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REVIEW ARTICLE

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Hyoscine butylbromide mode of action on bowel motility: From pharmacology to clinical practice

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Abstract

Background: Hyoscine butylbromide (HBB) has been available for use as an antispasmodic since 1951 and is indicated for the treatment of abdominal pain associated with cramps. A previous review in 2007 summarized the evidence on the mode of action of HBB in vitro and in vivo in both animal and human studies. However, since then, novel publications have appeared within the literature and also our knowledge of what represents normal motility in humans has evolved.

Purpose: This review is the result of the collaboration between a basic scientist and clinicians with the aim of providing an updated overview of the mechanisms of action of HBB and its clinical efficacy to guide not only use in clinical practice, but also future research.

KEYWORDS
colon, gastrointestinal tract, hyoscine butylbromide, large intestine, pharmacologic actions, scopolamine

1 | INTRODUCTION

Antispasmodics have been used for decades in the treatment of abdominal cramping pain in the gut, including for irritable bowel syndrome (IBS), based on the assumption that gut, and especially colonic smooth muscle, spasms contribute to digestive symptoms and pain in particular, hence, the term spastic colon.[1]

Hyoscine butylbromide (HBB; scopolamine butylbromide) is one of the most used anticholinergic and antispasmodic drugs on the market.[2] First registered as a pharmaceutical drug in Europe in 1952,[3] HBB has subsequently been registered in >80 countries and is available as oral formulations, an intravenous solution, and a suppository.[4,5] HBB is recommended as an antispasmodic in the guidelines of both the World Gastroenterology Organization Global and the American College of Gastroenterology.[6,7] It is indicated for the relief of gastrointestinal (GI) and genito-urinary spasms, as well as relief from the symptoms associated with IBS in some countries.[5]

A previous review in 2007 summarized the evidence on the mode of action of HBB[3]; however, since then, novel publications have appeared within the literature. Additionally, our knowledge of what represents normal motility in humans has evolved. This review aimed to update the current knowledge on the mode of action of orally administered HBB with regard to human motility, with a focus on the colon, to understand whether these findings could improve the use of HBB in clinical practice and also guide future research.

Abbreviations: Ach, acetylcholine; AE, adverse event; APC, abdominal pain associated with cramping; CI, confidence interval; EC50, half-maximal effective concentration; EFS, electrical field stimulation; ENS, enteric nervous system; GCP, Good Clinical Practice; GI, gastrointestinal; HBB, hyoscine butylbromide; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IC50, half-maximal inhibitory concentration; M (1, 2 and 3), muscarinic receptor; NO, nitric oxide; NPRS, numerical pain rating scale; PGI-C, patient global impression-change; p.o., orally; VAS, Visual Analog Scale.

2 | CHEMISTRY AND PHARMACOKINETICS

Hyoscyamine is a tropane alkaloid, purified from the leaves of the Solanaceae plant species, specifically the Duboisia plant, native to Australia (Figure 1).[8] A levorotatory isomer of atropine,[9] hyoscyamine is converted into hyoscine (also known as scopolamine) following a two-step process involving epoxidation.[10] An N-group butylbromide addition to hyoscine produces HBB, a molecule which has properties comparable to those of hyoscine, but with poor systemic absorption, improving the safety profile of HBB when compared with the precursor molecule.[3,11]

HBB is a compound initially developed as an authorized specialty >30 years ago. It is marketed as a spasmolytic in several countries within and outside Europe, in both oral and parenteral pharmaceutical form. The formulation authorized worldwide is that of a 10 mg sugar-coated tablet, which has been on the market for several decades, and only minor modifications have been made to the proposed formulation.[3] In addition, a number of country-specific analgesic combination products have been marketed in the form of sugar- or film-coated tablets. The objective of the development was to obtain a modern formulation of 20 mg film-coated tablets. Given the age of the product, the purpose was to select alternative excipients in order to improve the stability of the formulation.[3]

HBB is very polar, regardless of the surrounding pH, and consequently, when administered orally it is only partially absorbed (8%).[11] Blood levels are difficult to detect at therapeutic doses (30–60 mg)[3] with bioavailability being <1%.[4,5] Data on file have demonstrated that a single 500 mg dose produces a maximum plasma concentration of 5 ng/ml with 0.16% of drug found in the urine. After intravenous administration (100 mg), the half-life is 1–5 h with clearance of 1.2 L/min. Approximately 50% of the drug is excreted through the kidneys as unchanged, while the rest is metabolized through the hydrolytic cleavage of the ester bond. The metabolites that are excreted in the kidneys bind barely to muscarinic receptors and are not considered to contribute to the effect of HBB. After oral administration, 90% of radiolabeled HBB is excreted fecally and >0.7%–1.6% is excreted renally.[5] Following a single oral dose of HBB in the range of 100–400 mg, the terminal elimination half-life was found to be 6.2–10.6 h.[5]

Key Points

- HBB is suitable as a first-line treatment for abdominal pain in functional disorders where antispasmodics are normally used, as it is not easily absorbed in the GI tract and does not cross the blood–brain barrier, so minimizing systemic side effects.
- Oral HBB acts on the lower GI tract and has been shown to affect human gut secretion in vitro and reduce the sensitivity to rectal distension in patients with IBS-D, suggesting that HBB could be investigated for the treatment of IBS-D in future studies.
- HBB is effective when used as an as-needed treatment, suggesting that it could be taken on demand, but also as indicated in the summary of product characteristics; however, it is important that clinicians follow local guidelines regarding the use of HBB.

