rabbits)
1966	Ernst and Smelik (The Netherlands)	Site of action of apomorphine in rats: neostriatum
1967	Ernst (The Netherlands)	Apomorphine acts on dopaminergic receptors
1967	Andén et al. (Sweden)	
1979	Corsini et al. (Italy)	Combination of apomorphine and domperidone prevents nausea, drowsiness, sedation, and arterial hypotension
1984	Hardie et al. (England)	Apomorphine reverses parkinsonian off-phases when administered shortly after their onset
1987	Stibe et al. (England)	Subcutaneous infusion of apomorphine in the treatment of Parkinsonian on–off fluctuations
1995	Aguettant	Apokinon® 30 mg/3 mL authorization in France to treat Parkinson's disease (pen)
2001	Tap Pharmaceutical/Abbot Laboratories	Uprima® (sublingual form of apomorphine) to treat erectile dysfunction
2004	FDA (USA)	FDA approval of Apokyn® as a rescue therapy in Parkinson's disease to treat episodes of hypomobility

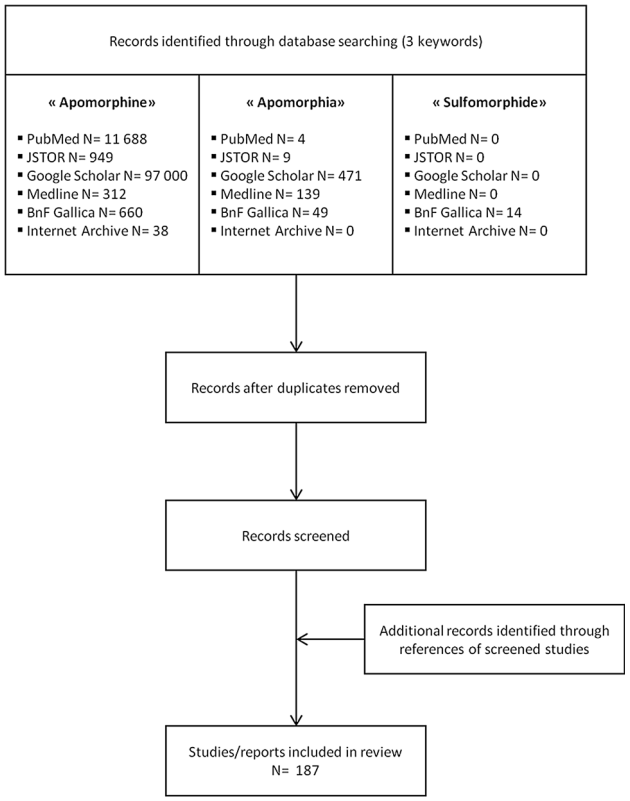

Fig. 1 Flowchart of the bibliographic search

symbol of the continual renewal of life, *N. caerulea* was extensively used as a motif in funerary art (pharaohs' tomb frescoes, jewelry, funerary ceramics) and as an ornament for the dead (wreaths of dry flowers were found in the mummified remains of Ramses II and Tutankhamun) [5, 7, 8]. Spread across Egyptian sites of religious activity between the 5th and 22nd dynasties [5, 9], the portrayal of buds or partially opened flowers is commonly associated with representations of mandrakes and opium poppies, suggesting mystical properties [5, 10], though there is no direct evidence that *N. caerulea* was actually made into a narcotic preparation [5, 7]. Its use in religious rituals is, however, reported in the *Papyrus of Ani*[1] [5, 11], and depicted in the rite of purifying the nostrils, a ritual of great importance in Egypt [5]. Reserved for the highest castes, *N. caerulea* was also reportedly used as an aphrodisiac [11, 12].

Nymphaea ampla (Salisbury) de Candolle, recognizable for its white flowers, thrives in Mesoamerican freshwater lakes [5]. Its use in religious and healing activities was first hinted at by Marlene Dobkin de Rios (cultural anthropologist), José-Luis Díaz (medical researcher), and William A. Emboden (botanist), collecting evidence from chemistry, botany, anthropology, art, literature, and history of religion [5]. The white waterlily figures prominently in pre-Columbian Mesoamerican iconography [10]. Abundant clues to its entheogenic properties are found in poems, ceramics, carved stone reliefs and frescoes, where it is constantly associated with representations of mythical beings, mushrooms,[2] human anatomy and death symbols [10, 13, 14, 56]. During the Classic Mayan period, *N. ampla* was associated with fertility and presumably used by a priestly caste to induce shamanic ecstasies and hallucinations [5, 7, 9, 14]. The *Dresden Codex* features the Waterlily Jaguar,[3] god of the Mayan netherworld, frequently associated with libations, drinking vessels and hallucinogenic enemas [5, 7, 13]. More recently, a recreational use of fresh, raw rhizomes of *N ampla* was reported in the seventies in some areas of Chiapas, Mexico [7], and aporphine alkaloids (apomorphine-like alkaloids, nupharine, nupharadine [5, 7, 9]) were subsequently isolated from its rhizomes and roots [5].

The abundant archeological and ethnographic evidence of the use of these *Nymphaea* for ritualistic purposes in both civilizations [5, 9] warrant further analytical investigation to assert the presence of apomorphine among the isolated alkaloids.

