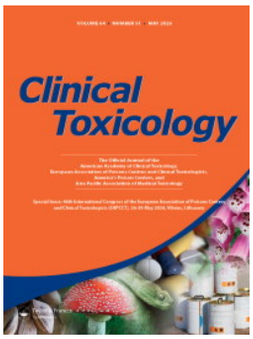

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POISON CENTRE RESEARCH

Bupropion overdose: insights on the role of upper gastrointestinal decontamination endoscopy

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ABSTRACT

Introduction: Although bupropion is known to be associated with pharmacobezoar formation, it remains understudied in this context. Upper gastrointestinal endoscopy has emerged as a potential adjunctive decontamination technique for managing acute overdoses associated with pharmacobezoar formation. We aim to evaluate its role in acute bupropion overdoses.

Methods: We retrospectively analysed intentional bupropion overdoses referred to the Pavia Poison Control Centre (2015–2024) in which upper endoscopy was performed. Data on patient characteristics, overdose details, co-ingestants, decontamination procedures, endoscopy indications, and findings were collected. Endoscopy outcomes were classified as positive (pharmacobezoars, intact tablets, or paste-like residues) or negative. In parallel, an *in vitro* model was used to assess the propensity of bupropion to form pharmacobezoars.

Results: Forty-seven patients were included (median age 44 years, IQR 27–55; 75% female). The median ingested bupropion dose was 4,500 mg (IQR 4,500–6,750 mg). The median ingested tablets count was 59 (IQR 29–100 mg), and co-ingestants were present in 79% of cases. Upper gastrointestinal decontamination endoscopy was positive in 28 cases (60%). Pharmacobezoars or tablet residues were identified even in patients who had undergone prior decontamination, including orogastric lavage (60%). The only variable significantly associated with positive endoscopic findings was the total number of ingested tablets ($P<0.05$). In our cohort, nearly three-quarters of patients ingesting ≥30 tablets showed a substantial rate of positive endoscopy 73%, compared to 33% of those ingesting <30 tablets. All positive cases resulted in successful endoscopic removal without complications. The *in vitro* experiment showed early pharmacobezoar formation within four hours of incubation, persisting for up to 72 hours.

Discussion: Acute bupropion overdoses, alone or with co-ingestants, can cause gastric pharmacobezoars and retained tablets/residues despite standard decontamination. Upper gastrointestinal decontamination endoscopy is effective early post-ingestion and may complement or replace conventional methods.

Conclusions: Gastric pharmacobezoars and tablet residues are frequently observed in bupropion overdoses, particularly with ingestions of ≥30 tablets, making these patients potential candidates for early endoscopic removal.

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Acute poisoning; bupropion; gastric decontamination; pharmacobezoar; upper gastrointestinal decontamination endoscopy

Introduction

Bupropion is an atypical antidepressant, structurally related to cathinone, that inhibits norepinephrine and dopamine reuptake and blocks various nicotinic receptors [1]. Bupropion overdoses have increased in recent years; indeed, it was the most frequently reported antidepressant in toxicology consultations in 2023 according to the Toxicology Investigators Consortium [2] and is associated with higher morbidity than other antidepressants [3]. Toxicity primarily involves cardiac and neurological manifestations, with no specific antidote available. Cardiac toxicity is characterized by QRS widening, likely mediated by cardiac gap junction

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inhibition, which is often unresponsive to bicarbonate therapy [4,5]. This may progress to shock, with severe cases requiring veno-arterial extracorporeal membrane oxygenation [6,7], while neurotoxicity is characterized by recurrent and delayed seizures [8,9]. In Italy, only modified-release bupropion formulations are marketed, comprising both sustained- and delayed-release forms. Although no harmonized definition of modified-release formulations exists, the term generally refers to any drug-delivery system designed to alter the pharmacokinetic profile of the release of the active substance, distinguishing it from immediate-release formulations [10]. Modified-release formulations include prolonged-, delayed-, and extended-release dosage forms, which have gained significant attention in the literature due to their potential to form pharmacobezoars in acute overdoses. Documented examples of drugs linked to pharmacobezoars include quetiapine extended-release [11], enteric-coated aspirin, clomipramine extended-release, nifedipine extended-release, venlafaxine extended-release, and verapamil extended-release [12]. The mechanisms by which modified-release formulations predispose to pharmacobezoar formation are still under investigation [12], but factors such as pharmaceutical excipients, the physicochemical properties of drug delivery systems, and the quantity and size of ingested tablets may all play a role [11,13]. Among drugs associated with pharmacobezoar formation, bupropion remains one of the least studied, with only a few cases described in the medical literature [14–18].