3 | BASIC PHARMACOLOGY OF HBB

Anticholinergic drugs prevent the effects of the neurotransmitter acetylcholine (ACh) by blocking its binding to muscarinic receptors at neuroeffector sites (e.g., GI smooth muscle, cardiac muscle, and exocrine gland cells, including GI epithelial cells) (Figure 2).

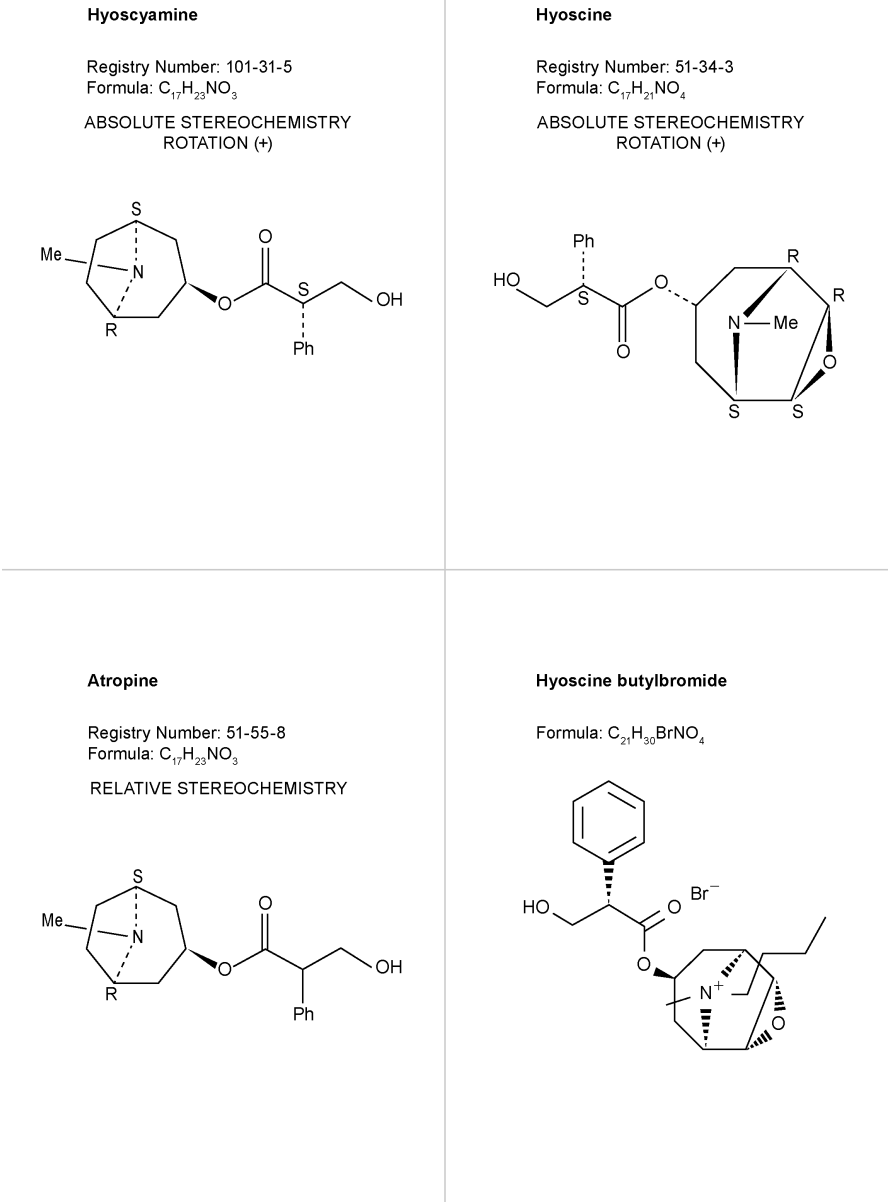
Muscarinic Ach receptors are G-protein coupled receptors which have Ach as their endogenous agonist. They are classified into five subtypes (M1–M5), with M2 and M3 being the main muscarinic receptor subtypes found in the GI tract.[12] The M3 receptor couples to Gq/G11 proteins, activating phospholipase C. Activation of M3 receptors causes smooth muscle depolarization, and induces opening of L-type calcium channels and calcium release from intracellular stores. This mechanism is responsible for smooth muscle contraction. In contrast, the M2 receptor couples to Gi/G0 pathways which inhibit adenylate cyclase and reverse the relaxation caused by stimulating the β-adrenoceptor.[13] The prototype of antimuscarinic drugs is atropine, and it is often used as a comparator.

M2 and M3 distribution has been recently measured using polymerase chain reaction and western blot analysis in different areas of the human GI tract. Higher expression of both M2 and M3 receptors was found in the human upper (esophagus and stomach), compared with the lower (jejunum ileum and colon) GI tract. M3 is expressed in higher concentrations than the M2 receptor in all the GI regions, and they are both expressed in the circular and longitudinal muscles.[14] However, high expression of a receptor in a particular zone does not necessarily correspond to an effect on smooth muscle cells since muscarinic receptors are also expressed in other locations, for example, in epithelial cells where their activation leads to secretion (Figure 2). HBB binds to both M2 and M3 receptors, and binding affinities of HBB and atropine for human muscarinic receptor subtypes have been estimated to be 233 and 1.9 nM, respectively, for M2 receptors, and 643 and 1.4 nM for M3 receptors.[14]

Anticholinergic drugs might also have antinicotinic properties. Nicotinic receptors are members of the Cys-loop family of transmitter-gated ion channels. All nicotinic receptors have a pentameric structure, which consists of five subunits containing four α-helical transmembrane domains. Several allosteric modulatory sites are contained within the nicotinic receptors.[15,16] Nicotinic receptors are expressed in enteric neurons in post-synaptic locations and their activation by Ach and nicotine causes neuronal activation[17] (Figure 2). According to studies in guinea pigs, nicotinic receptors might also be located in the nerve terminal (pre-synaptic), but their role is not yet known.[18] Hexamethonium is the prototype of antinicotinic drugs and is often used as comparator.