3 The 19th and 20th Centuries: From Apomorphine Synthesis to Understanding its Pharmacology

3.1 Synthesis

The credit for discovering apomorphine goes to the Finnish chemist Adolf Edvard Arppe, who synthesized it in 1845, in the form of its sulfate, by heating morphine with a slight excess of sulphuric acid [15, 16]. Soluble in caustic alkalinities, turning from white to green on keeping [15–17], the resultant product was classified as an amid by Auguste Laurent and Charles Frédéric Gerhardt and named *sulfomorphide* [16]. Of note, this different name may explain why Arppe's work tends to be overshadowed by that of Augustus Matthiessen and Charles Romley Alder Wright, who are usually regarded as the first to have synthesized apomorphine. In 1850, Thomas Anderson also obtained apomorphine by heating codeine with sulfuric acid [18–20], but none of this work seemed to stir much interest at the time. It was not until 1869, and Matthiessen and Wright's chemical investigation of the opium alkaloids, that apomorphine became known to the medical community [21, 22]. Heating morphine with concentrated hydrochloric acid, the two chemists synthesized

[1] 'The Papyrus of Ani' is referred to as *The Book of the Dead.*

[2] A well known sacred route to ecstasy in Mayan civilization.

[3] A jaguar wearing a waterlily headdress.

apomorphine *hydrochlorate*, the salt currently used in therapeutics [21], and named it *apomorphia*, to emphasize both its origin and difference from morphine[4] [21, 22]. It, too, turned green when exposed to air [21, 22]. Carrying out their research, they quickly found other ways of synthesis, repeating Arppe's experiment or heating codeine with hydrochloric acid or zinc chloride [17, 23].

3.2 Milestones Along the Road to Understanding the Pharmacology of Apomorphine

3.2.1 Chemical Formula and Structure

In 1869, apomorphine formula ($C_{17}H_{17}NO_2$) was found to be the morphine formula ($C_{17}H_{19}NO_3$) minus a water molecule (H_2O) [21], but its exact structure was only elucidated in 1902 [24]. In 1965, Anton Marie Ernst was the first to draw attention to the structure–effect relationship between apomorphine and dopamine receptors, stressing the importance of the chemical structure (OH– group or OCH_3– group at the para-position) in relation to the pharmacological effect [25–27]. The key part of the molecule in terms of its interaction with dopamine receptors was later found to be the dihydroxytetrahydroaminonapthalene moiety [28] or catechol moiety [29]. X-ray methods determined the absolute configuration of the active molecule to be 6aR [30].

3.2.2 Physiological Effects of Apomorphine

Though apomorphine was ignored for several decades following its discovery, it started to attract considerable interest after 1869, and soon became the subject of extensive clinical research, as evidenced by the abundant literature of the 19th century, particularly in the United Kingdom, France, and Germany [19, 20, 22]. The few pharmacological similarities between morphine and apomorphine were immediately noted [21, 31]: "in spite of its name, [apomorphine] is no more like morphine than sawdust is like sugar" [32]. Within a month of its synthesis, apomorphia was addressed to Dr Samuel Jones Gee for investigation [21, 22]. A wide range of physiological effects would be revealed, both in animals and humans, with interspecies and intraspecies variations in susceptibility and dose-related differential effects [20, 22, 33, 34]. The most salient characteristic was its nonirritant, certain, sustained but transitory emetic properties, when administered either orally or subcutaneously in dogs and humans [22]. "Lassitude, weakness, frequent headaches, constant nausea, and occasional sudden attacks of vomiting" were even noticed during the drug's preparation, owing to absorption through the skin [22, 31]. Stereotyped motor behaviors (dogs), excitement, pupil dilation, and epileptiform convulsions (cats) and sedation (humans) were also reported [22]. The earliest pharmacological studies, attributed to Vincent Siebert and Erich Harnack [33, 34], confirmed Gee's findings and highlighted cardiovascular, hemodynamic, and temperature changes [33, 34], as well as stereotyped behavior in a variety of susceptible species (Table 2 [22, 33, 34]).

3.2.3 Locus of Action

Early experiments led Gee to believe that apomorphine-induced symptoms were "referable to the nervous system" [22]. Subsequent experiments exploring movement, emesis, motivated behavior, respiratory control, and sensation strengthened the hypothesis of a powerful action on the central nervous system (CNS), in multiple brain centers, and not on the *nervus vagus* [9, 19, 20, 27, 33, 46–48]. Harnack emphasized two brain centers in particular: vomiting ('*Brechcentrum*') and respiratory ('*Respirationscentrum*') [33]. In dogs, Lazarus Thumas neutralized apomorphine-induced emesis by destroying a portion of the medulla oblongata [49], whereby the respiratory center was separated from the vomiting one [19, 50]. The powerful emetic action of apomorphine was attributed to a selective effect on the chemoreceptor trigger zone [32]. Experiments with decerebrate dogs showed that vomiting was induced when apomorphine was administered either *parenterally* or *locally* to the medullary chemoreceptor trigger zone, whereas depression of muscular rigidity only appeared when apomorphine was administered *parenterally* [50, 51]. Caesar Hans Amsler was the first to strongly associate the action of apomorphine with the striatum, abolishing the apomorphine-induced pecking syndrome in pigeons with the surgical removal of the *corpora striata* [39]. These findings were later strengthened by the induction of compulsive gnawing behavior in rats after the implementation of crystalline apomorphine in the dorsal part of the caudate nucleus and/or globus pallidus [26]. Pretreatments depleting central catecholamine stores or inhibiting monoamine oxidase failed to modify the gnawing-provoking action of apomorphine [27]. Ernst therefore concluded that apomorphine has a direct dopamine-like effect on receptors and may act as a substitute in the case of dopamine deficiency in the extrapyramidal structures (e.g., PD [27]), hence providing a post hoc explanation for the discovery by Robert S. Schwab and colleagues [52, 53]. These experiments spurred the resurgence of basic and clinical research on apomorphine [29] and have since become a classic in the literature [53]. Apomorphine-induced stereotyped behavior in rodents was then attributed to the direct stimulation of postsynaptic dopamine receptors [54].