Traditional gastrointestinal decontamination techniques, such as orogastric lavage, activated charcoal, and whole bowel irrigation may be ineffective when pharmacobezoar formation is suspected [19]. In recent years, endoscopy has emerged as a potential adjunctive decontamination method in overdoses in which conventional strategies may fail [19]. Although data on its clinical benefit remain limited, reports of successful pharmacobezoar removal suggest a potential role for upper gastrointestinal decontamination endoscopy in the acute management of selected cases of poisoning [20–22].

Given the limited literature on bupropion-related pharmacobezoars, the potential for severe toxicity, and the availability of modified-release formulations, we aim to evaluate the role of upper gastrointestinal decontamination endoscopy in the acute management of bupropion overdoses and to identify poisoning-related variables associated with positive endoscopic findings.

Methods

Setting

The study was conducted at the hospital-based Pavia Poison Control Centre, Laboratory of Clinical and Experimental Toxicology - National Toxicology Information Centre. The Pavia Poison Control Centre is an emergency service providing specialist toxicological advice, primarily to physicians, for the management of poisoned patients throughout Italy, supported by its own specialized laboratories.

A retrospective observational study was carried out on cases of acute intentional bupropion ingestion that underwent upper gastrointestinal decontamination endoscopy. As the Pavia Poison Control Centre collaborates with emergency departments nationwide, the enrolled patients were distributed across hospitals throughout the country. The study received approval from the local ethics committee (No. 2615 CEC).

An *in vitro* study was performed in parallel at our laboratory to assess the potential of bupropion to form pharmacobezoars and to complement the results of the retrospective study.

Inclusion criteria and analysed data

We included all cases of acute intentional bupropion ingestion referred to the Pavia Poison Control Centre from January 2015 to December 2024 in which endoscopy was performed as part of the clinical management. Cases without available endoscopy results were excluded. Since the study focused on endoscopy outcomes, patients were included even in the absence of a complete clinical follow-up.

For each included case, the following data were collected:

- **Patient-related:** demographics; clinical manifestations prior endoscopy and outcomes (when available).
- **Overdose-related:** time between ingestion and emergency department admission; bupropion-overdose details (number of ingested tablets/pills, total ingested dose); co-ingestants (total number of co-ingestants, total number of ingested tablets/pills and presence of other modified-release formulations).
- **Decontamination-related:** gastrointestinal decontamination procedures performed before endoscopy.
- **Endoscopy-related:** time from ingestion to endoscopy, indications for the procedure and

endoscopy findings. Findings were categorized as positive (aggregated tablets defined as pharmacobezoars, or unaggregated whole tablets, or amorphous residues in a paste-like form) and negative (absence of recognizable drug residues).

When possible, bupropion and hydroxybupropion serum concentrations were determined at the Pavia Poison Control Centre laboratory starting from 2022, as routinely performed in selected severe intoxications or upon the treating physicians' request. Blood samples were collected at the treating hospital and subsequently sent to our laboratory for analysis. Analytical methods are described in the Supplementary material.

Statistical analysis

Quantitative variables distribution is described by median, 25th–75th percentiles (Interquartile Range, IQR), minimum-maximum values (range). Categorical variables distribution is described by absolute frequency (relative frequency, %). Quantitative variables distribution was compared between endoscopy-positive and endoscopy-negative subjects using the Welch two sample t-test or by the Wilcoxon rank sum test, as appropriate. The association between categorical variables and upper gastrointestinal decontamination endoscopy positivity was tested using the chi-squared test with Monte Carlo simulations to compute *P*-values. The statistical significance level was set at $\alpha = 0.05$. Statistical analyses were performed using the R free software environment for statistical computing and graphics, v.4.2.2 (www.r-project.org).

In vitro experiment

Simulated gastric fluid was prepared according to the European Pharmacopoeia, following the protocol described by Hoegberg et al. [13], which represents the first model specifically developed to study the physical behaviour of pharmaceutical preparations in simulated gastric fluid (see Supplementary material). The simulated gastric fluid solution was transferred into a 2-litrer glass beaker containing 30 bupropion tablets, which had been previously wrapped in a nylon mesh bag to allow tablet interaction without compression and to prevent contact with the glass beaker walls. The number of tablets was chosen to simulate an overdose. The bag was secured to wooden sticks resting on the top of the glass beaker, which was then sealed with plastic paraffin film. The glass beaker was placed on a magnetic stirrer set at 30 rpm and thermostatically controlled at 37 °C. After four and 48 h, the pH was checked using pH indicator strips. Two different formulations of bupropion were studied: Wellbutrin® 300 mg XR, GlaxoSmithKline S.p.A. (formulation 1) and Bupropione DOC® 150 mg modified-release, DOC Generici S.r.l. 150 mg modified-release (formulation 2). Visual assessment was performed at 4, 8, 12, 24, and 72 h after incubation to evaluate pharmacobezoar formation, and a manual assessment was also conducted at the end of the experiment (72 h).

The authors used ChatGPT (GPT-5 mini) solely to improve the style and language of the manuscript; all content, data interpretation, and scientific conclusions are the authors' own work.