In an in vitro study conducted by Weiser et al. in the human neuronal cell line SH-SY5Y, application of Ach and nicotine induced comparable currents with EC50 values of 25.9 ± 0.6 μM

FIGURE 1 Chemical structure of hyoscine derivatives



and 40.1 ± 0.4 μM, respectively. HBB suppressed currents (IC50 0.19 ± 0.04 μM) in a concentration-dependent manner, which was seven times more potent than hexamethonium (1.3 ± 0.3 μM).[19] High concentrations of the agonists did not reduce the inhibitory effect of HBB, showing that HBB was a non-competitive antagonist possibly binding to an allosteric site of the nicotinic receptors.

4 | ROLE OF HBB IN THE MODULATION OF THE NEUROMUSCULAR RESPONSE OF THE GI TRACT

The enteric nervous system (ENS), located in the intestinal wall, regulates several intestinal functions such as motility and secretion.[20] In the ENS, motor neurons are those involved in the activation of neuromuscular response in the GI tract and are classified into excitatory and inhibitory motor neurons according to the neurotransmitters with which they associate (Figure 3). Excitatory motor neurons release Ach and tachykinins,[21,22] whereas inhibitory motor neurons release nitric oxide (NO) and adenosine triphosphate.[23-28]

In in vitro studies, two major approaches are usually performed to study the effect of drugs on neuromuscular response:

1. Effect of the drug after activation of muscarinic receptors. In this case, the effect of the drug is measured on pre-contracted smooth muscle using muscarinic agonists (Ach, carbachol, bethanechol, etc.) that directly activate muscarinic receptors on the smooth muscle cells.[14,29,30]
2. Effect of the drug after neural activation. In this experimental procedure, the effect of the drug is measured after the electrical

stimulation of neurons extrinsic (e.g., parasympathetic neurons) or intrinsic (usually called electrical field stimulation [EFS]) to the gut wall, inducing the release of neurotransmitters from motor neurons and triggering smooth muscle contraction or relaxation. EFS normally depolarizes all enteric neurons, resulting in the simultaneous activation of inhibitory and excitatory neurons. This causes a series of contractions and relaxations referred to as biphasic or triphasic responses and are recorded in animal and human tissues.[18,30,31]

These procedures can also be applied to characterize neurosecretion, that is, muscarinic agonists cause secretory activity in epithelial cells, which is blocked by antimuscarinic drugs, and EFS of enteric neurons causes secretion, which is reduced with antimuscarinic agents.[32] Notably, regional variations have been reported. In the human small intestine, ~50% of the neurosecretory response is sensitive to atropine (1 μM), whereas in the human colon only 25% of the neurosecretory response is sensitive to atropine (1 μM). Other neurotransmitters, such as vasoactive intestinal peptide and NO, can also contribute to the neurosecretory process.[30]

4.1 | In vitro animal studies

Benzi et al. assessed the effect of HBB in vitro across several intestinal tissues from guinea pigs and dogs.[33] Experimental procedures such as electrical stimulation of extrinsic and intrinsic neurons, as well as direct cholinergic stimulation, were performed in muscle bath experiments (Table 1). In all the experimental procedures, HBB dose-dependently decreased contractions in a sub μ-molar range, indicating a high potency of HBB as an antispasmodic drug acting on muscarinic receptors.[33]

Lecchini et al. published similar results.[34] In these studies, hyoscine and atropine were used as comparators and both were slightly more potent than HBB (Table 1). Unlike atropine, HBB was able to decrease the Ach released by neurons following pelvic stimulation (extrinsic neurons) and EFS (intrinsic neurons), supporting the concept of HBB also having post-synaptic nicotinic antagonist properties.[34]

Pomeroy and Rand investigated the anticholinergic response of HBB, assessing its activity on isolated sections of guinea pig ileum.[35] HBB abolished peristaltic activity when applied both to the serosal and mucosal side of the tissue (Table 1). The dosage necessary to obtain this effect was 4–6 μg/ml for the serosal side and 600–800 μg/ml for the mucosal side. The reduced effect noted following application to the mucosal tissue was believed to be due to the chemical properties of HBB which cannot easily pass through the epithelial barrier. However, the effect of HBB was more persistent when applied to the mucosal than the serosal side, as determined following washout of the compound from the organ bath. Passage through the intestinal wall was poor; however, HBB did pass through Peyer's patches more readily.[35]

In a study conducted by Hart et al., the effects of HBB were assessed on the circular and longitudinal muscle strips of horse ileum.[36] Carbachol-induced contractions were abolished by HBB in both the circular and longitudinal muscle, with a 4.5-fold lower concentration in circular than longitudinal muscle strips. Pretreatment with HBB prior to the application of the muscarinic agonist carbachol significantly prevented contractions (Table 1).[36] These experiments supported the use of HBB in veterinary medicine where the use of antispasmodic drugs is extremely relevant in equines.