[4] The prefix 'Apo' meaning 'away from'.

Table 2 Summary of the documented physiological effects of apomorphine in various species

	Humans	Rats	Mice	Dogs	Rabbits	Cats	Monkeys	Frogs	Pigeons	Guinea pigs
Movement	↓ Tremor in Parkinson's disease	Stereotyped behaviors: sniffing and head and limb movements (low-intensity component), gnawing, licking, biting, (high-intensity component)	Stereotyped behaviors: sniffing, licking, biting	Stereotyped behaviors: incessant running in circles	Stereotyped behaviors: licking, gnawing. Muscle paralysis, respiratory failure, convulsions and death (highest doses)	Repetitive movements	Stereotypic behavior (> 200 µg/kg)	Motor stimulation followed by paralysis	Stereotyped behaviors: pecking (sometimes mistakenly referred to as a *feeding hallucination*)	Stereotyped behaviors: agitation, gnawing
Body temperature	↓	↓	↓	↓	↑	?	?	?	?	?
Blood pressure	↓	↓	?	↓	↓	↓	?	?	?	?
Gastrointestinal tract	Nausea and emesis	Resistant to emesis ↑ Salivation	?	Emesis (but tachyphylaxis to the emetic effect)	Resistant to emesis	Inconstant emesis	Resistant to emesis	Resistant to emesis	Inconstant emesis	?
Hormone release	↑ Growth hormone ↓ Prolactin	↓ Plasma prolactin concentration in intact male rats	?	↑ Gastrin	?	↑ Gastrin	?	?	?	?
Heart rate and EEG changes	↓ Inhibition of sympathetic cardiac nerve function	Desynchronization of EEG activity	?	↑ (But no change in noradrenaline plasma levels) Potentiates vagal bradycardia	↓	↓	?	?	?	?
Central nervous system	Sedation Yawning Slight and transient delirium in one case of chronic Bright's disease	Yawning Intraspecies aggression	?	Nervousness or sedation, depending on the dose	Nervousness, agitation	Arousal	Yawning (25–100 µg/kg) Intraspecies aggression	?	Arousal	Arousal
Sexual behavior	Penile erections Spontaneous erections	Penile erections Spontaneous erections	Proerectile Genital grooming	?	?	?	Penile erections, masturbation (50–200 µg/kg)	?	?	?
Others	Diaphoresis Dilatation of pupils	?	?	?	?	Pupil dilation	?	?	?	?
References	[22, 28, 33, 35–38]	[28, 33, 36, 39, 40]	[36, 41]	[22, 33, 34, 36, 38, 42–44]	[33]	[20, 22, 33, 34, 43]	[36, 45]	[33]	[20, 39]	[39, 40]

↑ Increase, ↓ decrease, ? undocumented, *EEG* electroencephalogram

Typical stereotypies were provoked by intrastriatal microinjection of apomorphine in nialamide-pretreated rats, but blocked by a prior injection of chlorpromazine (dopaminergic antagonist), thus supporting the idea that apomorphine acts on dopaminergic receptors located in the striatum [55]. The paradoxical suppression of chorea and dyskinetic movements in humans led to the hypothesis that apomorphine acts primarily on presynaptic receptors [56]. Finally, the discovery that apomorphine does not solely act on the dopaminergic pathway was prompted by the observation that its effect on tremor can also be mediated by serotonergic neurons [57]. It is now known that apomorphine also acts on serotonergic and adrenergic receptors [58, 59].

3.3 Apomorphine as an Investigative Tool

The history of apomorphine is intrinsically linked to the development of pharmacology, neurobiology, and neurochemistry. By the 1960 s, apomorphine had become one of the most intensively studied drugs in neuropsychopharmacology and behavioral therapy, largely based on Ernst's work [25–27, 53, 60]. It has been frequently used as a pharmacological probe for investigating central dopaminergic neurotransmission and screening new drugs (Fig. 2).

Being a nonspecific dopaminergic agonist [58, 59], apomorphine can be used as a pharmacological tool and is suitable for stimulating dopamine receptors and exploring dopaminergic pathways [61]. Apomorphine-induced stereotyped behaviors in experimental animals have been used as an index of central dopaminergic activity and has contributed to the understanding of dopaminergic systems [62]. Apomorphine-induced yawning in rats and humans [29] is a biological marker for central dopamine system alterations (enhanced responsiveness is found in patients with migraine or heroin addiction) and a measurement of central dopamine function [28, 63, 64]. Although further studies are needed to assess the usefulness of apomorphine as a biological marker for substance-dependence disorders (changes in dopaminergic sensitivity), the first reports seem rather promising [65, 66]. Apomorphine has also been used as an endocrine challenge test to assess central dopaminergic responsiveness in Wilson's disease [67] and to investigate hypothalamic-adenohypophyseal function [68]. Because it can increase human growth hormone (GH) secretion and decrease prolactin secretion [29, 68], apomorphine was used to assess the adequacy of GH secretion in serum [68, 69] and investigate the effects of psychotropic drugs [29]. Apomorphine-induced changes in the GH response have been reported in schizophrenia [29, 70], anorexia nervosa, PD [29, 71], depression [29], Huntington's chorea, tardive dyskinesia, and obsessive-compulsive disorder [29, 72].