Results

Forty-seven patients were included, with a median age of 44 years (IQR 27–55 years; range 18–89 years). The total ingested bupropion dose was available for 27 patients (58%), and the number of ingested bupropion tablets for 28 patients (60%). The median dose was 4,500 mg (IQR 4,500–6,750 mg; range 1,500–9,000 mg), while the median tablet count was 30 tablets (IQR 26.5–31.8 tablets; range 10–90 tablets). When considering all ingested tablets, data were available for 35 patients (75%), with a median of 59 tablets (IQR 29–100 tablets; range 10–172 tablets). Co-ingestion occurred in 34 (72%) patients, ranging from one to nine co-ingestants, most commonly involving benzodiazepines (65%). In 14 cases, other modified-release formulations were co-ingested (quetiapine, valproic acid, venlafaxine, and clomipramine). Baseline demographic, overdose-related, and endoscopy-related data are summarized in Table 1.

Prior to endoscopy, clinical manifestations were observed in 44 patients (94%; Table 2).

Gastrointestinal decontamination was performed in 29 patients (62%): orogastric lavage in 28 (60%), activated charcoal in 13 (28%), cathartics in 11 (23%) and whole bowel irrigation in three (6%).

Endoscopy was performed at a median of 10 h from overdose (IQR 4-14.5 h; range 2–26 h) and at a median of two hours from hospital admission (IQR 1-7.3 h; range 0.5-22 h). Indications for endoscopy are summarized in Table 1, with a severe clinical picture and a high ingested tablet count representing the most frequent reasons.

Endoscopy was positive in 28 patients (60%, Table 3). Endoscopy timing and related outcomes are reported in Figure 1.

In all positive cases, endoscopic removal of bezoars, tablets, or residues was possible (Figure 2), with no

Table 1. Baseline characteristics of cases presentation.

Characteristic	*n*	
Patients, *n*	47	47
Female, *n* (%)		35 (74%)
Age, years, median (IQR), [range]		44 (27–55) [18–89]
Overdose-related, median (IQR), [range]		
Total bupropion dose (mg)	27	4,500 (4,500–6,750), [1500–9000]
Total number of bupropion tablets	28	30 (26.5, 31.8), [10–90]
Total number of tablets	35	59 (29, 100), [10–172]
Time from ingestion to emergency department admission (h)	37	3 (2–7), [0.5-15]
Reported co-ingestions, *n*(%)		
Modified release co-ingestants		34 (72%)
Benzodiazepines	47	14 (30%)
Quetiapine		22 (65%)
Selective serotonin reuptake inhibitors		10 (29%)
Antiepileptics		10 (29%)
Ethanol		9 (27%)
Other antipsychotics		7 (21%)
Serotonin–norepinephrine reuptake inhibitors		5 (15%)
Other antidepressants		4 (12%)
Cocaine		4 (12%)
Caustic		2 (6%)
Other xenobiotics		2 (6%)
		9 (27%)
Endoscopy-related, median (IQR), [range]		
Time from ingestion to endoscopy (h)	35	10 (4–14.5), [2–26]
Timing from emergency department admission to endoscopy (h)	47	2 (1–7.3), [0.5-22]
Indications for endoscopy[a]	47	17 (36%)
Severe clinical picture, *n* (%)		11 (23%)
High ingested tablet count, *n* (%)		8 (17%)
Worsening clinical picture, *n* (%)		6 (13%)
Unavailable patient history, *n* (%)		2 (4%)
Tablets detected in CT scan, *n* (%)		2 (4%)
Co-ingestion of caustic substance, *n* (%)		1 (2%)
Elevated bupropion concentration, *n* (%)		

n = number of non-missing observations. [a]Indications for endoscopy were established by the consulting medical toxicologist based on individual case assessment, without standardized protocols. An elevated number of tablets was defined as ≥30; severe clinical manifestations were defined as a Poisoning Severity Score ≥2 [33]; unavailable patient history refers to an unknown ingested amount of drug coupled with toxicity symptoms.

Table 2. Clinical manifestations of included patients prior to endoscopy.

	Bupropion alone	Bupropion and co-ingestants *n* = 34 (72.3%)
	n = 13 (27.7%)	*n*(%)
	n (%)	
Asymptomatic	–	3 (9%)
Symptomatic	13 (100%)	31 (91%)
Gastrointestinal		
Vomiting	2 (15%)	2 (6%)
Neurological		
Agitation	3 (23%)	7 (21%)
Tremors	3 (23%)	4 (12%)
Seizures	6 (46%)	10 (29%)
Drowsiness	9 (69%)	15 (44%)
Coma	4 (31%)	14 (41%)
Hallucinations	1 (8%)	–
Cardiovascular		
Tachycardia	4 (31%)	15 (44%)
Hypertension	–	1 (3%)
Hypotension	–	8 (24%)
QRS enlargement	2 (15%)	2 (6%)
QTc prolongation	4 (31%)	7 (21%)
Cardiac arrest	2 (15%)	1 (3%)
Syncope	1 (8%)	–

Table 3. Outcome of endoscopy.