4.2 | In vivo animal studies

In vivo studies measuring colonic motility have been performed in anesthetized guinea pigs.[33] Stimulation of the pelvic nerve caused a contraction of the colon that was dose-dependently decreased with intravenous administration of hyoscine (ED50 = 12.5 μg/kg), HBB (ED50 = 26 μg/kg), and octammonium (ED50 = 325 μg/kg). The relative potency of each compound (related to mol/kg) was 29.4 (hyoscine), 16.4 (HBB), 1.7 (octammonium), and 1 (diprosine). Similar results were obtained in anesthetized dogs, since HBB reduced colonic contractions induced by Ach (ED50 = 12.3 μg/kg).[33]

In a study performed in rats using radiolabeled HBB, a poor gastrointestinal absorption (7%–8%) was reported.[37] This value is similar to those reported in humans; therefore, rats might be a suitable model to determine the distribution of HBB in different tissues. Following oral administration of HBB (24 h), the radioactivity accumulated (~20%) in the intestinal wall of the distal small intestine. Notably, radioactivity was found at both the mucosa and the muscular level. The authors concluded that despite low bioavailability, HBB can act locally and reach muscarinic receptors inside the intestinal wall.[37]

Application of HBB into the dog ileal or colon fistula (0.3–3 mg/kg) caused a long-lasting and potent inhibition of ileal phasic motility index (31%–71%) and colonic contractions (39%–59%), respectively. It was concluded that HBB present in the intestinal lumen, although poorly absorbed, exerts local spasmolytic actions without systemic effects.[38]

4.3 | In vitro human studies

Studies using human tissue are less common compared with those involving animals. One study was conducted with scopolamine and two with HBB.

Cellek et al. observed three distinct types of response in human colonic circular muscle strips following EFS: monophasic cholinergic contractions (which arise during the EFS); biphasic response (nitrergic relaxation during the EFS, followed by cholinergic contraction after termination of the stimulation); and triphasic response (a cholinergic contraction followed by nitrergic relaxation mid stimulation and a tachykinergic contraction after stimulation).[31] These responses were modified with the addition of NO synthase inhibitor NΩ-nitro-L-arginine methyl ester, which blocks the inhibitory

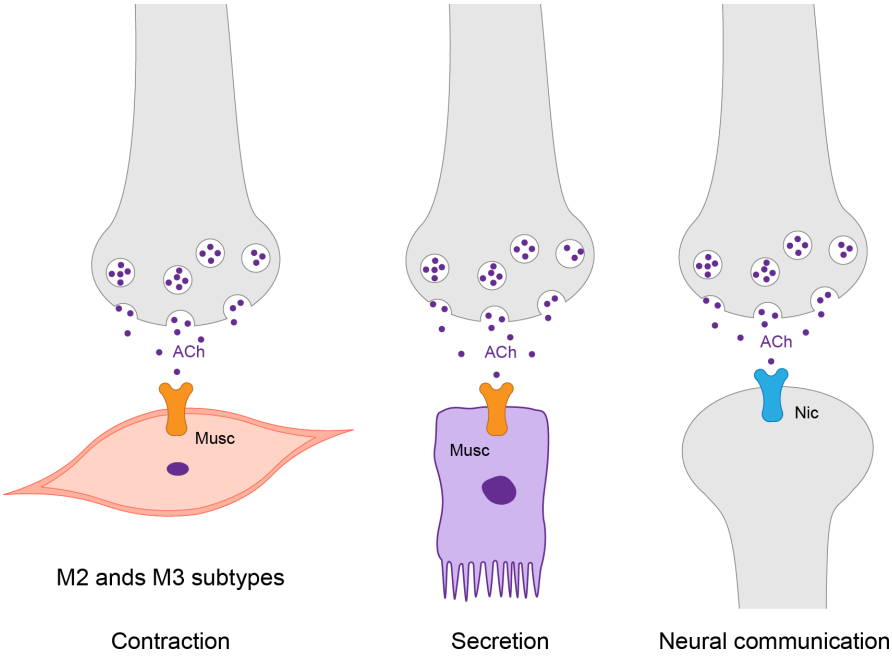


FIGURE 2 Pharmacological targets of HBB. Muscarinic receptors participate in smooth muscle contractions (left) and epithelial secretion (middle) whereas nicotinic receptors are involved in neural communication between neurons of the ENS (right)

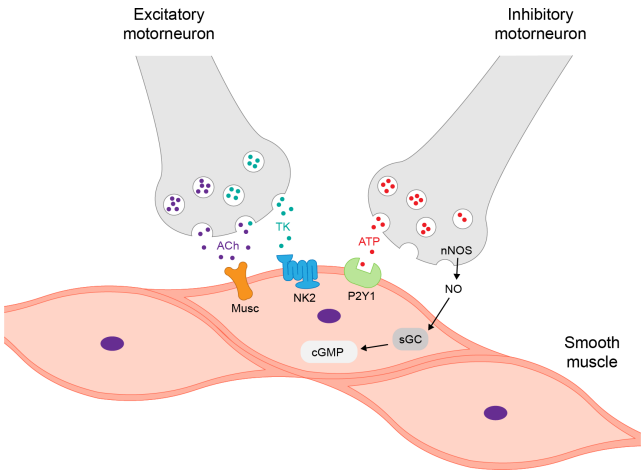


FIGURE 3 Representation of the neuromuscular interface, showing the receptors and neurotransmitters involved in its modulation. Excitatory motor neurons release ACh and TK and cause muscle contractions; inhibitory motor neurons release NO and ATP or a related purine which acts on soluble guanylyl cyclase and P2Y1 receptors, respectively, resulting in smooth muscle relaxation

component of each profile. Scopolamine reduced contractions in the monophasic response by 98%, the secondary contraction of the biphasic response by 90%, and the initial contraction in the triphasic response by 85% (Table 2).[31]