Apomorphine-induced behaviors have been used through animal models to test compounds for therapeutic properties and to define comparable potencies. Apomorphine-induced emesis has been used to assess antiemetic agents [73] and antagonism of apomorphine-induced stereotypy has been widely used in the study of neuroleptics and the screening of drugs for psychotropic activity, including haloperidol and risperidone [42, 69, 74–76].

4 From the 19th to the 21st Century: Treating Animals and Humans

In almost 150 years, an extensive body of literature has been published on apomorphine, attesting to its use in a broad range of conditions (Fig. 3). However, most of it consists of case reports and uncontrolled studies.

4.1 Veterinary Medicine

Following Gee's experiments, apomorphine was used as an emetic in cases of poisoning and esophageal foreign bodies in dogs, pigs, and cats to rapidly induce forced emesis (even if cats do not respond consistently to it [76]). Today, apomorphine remains the emetic of choice in dogs, administered either parenterally or topically in the conjunctival sac of the eye [77]. Other veterinary uses are now confined to history books: expectorant in dogs, pica (licking sickness) in cattle [76], or acute strychnine poisoning in dogs [78, 79]. Conflicting reports are found for the latter, some highlighting positive results through emesis and spasm relaxation [78, 79] while others describe inefficacy [78, 80].

4.2 Clinical Uses Across Time

As soon as apomorphine had been deemed suitable for subcutaneous injections [17, 22, 81], it started to be used in human medicine, albeit initially as quite an expensive treatment [19]. Interestingly, apomorphine has always had its supporters and detractors, regarded by some as "remarkable" [79] but by others as "curious, dangerous, obsolete and antiquated" [82, 83]. Thus, although it was studied and prescribed for a wide range of medical conditions, it remained "insufficiently recognized" [84] and considered a "sort of taboo" subject [32] by "doctors who w[ould] cheerfully inject cobra venom or malaria into their patients [but] refuse[d] to inject apomorphine", as stated provocatively by Dent [32]. Taken together, poor study design, uncontrolled studies, small sample sizes, calls for caution following alarmist case reports (exceptional cardiovascular collapse in children and adults), untoward accidents (confusion between morphine and apomorphine),

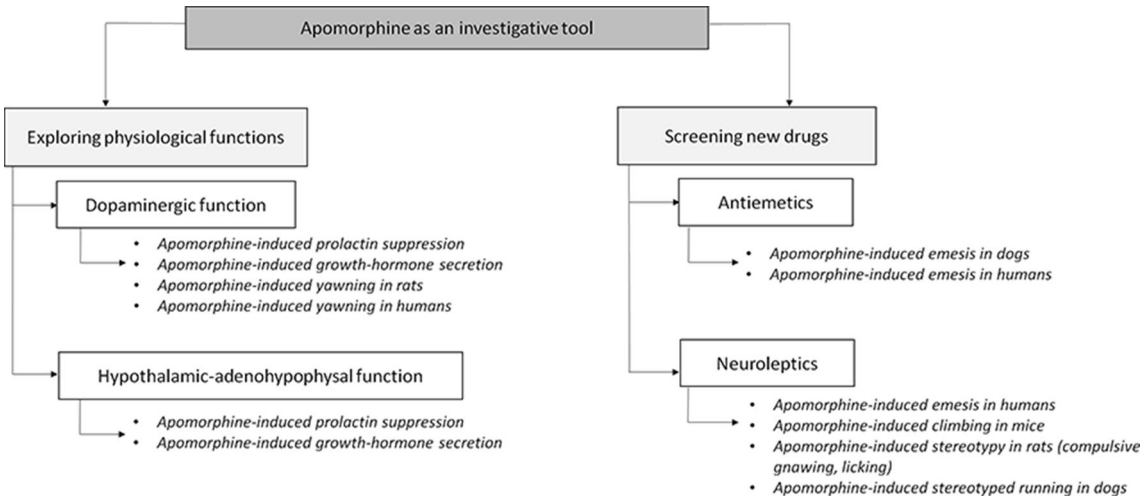

Fig. 2 Uses of apomorphine as an investigative tool. The different apomorphine tests described in the literature are exposed, relating to their main goals

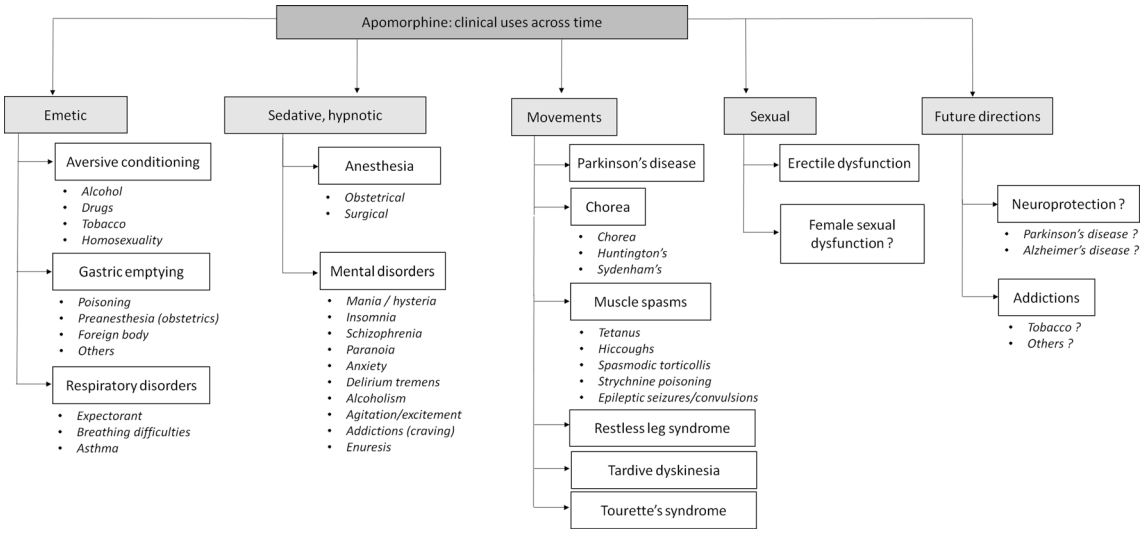

Fig. 3 Clinical uses of apomorphine across time. Indications retrieved from the literature review and classified according to the main uses