	Bupropion[a]	Bupropion + tablets co-ingestants
	n = 20	*n* = 27
	n (%)	*n* (%)
Negative	9 (45%)	10 (37%)
Positive	11 (55%)	17 (63%)
Pharmacobezoar	1/11 (9%)	9/17 (53%)
Whole/Unaggregated tablets	7/11 (64%)	8/17 (35%)
Amorphous residues	3/11 (27%)	4/17 (12%)

[a]Bupropion group: includes both bupropion-only ingestions and co-ingestions with non-tablet formulations (eg, liquids), as material retrieved via endoscopy consisted exclusively of bupropion residues.

procedure-related complications. Endoscopic procedures were not standardized, as they were performed at different centres. Bezoar removal was performed using loop baskets or various types of forceps (with nets or polyp forceps), tailored to each case based on gastric findings and bezoar consistency. Procedures were assisted by direct endoscopic suction and an irrigation pump. Multiple fragmentation cycles and repeated passes were performed as needed to achieve complete removal.

Orogastric lavage was performed before endoscopy in 16 patients (57%) with positive endoscopy and in 12 (63%) with negative endoscopy. Nineteen patients (40%) required orotracheal intubation prior to endoscopy.

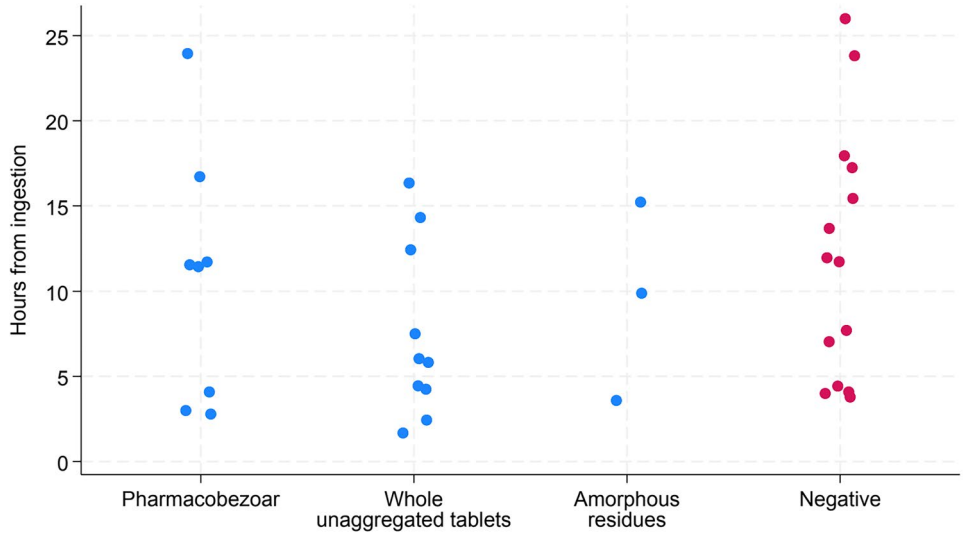

Figure 1. Timing of upper endoscopy (hours post-ingestion) by endoscopic findings. All four types of findings were observed regardless of timing. Data were available for 35 patients.