Following the study by Weiser et al. which determined that HBB was able to block nicotinic Ach receptors in vitro in a human cell line,[19] the antimuscarinic effect of HBB was investigated in human tissue by Krueger et al. who conducted a comprehensive study on the effects of HBB in human small and large intestinal samples.[30] HBB reduced the muscle contractions, as well as calcium increases, in smooth muscle cells and epithelial secretion induced by the muscarinic agonist bethanechol, with IC50 values of 429, 121, and 224 nM, respectively. In this study, the EFS caused a biphasic response with a small contraction during stimulation (on-contraction) followed by contraction after stimulation (off-contraction). Under these experimental conditions, 1 μM HBB abolished the on-contraction but only partially (~30%) reduced the off-contraction. High concentrations of HBB (10 μM) were needed to block nicotinic responses in firing activity of enteric neurons from the submucous plexus. Similar results were obtained when secretion was studied. Due to the high concentration needed to block nicotinic responses, it was suggested that nicotinic antagonism is possibly not the primary route through which HBB acts (Table 2).[30]

Zhang et al. confirmed that HBB reduced (80%) smooth muscle contractions induced with exogenous bethanechol but found that it also slightly inhibited (30–40%) spontaneous smooth muscle activity of both circular and longitudinal colonic muscle strips. A higher potency in response against bethanechol-induced contractions was observed in the lower (small intestine and colon) compared with the upper (esophagus and stomach) GI tract. Similar IC50 values were reported in both muscle layers.[14]

Limited studies have been performed using pathological human samples. A study conducted by Alvarez-Berdugo et al. investigated the excitatory neuromuscular transmissions within the circular muscle strips from the sigmoid colon of patients with diverticulosis.[29] Compared with healthy controls, the patients with diverticulosis had a greater contractile response to cholinergic and tachykinergic agonists (carbachol and neurokinin A). However, M2 and M3 receptors were not upregulated in these patients and the mechanical response to EFS was comparable with controls. HBB reduced the on-contraction by 80% both in the control and diverticulosis tissues,

TABLE 1 Effect of HBB on tissues from laboratory animals in in vitro experiments

Animal tissue (Technique)	Stimulating agent	Variable	HBB	Comparator	Study
Guinea pig colon (muscle bath)	Pelvic nerve stimulation	ED50	3×10^{-7} M	Hyoscine: 1.25×10^{-8} M	Benzi et al. 1974[33]
	Transmural stimulation		1.24×10^{-7} M	Hyoscine: 4.8×10^{-9} M	
	Acetylcholine (1×10^{-7} g/ml)		7.6×10^{-8} M	Hyoscine: 1.94×10^{-9} M	
Guinea pig colon[a] (muscle bath)	Pelvic nerve stimulation	ED50	8.13×10^{-8} M	Atropine: 2.59×10^{-9} M	Lecchini et al. 1969[34]
	Transmural stimulation		1.15×10^{-7} M	Atropine: 5.41×10^{-9} M	
	Acetylcholine (1×10^{-7} g/ml)		2.54×10^{-7} M	Atropine: 9.95×10^{-9} M	
Guinea pig ileum (Trendelemburg's Method) Serosa side	Transmural stimulation	Concentration needed to abolish the response	0.1–0.6 μg/ml	NA	Pomeroy and Rand 1969[35]
	Peristaltic response		4–6 μg/ml	NA	
Mucosa side	Transmural stimulation		600–800 μg/ml	NA	
	Peristaltic response		600–800 μg/ml	NA	
Horse ileum (muscle bath) Circular muscle	Carbachol (10^{-9}–10^{-5} M)	Shift of concentration response curve	10–300 μM	NA	Hart et al. 2015[36]
Longitudinal muscle	Carbachol (10^{-9}–10^{-5} M)			NA	

Abbreviations: ED50, half-maximal effective dose; HBB, hyoscine butylbromide; NA, not applicable.

[a]HBB caused 18% and 31% reduction of acetylcholine output in transmural and pelvic stimulation, respectively.

whereas otilonium bromide, another antispasmodic drug, reduced the on-contraction by only 20%–40% (Table 2).[29] In these studies, the IC50 of HBB was 1–10 μM.

4.4 | In vivo human studies

Six double-blind, randomized controlled studies investigated the effect of HBB on gastric and duodenal motility in healthy subjects. Only two evaluated the effect of oral HBB.[39-44]

One randomized crossover study has compared the effect of HBB 60 mg, cyclotropium bromide 60 mg and placebo on the gastric emptying and antral motility in response to a semisolid meal as recorded by scintigraphy (N = 24 healthy individuals).[43] Both active medications significantly delayed percentage of gastric emptying but cyclotropium had a greater effect versus HBB. Only cyclotropium significantly increased half emptying time compared with placebo. Both active medications significantly reduced the amplitude of antral contractions, but cyclotropium had a higher effect versus both placebo and HBB. No effect was demonstrated on the frequency of the antral contractions, and no side effects were recorded.[43]

No effect of oral HBB was recorded on small bowel motility, both in fasting and postprandial condition, as measured by an ingested pressure-sensitive radiotelemetry capsule tethered at the duodenojejunal flexure in an open-label study where 20×10 mg tablets of HBB were administered.[44]

In a more recent study, 118 patients with IBS (n = 43 with constipation, n = 25 with diarrhea, and n = 50 with pain and bloating), diagnosed using Rome II criteria, and 45 healthy individuals were studied at baseline and after 2 weeks' therapy with either oral tablet of HBB (20 mg×3 per day, n = 37), a HBB suppository (30 mg once daily, n = 21), oral drotaverine (80 mg×3 per day, n = 30), calcium gluconate tablets (one three times daily, n = 16) as a control for oral agents, or calendula suppository (once daily, n = 14) as a control for those who received a suppository.[45] Pain severity was evaluated using the Visual Analog Scale (VAS) pain score. Sensory response to rectal latex balloon stimulation was studied at baseline and after 2 weeks of treatment. Sigmoid and rectal motility were also assessed.[45]