poor conservation, and differences in doses (resulting in the consecutive stimulation of pre- and/or post-synaptic dopaminergic receptors), forms (amorphous or crystallized), routes of administration, and even purity between suppliers in the early 20th century, not to mention the heterogeneity of patient populations in psychiatric investigations, may explain the discrepant and unreliable results found in the literature, and thence the failure to translate these findings into standard clinical care, as well as the general distrust surrounding apomorphine [19, 20, 29, 47, 48, 62, 82, 85–88].

4.2.1 Emetic Potency

One of the best documented effects of apomorphine is emesis. It is striking to note that what is now viewed as a troublesome but treatable side effect in the treatment of PD [4] remained the main indication of apomorphine for a whole century, overshadowing all other uses.

4.2.1.1 Gastric Emptying Apomorphine is the most effective known centrally acting emetic drug [60], and was the drug of choice for any condition requiring prompt emptying or cleaning of the stomach and ejection of esophageal foreign bodies [19, 89, 90] until the 1970's [91]. The possibility of subcutaneous administration was greatly appreciated, particularly when oral administration was impracticable (refractory child or adult, coma or delirium) [90]. Poisoning was usually treated with ipecac syrup, but as apomorphine could produce rapid, nonirritant, efficient and controlled emesis, its use, either orally, hypodermically, or rectally, became extremely widespread

[22, 31, 48, 86, 89, 90]. Many case reports advocated the use of apomorphine to treat various types of poisoning (opium, acid, mushroom, metal, or arsenic [86, 92, 93]), particularly for accidental poisoning in children [86, 92] or suicide attempts [94] and acute alcohol poisoning, being mentioned as early as 1869 in Dr Philip John Hensley's experiments [22, 32]. Some clinicians were, however, reluctant to use it, owing to the difficulty of monitoring toxicity signs [95], as the vomiting was usually followed by sleep [32]. Anecdotal reports from the late 1800's show that apomorphine was also used to clean an 'upset stomach' [86] or to induce vomiting in cases of sunstroke [35], meningitis [96], and ardent fever [97]. From the mid-1950 s to the end of the 1970 s, apomorphine was given intravenously as a pre-anesthetic emetic in labor to prevent inhaled vomitus (a common cause of death from general anesthesia in obstetrics) [98–100], inducing complete emptiness of the stomach prior to analgesia. Though considered to be a good alternative to stomach tubes [98–100] and not deleterious to either the mother or the newborn [98–100], this approach was rejected by the majority of anesthesiologists, based on the observation that apomorphine did not always induce vomiting at the prescribed doses [101].

4.2.1.2 Respiratory Disorders Used mainly as an oral, nasal, cutaneous, or subcutaneous expectorant [19, 31, 32, 81, 86], administered either alone or in combination with morphine, apomorphine was prescribed in the 19th century to reduce coughing in breathing difficulties or thick, tenacious mucus [81], as in *winter cough* (chronic bronchitis, bronchial catarrh), bronchorrhea [81, 86, 90], catarrhal laryngitis [90], pneumonia [31], dyspnea, hemoptysis [19, 86], and croup [86, 90]. It also relieved angina pectoris and asthma thanks to its relaxing effect, in combination with scopolamine [79, 90, 102]. The effect of apomorphine on dopaminergic control of the cough reflex was demonstrated in cats more than a century later [103].

4.2.1.3 Aversive Conditioning Apomorphine was extensively used in the first half of the 20th century to induce aversive conditioning, through its emetic and sedative properties [32, 104]. The apomorphine aversion conditioning method consisted of provoking nausea and vomiting timed to the administration of the addictive substance, thereby inducing a conditioned repulsion. Its combination with emetine or caffeine was sometimes advocated [105]. As part of the conditioned reflex aversion treatment of alcoholism [32, 83, 105–108], apomorphine became an agent of choice in the mid-20th century across Europe and the US [32, 108], many decades after being a key component of the *Keeley Cure*, which was famous in the late 1800 s for inebriety [106]. John Yerbury Dent was a fervent advocate of apomorphine for treating alcoholism, on account of both its aversive capacity and its ability to prevent craving through an *action in the brain* [32, 60, 83, 105]: "this is one of the very few treatments in which the patient can expect a miracle" [32]. Walter Voegtlin, by contrast, was convinced that exact timing was essential for true Pavlovian conditioning, and discarded apomorphine because of its short duration and sedative effect, which he viewed as hindrances to true conditioning [105, 108]. Treatment duration varied between days and weeks, depending on addiction severity [60]. Conflicting results are found, for while a randomized, double-blind, clinical trial on the effects of oral apomorphine on alcohol post-intoxication symptoms [109] failed to yield any positive results, other studies reported high levels of success [84], amply relayed by William S. Burroughs (who extensively described his own experience and recovery in his books: *Health Bulletin: APO-33*, *a metabolic regulator*, 1965; *The Naked Lunch*, 1967), greater attendance in sober states for continuing treatment, and a "non-significant tendency to manage better both motorically and mentally" [110]. Alcohol addiction was not the only indication for apomorphine, as it was used in cases of morphine, heroin, barbital, methadone [9, 12, 40, 105, 109, 111], or tobacco [105, 111] addiction and also, shockingly, in homosexuality, to induce nausea concomitant to the presentation of male nude pictures, alongside electric shocks and psychotherapeutic techniques [112, 113].