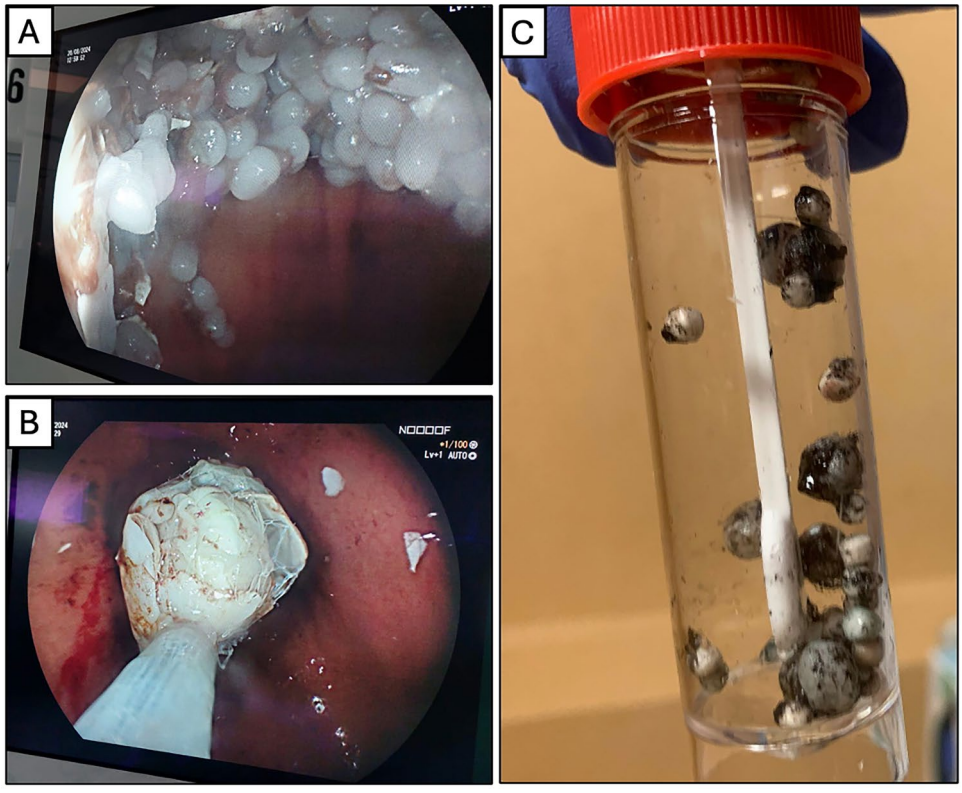

Figure 2. (A) Example of pharmacobezoar formed by numerous aggregated bupropion tablets in a patients found comatose with empty blisters of bupropion nearby (number of tablets not reported). (B) After fragmentation removal of pharmacobezoar was possible through wire-basket. (C) Example of unaggregated tablets retrieved by upper gastrointestinal decontamination endoscopy.

Among patients with available data, the relationship between endoscopic findings, overdose characteristics, timing, and most common pre-procedural clinical manifestations was assessed (Table 4). A higher total number of ingested tablets was significantly associated with positive endoscopic findings ($P<0.05$). Among patients who ingested ≥30 total tablets ($n=25$), 73% had positive endoscopic findings, compared to 33% among those who ingested <30 tablets ($n=9$). The rate of positive findings increased to 78% among those who ingested ≥50 tablets ($n=18$). Similar proportions were observed when considering bupropion

Table 4. Patients' characteristics by upper gastrointestinal decontamination endoscopy results.

		Upper gastrointestinal decontamination endoscopy		
	N	Negative (*n* = 19)	Positive (*n* = 28)	*P* value
Overdose data				
Total bupropion dose (mg)	27	4,500 (4,350, 8,250)	5,250 (4,500, 6,000)	0.7795
Total number of bupropion tablets	28	30 (22.5, 30)	30 (28.5, 40)	0.2702
Total number of tablets	35	30 (24, 60)	68 (40, 100)	**0.0299***
Modified release co-ingestants	47	5 (26.3%)	9 (32.1%)	0.7564
Time from ingestion to UGDE (h)	35	11.5 (5.6, 16.5)	8 (4, 13)	0.1932
Time from emergency department admission to UGDE (h)	47	3 (1.5, 11.8)	2 (1, 4.9)	0.4092
Symptoms prior to endoscopy				
Drowsiness	47	9 (47%)	15 (54%)	0.7714
Coma	47	6 (32%)	12 (43%)	0.5540
Seizures	47	5 (26%)	11 (39%)	0.5390
Tachycardia	47	5 (26%)	14 (50%)	0.1428
Agitation	47	2 (11%)	8 (29%)	0.1680

n = number of non-missing observations; Negative = variables distribution in subjects with negative endoscopy; Positive = variables distribution in subjects with positive endoscopy. Continuous variables are reported as median (IQR), and categorical variables as number (percentage). UGDE: Upper GI decontamination endoscopy.

Table 5. *In vitro* experiment results.

Formulation	Time (h)	Pharmacobezoar	Consistency	Notes
Formulation 1	4	Yes	Sticky	• Tablets progressively swelled • Gel-like layer covering tablet (Figure 3A)
	8–12	Yes	Firm	• Tablets firmly adherent to one another
	24	Yes	Firm	• Unchanged
	72	Yes	Firm	• Tablets worn on the surface (Figure 3B) • Sticky mass; difficult tablet separation • Hollow tablets after crushing
Formulation 2	4	Yes	Firm	• Tablets slightly swelled
	8–12	Yes	Firm	• Thin film coating adjacent tablets (Figures 3C and 4)
	24	Yes	Firm	• Unchanged
	72	Yes	Firm	• Unchanged appearance • Sticky mass; difficult tablet separation • Hollow tablets after crushing (Figure 3D)

tablets alone: 61% for ≥30 tablets (*n* = 18) and 75% for ≥50 tablets (*n* = 5).

Analytical bupropion and hydroxybupropion concentrations were determined in five cases (Supplementary Table 1).