HBB (tablet or a suppository), but not drotaverine, produced a significant reduction in pain score among IBS patients with predominant diarrhea (before: 10.3±2.3, after: 3.2±1.1, and before: 10.2±2.2, after: 4.3±1.6, respectively, both $p<0.05$). Following treatment with oral HBB, a significant increase in the sensitivity threshold to rectal distension (reduction of hypersensitivity) was observed only in the group of IBS patients with predominant diarrhea (from 21.78±2.8 to 39.60±2.4 mmHg, $p<0.05$). Notably, these patients had a significantly lower threshold for sensation (rectal hypersensitivity) at baseline. No significant effect was observed with drotaverine, and none of the interventions had any effect on any of the parameters of sigmoid and rectal motility, as measured by multiple balloon manometry. Whether the effect on sensitivity is

TABLE 2 Reduction in contractions following EFS stimulation in human tissue

In vitro studies			
Study	**Treatment**	**Change in EFS-induced contraction**	**Sample size (*n*)**
Cellek et al. 2006[31]	Scopolamine 10 μmolL^{-1}	Monophasic contraction: 98% inhibition	4
		Biphasic contraction: 90% inhibition	4
		Triphasic contraction: 85% inhibition of initial contraction; 44% enhancement of contraction post-EFS	5
Krueger et al. 2013[30]	HBB 1 μmolL^{-1}	On-contraction: abolished; off-contraction: significantly reduced[a]	4
	HBB 10 μmolL^{-1}	On-contraction: abolished; off-contraction: significantly reduced[b]	6
Zhang et al. 2016[14]	HBB 10^{-5} M	~50%–60% reduction[c]	9
Alvarez-Berdugo et al. 2015[29]	HBB 10^{-4} M	70% reduction for 40 Hz on-contraction in healthy tissue	20
		70% reduction in on-contraction in diverticulosis tissue	14
	Otilonium bromide 10^{-4} M	40% reduction in 40 Hz on-contraction in healthy tissue	20
		20%–30% reduction in on-contraction in diverticulosis tissue	14

Abbreviations: EFS, electrical field stimulation; HBB, hyoscine butylbromide.

[a]Following HBB 1 μmolL^{-1}, on-contraction: −3.0 ± 2.9 mN versus 10.0 ± 3.6 mN, $p = 0.028$; off-contraction: 45.6 ± 19.6 mN versus 98.5 ± 24.7 mN, $p = 0.048$.

[b]Following HBB 10 μmolL^{-1}, on-contraction: −5.4 (−7.8/−2.5) vs 16.9 (9.0/29.0) mN, $p = 0.031$; off-contraction: 29.7 ± 3.5 mN vs 78.4 ± 10.4 mN, $p = 0.004$.

[c]In this study, the authors did not distinguish between on- and off-contractions.

mediated by an effect on motor response not detected by the low-resolution manometry as compared with the gold-standard barostat remains to be clarified.[45]

5 | CLINICAL STUDIES

Eleven placebo-controlled studies evaluated the effect of HBB in patients with functional abdominal pain. Five of these included up to a maximum of 50 patients treated with HBB oral form before application of the Good Clinical Practice (GCP) guidelines and are summarized in Table 3.[46-55] The remaining studies are reported below.

One of the studies was a randomized double-blind study comparing the effect of 4-day treatment with HBB (20 mg oral tablets or 10 mg suppositories), the papaverine-like antispasmodic proxazole (200 mg oral tablets or 400 mg suppositories), HBB plus the analgesic dipyrone (20 mg tablets and 500 mg tablets or 10 mg suppositories and 1000 mg suppositories, respectively) or placebo on abdominal pain, "more or less continuous and of average intensity" considered to be related to GI, biliary, and urinary tract smooth muscle spasm ($N = 818$ patients; $n = 463$ received oral, while the remainder received rectal treatment).[46] The response to treatment was evaluated using a rating scale from good ("no pain or more or less so on 2nd, 3rd, and 4th day") to none (no effect on pain). The patients were also asked to rate the intensity of their spontaneous or provoked (induced by abdominal palpation) pain. The study suggested that all three treatments, whether oral or rectal, improved abdominal pain compared with placebo.[46]

Another study was a Phase III, double-blind, randomized parallel group trial conducted to support the approval of the fixed-dose combination of HBB plus paracetamol.[54] This study evaluated the efficacy of 4-week treatment with HBB (30 mg/day orally [p.o.]) plus paracetamol (1500 mg/day p.o.); HBB (30 mg/day p.o.); paracetamol (1.500 mg/day p.o.); or placebo (3 tablets/day p.o.) in 712 adult patients with IBS excluding patients with IBS with diarrhea (IBS-D). The efficacy was evaluated by the physicians who defined patients as "responders" and "non-responders". Patients also kept a diary and entered a daily rating of their symptoms using a VAS score. At the end of the 4 weeks, the differences between the HBB plus group and HBB only group compared with placebo were statistically significant (Table 3). The VAS daily rating also showed a statistically significant improvement in abdominal pain intensity in the HBB plus paracetamol group versus the placebo group and in the HBB plus paracetamol group versus the paracetamol group. Thirty-eight patients (5%, no differences between the treatment groups) experienced adverse events (AE) that did not require treatment.[54]