4.2.2 Sedative and Hypnotic Effects

The sedative and hypnotic properties of apomorphine were first described by Gee and outlined by Charles J. Douglas [22, 104, 114]. Appearing at subemetic doses with a prompt, dependable and safe effect, they led to clinical applications for a variety of conditions characterized by excitement, anxiety and/or agitation [22, 82, 83, 114]. Following the observation that it was "of special value in all forms of mania" [114], apomorphine was deemed to be of "noteworthy value in the care of disturbed psychiatric patients" [84]. As early as 1912, Dr Francis Hare praised the use of hypodermic injections of apomorphine in a book where he listed three main uses: "(1) in maniacal or hysterical drunkenness; (2) during the paroxysm of dipsomania, in order to still the insistent craving for alcohol; and (3) in essential insomnia of a special variety" [115]. The emetic and sedative effects of apomorphine allowed inebriated patients to sleep calmly and awaken without hallucinations or delirium, and even in some cases without any desire for alcohol [32, 79, 82, 114, 115]. Over time, indications extended to other psychiatric conditions [32, 60, 79, 82, 83, 105, 107, 114–117], with abundant descriptions of cases that were satisfactorily treated with

apomorphine (either alone or associated with scopolamine [107, 118]): mania [22], alcoholic mania [32, 79, 82, 114, 115], hysteria and hysteroid attacks [32, 47, 86, 119–123], alcoholic insomnia [107, 114, 115], schizophrenic excitement (sedative action, reduction of hallucinations and delusions [29, 32, 84, 124, 125]), paranoia [84], panic states of acute or alcoholic anxiety [32, 60, 105, 107, 115], anxiety associated with grieving, suicidal thoughts, agoraphobia, or melancholia [32], agitation linked to depression [32], delirium tremens (although caution was advised, owing to the depressing action of apomorphine [32, 79, 82, 114]), senile dementia [84], posttraumatic excitement [84], postoperative and postpartum excitement [82, 84, 126–128], acute hyperthyroidism crisis [84], barbiturate reactions, confusion and restlessness following electroshock treatment or diverse organic states [84], and even pediatric enuresis of nervous origin [79]. As the above series shows, apomorphine was long associated with the treatment of alcohol-related disorders [32, 104, 107, 114]. It was also used as a premedication for emergency surgeries, or during recovery from anesthesia complicated by an agitation produced either by scopolamine, alcoholism, *delirium tremens* or morphine addiction [82, 107, 126–128]. The use of apomorphine-potentiated scopolamine analgesia in labor, tested on thousands of women [128], was found to be safe for both mother and baby, did not interfere with the progress of labor, and even reduced the incidence of postpartum respiratory complications [126, 128]. However, this technique was not recommended as a routine procedure [127].

4.2.3 Treating Sexual Disorders

Spontaneous apomorphine-induced penile erections were incidentally reported during the treatment of alcoholics [116, 129], and subsequently confirmed in rats, human control participants, and impotent patients [29, 116, 117, 129–133], highlighting the involvement of central dopamine receptors in normal erectile function and its impairment in a subgroup of patients [132]. A throwback to the early use of apomorphine in ancient civilizations, sublingual (SL) [134] apomorphine was commercialized at the beginning of the 2000's as the first centrally acting agent to be approved for the treatment of erectile dysfunction. However, despite their efficacy, safety, and benefits to patients [58], Ixense® (Takeda) and Uprima® (Abbott) were removed from the market in 2004 and 2006 in the face of competition from PDE5 inhibitors.

Since then, apomorphine has been suggested in the treatment of female sexual dysfunction [135–138].

4.2.4 Treating Movement Disorders

Despite being the first dopaminergic agonist to be used in PD, apomorphine suffered decades of neglect in the field of movement disorders.

4.2.4.1 Chorea, Spasms, Convulsions and Other Movement Disorders As early as 1870, a beneficial effect on choreic movements was observed in a child exhibiting chorea associated with rheumatic fever [31]. Surprisingly though, Pierce disregarded apomorphine as a treatment for movement disorders, stating that it was "only as an emetic that [he] would draw attention to it" [31]. These effects were later reproduced [139, 140] and apomorphine was mentioned as a treatment for acute chorea in the 1915 edition of *The Practitioner's Encyclopaedia of Medical Treatment*. Sydenham's chorea could likewise be alleviated with apomorphine [84], as could congenital choreoathetosis, spontaneous orofacial dyskinesia [56], and Huntington's disease (HD) [141–143]. In HD, apomorphine decreases the intensity of chorea, and improves motor impersistence and the ability to suppress associated movements [143]. Those effects are counteracted by haloperidol and sulpiride [142]. More recently, a double-blind, randomized, crossover trial ($N = 5$) showed that continuous infusion of apomorphine produces a sustained improvement in choreic symptoms, without affecting depressive symptoms [144]. These results need to be confirmed by more studies, but they already suggest that continuous apomorphine infusion should be considered in some patients with HD [144]. Apomorphine improves tics in Tourette's syndrome [145, 146]. In tardive dyskinesia, results are variable, with either improvements (dyskinetic movements being alleviated in some patients, presumably through presynaptic effects [56, 124, 147]), or no effect at all [37].