Complete follow-up was available for 32 patients (68%). Among them, 24 (75%) fully recovered without further clinical manifestations, while seven (25%) experienced clinical deterioration. Worsening was due to progressive decreased level of consciousness requiring orotracheal intubation (*n* = 2), seizures including one case of status epilepticus (*n* = 5), severe agitation (*n* = 2), cardiotoxicity (*n* = 1) and hemodynamic shock (*n* = 1). All patients ultimately recovered, and none required veno-arterial extracorporeal membrane oxygenation support.

In vitro model

Results of the visual inspection are reported in Table 5 and illustrated in Figures 3 and 4.

Discussion

Endoscopy has been increasingly described as part of the acute management of intoxicated patients as a novel technique for gastrointestinal decontamination. However, available data are limited to single case reports or small case series, often reporting only cases where pharmacobezoars were found [11,22], limiting conclusions regarding its efficacy and optimal timing. Our study provides additional observations on endoscopy as a decontamination method. Importantly, including patients with negative endoscopic findings allowed direct comparison with positive cases to identify potential factors predisposing to positive findings. Moreover, endoscopic findings were categorized into three groups - pharmacobezoars, intact unaggregated tablets, or amorphous paste-like residues - to better characterize gastric content, as these differences may have both therapeutic and clinical implications. Miyauchi et al. [23] conducted the only study evaluating endoscopy as the sole decontamination technique to quantify residual gastric content in the emergency setting, in patients admitted to the emergency department for acute drug overdoses. Their study has the strength of having performed endoscopy in a single centre with a standardized protocol. However, its main limitations include the absence of information on the ingested drugs or the possible presence of modified-release formulations, as well as the lack of

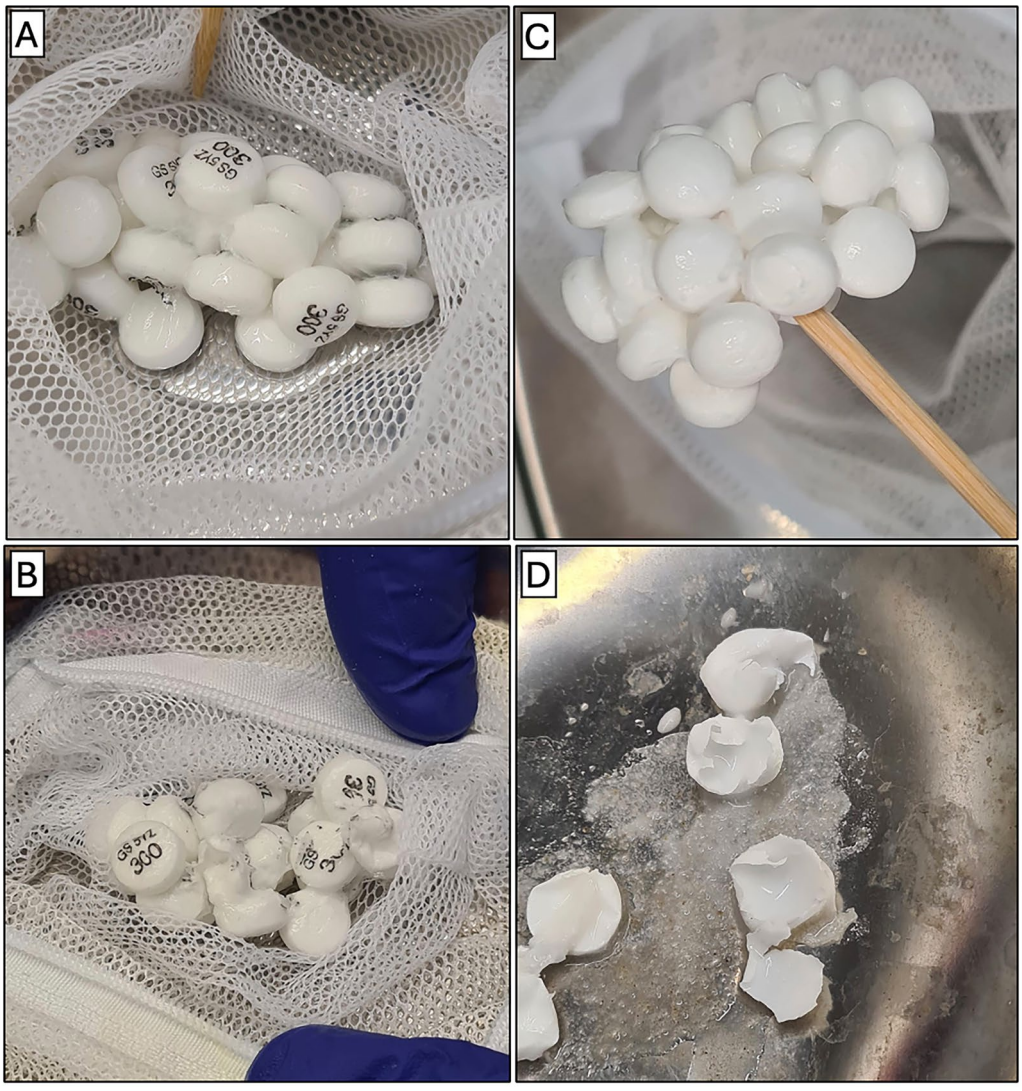

Figure 3. Formulation 1 at 4 h (A) and at 72 h (B), Formulation 2 at 12 h (C) and at 72 h after manual crushing (D).