Another study evaluated the effect of the three treatments as in the study above.[49] After a 1-week run-in period, 1637 patients

were enrolled in one treatment for 3 weeks: HBB 30 mg daily, paracetamol 1500 mg daily, the combination of both or placebo. Patients were adults reporting recurrent crampy abdominal pain (present for at least 2 months and serious enough to interfere with everyday activities) regardless of the defecation pattern. Patients were not formally diagnosed with IBS according to Rome criteria. The primary endpoint of the study was the mean change in the VAS score of the pain intensity over the treatment phase, calculated as the absolute difference between the mean of the VAS entries in the 21 days of the treatment phase and the baseline value on the last day of the placebo run-in phase. All the active treatments were significantly more effective than placebo (Table 3). The effect of the three active medications was 23% above that of placebo. The treatment effect was evident immediately from Day 1, and the mean improvement from baseline on active treatment was almost 50% after 1 week of treatment and 65% after 3 weeks. Significant effect was also found on pain frequency and global efficacy of the treatment. Lack of an additive effect in the combined treatment is likely to be related to the fact that participants were requested to score the daily most severe pain, and therefore, the average pain intensity could have been improved with combined medication. Of the total 1637 patients who were exposed to at least one dose of the trial medication, 16%, 14%, 17%, and 11% of the patients in the hyoscine, paracetamol, HBB plus paracetamol, and placebo groups, respectively, reported at least one AE. These were of mild to moderate intensity, and most of them were not considered to be treatment related. Most of the patients rated the drug tolerability as good. Notably, none of the patients reported occurrence of systemic anticholinergic AEs such as dry mouth.[49]

In a randomized, double-blind, placebo-controlled, two-arm parallel study, after a 4-week run-in period, 175 patients were assigned to use HBB to treat two distinct episodes of abdominal pain associated with cramping (APC).[56] Patients were adults with recurrent episodes of APC which had been present for at least 3 months, with at least two episodes during the 4-week run-in period and at least moderate intensity (i.e., 5 or above on the 0- to 10-point numerical pain rating scale [NPRS]) and had to last at least 1 h. Patients were not formally diagnosed with IBS according to the Manning or Rome criteria. Following the initial ingestion of the study medication, the patient could take an additional medication as needed at 30-minute intervals during the 2 h following initial ingestion for a total of 1–5 tablets (i.e., 20–100 mg of HBB or placebo). The intensity of APC was rated using an NPRS prior to the first dose of medication and then at 15-min intervals for the first hour, up to 3 h. In addition, the patients rated their change in symptoms by responding to a patient global impression-change (PGI-C) question. Primary endpoint was the change from baseline in intensity of APC.

Within 15 min of taking the first dose of study medication, there was a significant difference in the mean change from baseline (points on the NPRS). After 2 h of taking the first dose of study medication the difference increased to −1.1 points (Table 3). Patients in the HBB group recorded a reduction of at least 2 points on the NPRS (approximately 30% pain relief) earlier than patients in the placebo group. The adjusted mean difference for the change from baseline during the 4-h observation period for a reduction in abdominal pain was −0.7 for episode 1 and −0.6 for episode 2. The difference in responder rates of "very satisfied" based on the VRS was statistically significant for episode 1 but not for episode 2 (Table 3). The percentage of patients with drug-related AEs was 3.4% ($n = 3$) in the HBB group and 4.6% ($n = 4$) in the placebo group. The most frequently reported AEs during the treatment period in the HBB group included abdominal pain, diarrhea, and joint sprain ($n = 2$ with one of these AEs, 2.3%). Assessment of tolerability indicated that the majority of patients in the HBB treatment group were "very satisfied" for both episodes (52.2% and 56.7%, respectively) compared with placebo (31.6% and 41.5%, respectively).[56]

6 | WHAT HAVE BASIC SCIENTISTS LEARNT FROM THIS LITERATURE?

The interest of HBB from a pharmacological point of view is that HBB significantly affects the on-contraction induced by EFS and the contraction induced by bethanechol, while partially affecting the off-contraction and the spontaneous activity.[14,30,31,36] The effect of HBB on the on-contraction induced by EFS was more pronounced compared with that of otilonium bromide.[29] A recent translational consensus, led and authored by two of the co-authors of this review, has indeed reported the putative correlation between the colonic motility studied in vitro in human and animal samples and that studied in vivo in humans.[57] The spontaneous activity recorded on human smooth muscle has characteristics of frequency as these of the recently described colonic pressurizations that are the most frequent colonic motor pattern in healthy humans.[57] The contraction induced by bethanechol and the on-contraction induced by EFS could represent the correlate of in vivo human gut motility after the activation of the cholinergic system. The fact that HBB significantly reduces the cholinergic mediated smooth muscle contraction but not the spontaneous motility could prevent the occurrence of significant alteration of gut motility in vivo in patients. Ongoing studies will confirm the different effects of HBB and otilonium bromide and whether this, applied to other antispasmodics, possibly translates into a different effect in humans in vivo.