Subcutaneous injections of apomorphine were used in the past to prevent or curtail epileptic seizures [47, 86, 90, 139, 140], alcohol-induced convulsions, eclampsia, and puerperal convulsions [90]. It also transiently blocked photosensitive epileptic discharge [148]. Following successful cases, apomorphine was considered to be effective in controlling muscle spasms, including nervous spasms (hiccoughs [90, 139] or spasmodic torticollis [29, 45], reducing the "marked muscular and psychic overactivity occasionally seen after […] scopolamine or atropine" [82]. It has been credited with cases of recovery after ingestion of presumably lethal amounts of strychnine [78] or even counteracting the tetanic state [22, 90].

Growing evidence suggests that apomorphine (either as boluses or CSAI) effectively improves periodic leg movements in restless leg syndrome (RLS) [149–151]. This indication needs to be further explored, particularly

with CSAI. To be noted, RLS is also a frequent symptom in PD [150].

4.2.4.2 Parkinson's Disease Dr. Edmond Weill was the first to suggest that apomorphine might be useful in tremor and PD [139], bolstered by his success in treating chorea. A forgotten clinical note in *The Canadian Medical Association Journal* reports a use of apomorphine to alleviate spasticity in patients with *paralysis agitans* as early as 1935 [79], long before Schwab's experiments [52]. Its author felt "justified in [his] choice of a sedative which can, with perfect safety, be administered for long periods of time" [79]. Dordoni's work on decerebrate rigidity in dogs [51] paved the way for Schwab's first use of apomorphine in PD in 1951 [52]. Despite a marked (albeit short-lived) improvement in symptoms and Ernst's suggestion that apomorphine could successfully replace dopamine in PD [26], interest in the drug as an agent for managing movement disorders almost vanished when Georges Cotzias and collaborators launched the levodopa era [152]. Decades after, double-blind controlled studies initiated by Cotzias and colleagues demonstrated that apomorphine was a valuable drug in the antiparkinsonian armamentarium [60, 152, 153], especially when combined with metoclopramid [154, 155], haloperidol [155], or domperidone [156] to block the induced nausea. Stibe et al. updated the use of apomorphine in PD by demonstrating its beneficial effect on Parkinsonian on–off fluctuations, opening the way to further uses [157]. Apomorphine has since been used in the diagnosis (assessment of levodopa responsiveness) and treatment of PD in Europe, either as a pen injection or through continuous infusion [1–4, 12, 58, 59, 158]. Despite abundant evidence of its efficacy in treating advanced PD and its positive impact on patients' quality of life [159, 160], apomorphine remains underused and unavailable to many patients worldwide [158]. Once again, work needs to be done to promote its use and improve its access. The TOLEDO study (ClinicalTrials.gov Identifier: NCT02006121), confirming the efficacy and safety of apomorphine, is a useful first step [161].

5 Apomorphine and Its Newest Challenges: Where Do We Stand Now?

More than a century has passed since apomorphine was first synthesized, during which time it has been abundantly studied. Although it has already been administered in many conditions and through all possible routes (hypodermic, oral, rectal, inhalation, IV, intranasal, sublingual [162, 163]), there is still room for improvements and new discoveries [162].

5.1 Challenges in the Treatment of Parkinson's Disease

If apomorphine is currently only indicated for the motor fluctuations that usually occur after several years of levodopa treatment, growing evidence suggests other potential uses in PD, particularly for nonmotor PD subtypes [164], young patients (EARLYPUMP study, ClinicalTrials.gov Identifier: NCT02864004) and in cases where oral dopaminergic medications are withdrawn. However, apomorphine therapy is not devoid of adverse events (e.g., cutaneous lesions) that need to be addressed in the future.

5.1.1 Withdrawal of Oral Dopaminergic Medication

Missing antiparkinsonian medication has various consequences, and not all patients can tolerate being off medication due to severe off-state pain and dystonia [165, 166]. Withdrawal of oral dopaminergic medication can occur during surgery (general surgery or deep-brain stimulation [DBS]) but also in many cases where oral administration is hindered: loss of consciousness, intestinal occlusion, acute infection, or even during terminal care. Anecdotal evidence, associated with a few reports of local neurosurgical practice, suggests that apomorphine could be particularly useful in such situations.

5.1.1.1 Surgery PD patients are particularly at risk of complications when undergoing surgery, both during and after the procedure—this risk being related to the disease itself and/or to the omission of medication [167–170]. Being unable to ingest oral medication because of hindered oral administration or poor gastrointestinal (GI) tract absorption (postoperative ileus, delayed gastric emptying) has major consequences [167, 169]. Dopaminergic deprivation can precipitate the deterioration and/or worsening of motor symptoms (rigidity, bradykinesia, swallowing difficulties, or inability to clear oral and pulmonary secretions) and lead to perioperative complications [165, 169, 170] including confusion, aspiration pneumonia, postoperative respiratory failure, bacterial infection (urinary tract infection), deep-vein thrombosis, pulmonary embolism, postoperative GI motility abnormalities, neuroleptic malignant-like syndrome (rarely), falls, and a prolonged postoperative hospital stay [167–170]. A few studies [167–170] suggest that parenteral apomorphine (subcutaneous injections [168] or continuously [167]) could be a good option for avoiding suboptimal treatment and alleviating nonmotor off-period symptoms—particularly digestive and urinary autonomic symptoms [168]. By preventing symptom resurgence and postoperative complications, subcutaneous apomorphine may facilitate nursing care and hasten surgical recovery [168].