Figure 4. Sticky surface of tablets adhering to the mesh bag upon visual assessment of formulation 2 after eight hours of incubation.

details regarding the patients' clinical conditions. Nevertheless, it represents the first attempt to characterize residual gastric content relative to time since ingestion, categorizing it into three phases: the tablets/food phase, the soluble/fluid phase, and the reticular/empty phase. Specifically, intact tablets were present within six hours of ingestion in 38% of enrolled patients ($n = 137$). Their methodological approach and gastric content characterization could be applicable in the clinical setting to the phenomenon of pharmacobezoar formation in acute drug overdoses.

Despite the lack of a consensus definition, a pharmacobezoar is generally defined as a concretion of tablets, pills, or insoluble medication vehicles that adhere to one another and become retained in the gastrointestinal tract [12]. Endoscopic removal of pharmacobezoars requires bezoar disintegration, a process that can be difficult and time-consuming, particularly due to the adhesive or sticky consistency of the concretion [11]. This often requires coupling endoscopic suction and irrigation with additional techniques, such as the removal of pharmacobezoar fragments using a loop basket or polyp forceps [11]. Since multiple extraction cycles may be required, airway protection and the use of an oesophageal overtube should be considered to minimize potential complications based on the patient's clinical status. Pharmacobezoars may prolong active drug release compared to individual tablets or cause massive drug absorption due to sudden bezoar breakage [13]. Hoegberg et al. demonstrated *in vitro* that drug release from pharmacobezoars was reduced by up to 50% relative to single tablets [13], an observation consistent with cases described in the literature [24]. Even when endoscopy does not find true pharmacobezoars, removing unaggregated tablets or paste-like residues may still reduce drug absorption. This highlights the clinical relevance of endoscopic extraction, particularly as our study suggests that conventional decontamination methods may fail. Indeed, 60% of patients in our study underwent orogastric lavage. Despite this, endoscopy was positive in most cases; specifically, 57% of those with positive findings had previously undergone orogastric lavage, suggesting its potential inefficacy in removing pharmacobezoars or residual tablets. This aligns with early data described by Saetta et al. in 1991 showing that 88% of patients still presented with residual intragastric solid material despite orogastric lavage [25]. In Italy, orogastric lavage remains a routine procedure in the emergency management of poisoning and is typically performed using standard large-bore orogastric tubes. However, modified-release bupropion tablets are designed to maintain their structural integrity and, especially if pharmacobezoars are formed, they often exceed the diameter of the tube and its side openings, preventing their retrieval during the procedure.

In our study, endoscopy was positive between two and 24 h after ingestion. As shown in Figure 1, no temporal correlation was observed between endoscopy timing and findings, confirmed by the lack of statistical significance. Notably, pharmacobezoars were detected as early as three hours post-ingestion, in line with our *in vitro* experiment.

Our experiment highlights key aspects of bupropion behaviour relevant to the role of endoscopy in the overdose setting. Specifically, it confirms that modified-release bupropion exhibits pharmaceutical properties predisposing to pharmacobezoars, which may occur early after overdose. Consistently, pharmacobezoar formation was observed as early as four hours after incubation. This predisposition is likely related to the partially synthetic cellulose ethers used in modified-release formulations. Formulation 1 contains ethylcellulose (E462) as the first coating layer of the tablet core, while formulation 2 includes both ethylcellulose and hypromellose (E463), with the latter also present in the tablet core. Due to their adhesive properties in aqueous environments, these excipients are potential risk factors for pharmacobezoar formation [13]. These findings support the utility of early endoscopic decontamination, which may effectively remove pharmacobezoars within the first hours after ingestion, as observed in our patients. A second key experimental finding is that while pharmacobezoars remained stable for up to 72 h, upon manual manipulation, the tablets appeared devoid of active substance, consisting only of "ghost pills". This aligns with a reported case [14] of severe bupropion poisoning where endoscopy performed at 34 h after ingestion retrieved 236 tablets; despite being identified as bupropion, analysis revealed no detectable active compound. These data suggest that late endoscopic decontamination, despite the potential retrieval of tablets or pharmacobezoars, is likely ineffective once drug release is complete. The primary limitation of our *in vitro* study is that no analytical measurements of drug release kinetics were performed, preventing definitive pharmacokinetic conclusions. In published case reports where endoscopic removal of pharmacobezoars or intact tablets was performed at later stages of poisoning (beyond 24–48 h) due to severe or prolonged clinical manifestations, the clinical course was often associated with serious or fatal outcomes [24,26–28]. Conversely, cases where endoscopy was performed earlier in the course of poisoning were associated with more favourable outcomes [11,20,29]. In our patients, endoscopy was

performed relatively early, with a median time of 10 h from ingestion and two hours from hospital admission. Although the impact of timing on clinical outcomes is difficult to assess, all our patients ultimately recovered.

In our cases with serial concentration measurements, the first determination consistently showed the highest bupropion concentration, followed by a progressive decrease; conversely hydroxybupropion concentration peaked at the second measurement in two cases. This pattern aligns with literature data [30,31] and suggests that in bupropion overdose, drug release peaks within the first hours post-ingestion, making this the optimal window for endoscopic intervention.

A key finding of our study is that the total number of ingested tablets was statistically associated with positive endoscopic findings, confirming a previously hypothesized but unproven relationship. In contrast, neither the total ingested dose of bupropion nor the number of bupropion tablets alone showed a significant association. It is possible that co-ingestants, particularly other modified-release formulations, may contribute to the persistence of a quantitatively relevant amount of material in the stomach, helping identify patients who could benefit from early endoscopic decontamination. Furthermore, unpredictable individual variables, such as gastric pH, stomach anatomical variations, and drug-induced effects like hypomotility or delayed gastric emptying, may further affect residual gastric content.

Finally, regarding the indications for endoscopy at our centre, computed tomography scans were rarely used. In our cohort, as endoscopy serves both diagnostic and therapeutic purposes, indications were primarily based on patient history and clinical manifestations. When reliable, patient history is highly informative, as the total number of ingested tablets was the only factor statistically associated with positive endoscopic findings. However, relying solely on history may underestimate the risk, as such information is often unreliable or unavailable in acute overdose settings. While severe clinical manifestations may help identify patients who could benefit from endoscopic decontamination, no single symptom was statistically associated with positive findings. In such cases, performing early endoscopy may prevent further drug absorption and reduce the risk of clinical deterioration. Although computed tomography scans could represent a useful diagnostic tool to implement in this setting, their sensitivity for detecting gastric bezoars is not well established, and previous reports have described cases in which computed tomography failed to identify them [28,32].

Our study has some limitations. First, its retrospective nature may have limited the collection of certain anamnestic or clinical information, and the relatively small sample size may have reduced the statistical power. Despite these limitations, our study provides further insight into the role of endoscopy as part of patient management in the acute overdose setting. As both orogastric lavage and endoscopy were performed across multiple centres, procedural differences between sites cannot be excluded, and operator-dependent factors may have influenced the efficacy of orogastric lavage. Similarly, the findings and efficacy of endoscopic decontamination may have been affected by the individual operator's technique and interpretation. Bupropion and hydroxybupropion plasma concentrations were available for only a very limited number of cases, as the analytical method was established in our laboratory in 2022, and sample collection from hospitals across Italy was limited. This aspect should be addressed in future studies to evaluate the potential impact of endoscopy on bupropion pharmacokinetics. Another limitation is the heterogeneity of our population, which also included acute bupropion overdoses involving co-ingestants. Nevertheless, we analysed clinical manifestations and outcomes separately for single bupropion ingestions and mixed intoxications, and the *in vitro* study specifically evaluated bupropion alone. While studying single drug ingestion is important to understand the potential benefit of endoscopic decontamination, in real-world settings most intentional acute overdoses involve multiple substances. Therefore, evaluating also the context of co-ingestion provides insights for clinicians managing potentially severe overdoses and selecting the most effective decontamination strategy to reduce toxicity risk.

Conclusions

Acute modified-release bupropion overdoses, whether involving a single substance or combined with other drugs, are associated with pharmacobezoar formation and the persistence of intact tablets or residues in the stomach, even after standard decontamination. Our study provides insights into critical questions regarding endoscopic decontamination: which patients are most likely to benefit from this procedure, and what is the optimal therapeutic window to maximize active substance removal. While a definitive clinical profile for identifying candidates for endoscopic decontamination remains to be fully established, our findings suggest that pharmacobezoars can form within the first hours of overdose. Consequently, endoscopy is also effective

in the early stages of patients management to prevent active release from residual drug material. Notably, the total number of ingested tablets emerged as a key predictor, with patients ingesting ≥30 tablets already showing a substantial rate of positive endoscopy (73%). In the future, implementing the elements required to reach a clinical decision - including availability of analytical bupropion concentrations and a deeper understanding of the mechanisms coupled with patient history and clinical evaluation, may further help in identify patients who could benefit from endoscopy as the decontamination technique of choice.

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The authors report there are no competing interests to declare.

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Data availability statement

The data can be obtained from the corresponding author upon reasonable request.

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