Dopaminergic deprivation (generally starting 72 h prior to surgery) and awake testing are usual in DBS procedures, but put patients at risk of neurological and respiratory deterioration [171] or severe off-medication motor symptoms [166, 171]. Data from a single-center ($N = 72$ [171]) and anecdotal reports ($N = 3$ [170]; $N = 1$ [166]) strongly suggest that apomorphine, administered either via a pump or through repeated injections, is helpful during awake DBS surgery for relieving patients' discomfort [166, 170, 171]. In some centers, apomorphine has even been added to preoperative guidelines [170, 171]. Domperidone can be introduced 2 days prior to surgery to avoid nausea [171]. Though no data is currently available, apomorphine may also be considered as an emergency treatment (for instance with pen injection at a predetermined dose) in case of acute stimulator failure in DBS patients, thanks to its rapidity of action [171].

5.1.1.2 Others Though data are still scarce ($N = 2$), apomorphine injections may be particularly useful in the management of acutely ill PD patients (i.e., chest infection or stroke) who are unable to take their usual oral dopaminergic medication and/or tolerate a nasogastric tube [169]. In certain cases, apomorphine can be administered in the acute phase without prior administration of domperidone [169].

A single case report highlighted the pragmatic use of apomorphine in a terminally ill patient (73-year-old man with a 14-year history of PD) unable to take oral medication [172]. Signs of discomfort were alleviated with the injection of apomorphine 2 mg, alongside rectal administration of domperidone [172]. More studies are needed to confirm those results, but subcutaneous apomorphine deserves to be considered in PD terminal and/or palliative care.

Apomorphine has also been anecdotally reported to successfully treat neuroleptic malignant syndrome following abrupt reduction of chronic levodopa treatment in PD patients [165, 173].

5.1.2 Nonmotor Symptoms

Although subcutaneous apomorphine efficacy on parkinsonian nonmotor symptoms has been recently reviewed [174], there has been scant research on this particular topic, though it is of paramount interest. Preliminary data are encouraging and need to be confirmed in controlled and randomized studies.

Improvements induced by an apomorphine pump in the gastrointestinal domain of the Non-Motor Symptoms Scale have been recently demonstrated in 43 patients [159], supporting the results of previous studies on swallowing disorders and anorectal dysfunction in PD [175–177]. A beneficial effect on urinary symptoms (e.g., nocturnal urinary frequency, incontinence) has also been reported [159, 178, 179], though effect on detrusor hyperreflexia is inconsistent [179]. Sexual disorders are common in PD, but fail to receive the recognition they deserve, considering their impact on quality of life for both patients and their partners [179]. SL apomorphine has been used to treat erectile dysfunction in the general population but, surprisingly, no study has been led among PD patients; research is therefore needed as SL apomorphine is safe to administer and may improve sexual dysfunction [179].

Sleep disorder and nocturnal disabilities are frequent and varied in PD [180]. There is growing evidence that apomorphine, administered through a pump, brings some improvement in patients' overall condition [159], with reduced nocturnal awakenings, off periods, pain, dystonia, nocturia, periodic limb movements or RLS, and insomnia [150, 159, 180]. To address the question of continuous overnight infusions, a randomized, cross-over study is currently underway in France to explore the effects of CSAI on sleep disorders in insomniac parkinsonian patients (APOMORPHEE study, ClinicalTrials.gov Identifier: NCT02940912).

5.1.3 Overcoming Adverse Events

Cutaneous adverse events linked to needle-based apomorphine therapy remain one of the biggest challenges in PD and may explain some of the reluctance surrounding its use. Avoiding toxicity and/or developing new delivery strategies are the two main research areas of CSAI [162]. Studies to understand the mechanisms linked to subcutaneous toxicity and to develop novel apomorphine formulae are underway [181].

Creating new and more practical pump devices is another area where further improvements could be made. Alternative delivery strategies that are currently being investigated include inhaled or SL apomorphine, oral delivery, and patch pump technology [162, 181].

If conflicting results are found on the neuropsychiatric effect of apomorphine, growing evidence tends to suggest that it is safe, and could even be beneficial for mood and apathy [59, 159], as well as induce a decrease in visual hallucinations [182–184] caused by visual problems [183, 185], possibly through an action on the serotonin 2_A receptor [183]. Further work is needed to better understand this phenomenon.

5.2 Advances in Neurochemistry: New Indications for the Future?

New neuromolecular probes are emerging on the properties of apomorphine, suggesting that its neuroprotective effects

could be harnessed as a potential modifier of amyloid deposition [162, 186].

Decades after its use in aversive conditioning for smoking cessation [105, 111], growing evidence suggests that apomorphine could be repurposed for tobacco use disorder, through its action on dopaminergic and serotoninergic receptors, both key to tobacco dependence mechanisms [88]. Administering low doses of SL apomorphine during the quitting process could stabilize the dopaminergic system, reverse hypersensitivity to nicotine, modulate serotoninergic pathways and counteract reinforcement cues [88]. Moreover, apomorphine is able to block ethanol and nicotine responses in the larval zebrafish locomotion model, suggesting that it could be used in tobacco dependence treatment, especially in combination therapy [187]. Further work is needed, but these studies highlight the undeniable value of this pharmacological agent.

6 Conclusion

Apomorphine is a remarkable example of an old drug being rediscovered. Its peculiar pharmacological profile (non-specific dopaminergic and nondopaminergic agonist [58, 59]) has made it one of the most intensively studied drugs, and it can be safely assumed that apomorphine will continue to intrigue scientists and clinicians in years to come. Thanks to technical and galenic development, it is destined to become a key feature of future therapeutic strategies, and rightly so.

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