Another interesting and under-exploited effect of HBB, associated with its antimuscarinic effect, is its anti-secretory property. Therefore, HBB can be useful for decreasing secretory diarrhea since cholinergic neurons are involved in this process. It would be interesting to confirm whether the effect of HBB observed in predominant diarrhea IBS is confirmed in ad hoc studies.[45] Although the absorption mechanism of HBB is unclear, based on in vitro studies, it has been proposed that HBB has a local effect at the intestinal wall level.[38] These results are supported by in vitro studies comparing the effect of the drug administered at the mucosa side compared with the effect of the drug administered at the serosa side. Antimuscarinic effects are observed in both cases, although, as expected, the concentration required to achieve these effects is higher when HBB is administered at the serosa side.[35]

TABLE 3 Randomized, placebo-controlled efficacy studies of HBB for treatment of functional gastrointestinal pain

Study	Number of patients	Symptoms/condition	Treatment groups	Treatment duration	Overview of results
Sanchez Martinez 1988[53]	45	Acute abdominal pain	HBB (20 mg, single dose, $n = 15$), HBB + PAR ($n = 15$), placebo ($n = 15$)	1 day	• Pain disappeared rapidly in 14/15 HBB + PAR patients; pain diminished variably among HBB patients; and pain decreased in 1/15 placebo patients • No adverse events were reported
De Gregorio et al. 1969[46]	818	Abdominal pain	HBB (20 mg TID [$n = 79$] or 10 mg BID rectally [$n = 43$]), proxazole ($n = 275$), HBB + dypirone ($n = 150$), placebo ($n = 271$)	4 days	• Significant difference in the antalgic effect of proxazole, HBB, HBB + dypirone vs placebo ($p < 0.001$) (both oral and rectal administration)
Miyoshi et al. 1976[48]	105	IBS	HBB (20 mg TID, $n = 51$), placebo ($n = 50$)	7 days	• Symptom improvement in 60.8% HBB patients vs 40.8% placebo group ($p < 0.05$); and in patients with moderately severe pain who received HBB vs placebo ($p < 0.025$) • Adverse events were generally mild, and almost no difference was recorded in frequency or type between the groups
Sieg et al. 1974[55]	55	Pain from ulcus ventriculi	HBB (40 mg 5x/day, $n = 28$), placebo ($n = 27$)	10 days	• Statistically significant reduction in the use of additional pain medication (analgesics, antacids, spasmolytics; in mono- or combination therapy) in the HBB group compared with the placebo group—15 HBB patients did not need additional medication vs 6 in the placebo group ($p < 0.025$) • No anticholinergic adverse effects were reported
Mueller-Lissner et al. 2006[49]	1637	Abdominal pain and cramps	HBB (10 mg TID, $n = 415$), HBB + paracetamol ($n = 403$), PAR ($n = 405$), placebo ($n = 414$)	3 weeks	• Pain intensity on the VAS was reduced in all groups: adjusted mean change from baseline was 2.3 cm for HBB, 2.4 cm for PAR and 2.4 cm for HBB + PAR vs 1.9 cm for placebo ($p < 0.0001$) • Statistically significant decrease in verbal rating score across all groups compared with placebo ($p < 0.0001$) (HBB: 0.7; PAR: 0.7; HBB + PAR: 0.7; paracetamol: 0.5) • At least one adverse event was reported in 16%, 14%, 17%, and 11% of patients on HBB, PAR, HBB + PAR and placebo, respectively

(Continues)

TABLE 3 (Continued)

Study	Number of patients	Symptoms/condition	Treatment groups	Treatment duration	Overview of results
Lacy et al. 2013[56]	175	Cramping abdominal pain	HBB (20–100 mg/day, $n = 88$), placebo ($n = 87$)	4 weeks	• Significant difference in the mean change from baseline (points on the NPRS) within 15 min (episode 1: −0.4 points, 95% CI −0.7, −0.1, $p = 0.0137$; episode 2: −0.3 points, 95% CI −0.7, 0.0, $p = 0.0583$). Difference increased to −1.1 points 2 h after the first dose of HBB (episode 1: 95% CI −2.2, −0.0, $p = 0.0448$; episode 2: −0.4 points, 95% CI −1.6, 0.8, $p = 0.4781$). HBB patients had a clinically relevant reduction of ≥2 points on the NPRS (~30% pain relief) earlier than patients receiving placebo (HBB, 45 min; placebo, 60 min) • Reduction in abdominal pain was −0.7 (95% CI −1.3, −0.1, $p = 0.016$) for episode 1 and −0.6 (95% CI −1.2, 0.0, $p = 0.051$) for episode 2. The difference in responder rates of "very satisfied" based on the VRS (HBB 30.4%, placebo 15.8%) was statistically significant for episode 1 (OR 2.47; 95% CI 1.09, 5.60; $p = 0.030$) but not for episode 2 (HBB 43.3%, placebo 32.3%; odds ratio 1.65; 95% CI 0.81, 3.38; $p = 0.167$) • Adverse events were infrequent in both HBB- and placebo-treated patients
Schafer and Ewe 1990[54]	712	IBS	HBB (10 mg TID, $n = 182$), HBB + PAR ($n = 177$), PAR ($n = 175$), placebo ($n = 178$)	4 weeks	• Significantly more responders at 4 weeks in the HBB + PAR and HBB groups vs placebo: 81% for HBB + PAR, 72% for PAR and 76% for HBB vs 64% for placebo. Significant improvement in abdominal pain intensity in the HBB + PAR group compared with placebo or paracetamol • 5% of patients experienced adverse events
Nigam et al. 1984[50]	168	Abdominal pain	HBB (10 mg QID, $n = 21$) HBB + amitriptyline + chlordiazepoxide ($n = 21$), psyllium ($n = 21$), four other combinations ($n = 84$), placebo ($n = 21$)	3 months	• Symptom improvement in 66 patients (39%) was maintained for 3 months. Significant improvements occurred with all combinations containing at least one therapeutic agent. Amitriptyline and chlordiazepoxide combination therapy exhibited significant improvements when alone or in combination with other agents, 33.3% and 53.9%, respectively • Adverse events were mild and did not result in any discontinuations
Ritchie and Truelove 1979[52]	96	IBS	HBB (10 mg QID, $n = 12$), HBB + lorazepam ($n = 12$), psyllium ($n = 12$), four other triple combinations ($n = 48$), placebo ($n = 12$)	3 months	• Improvement in 36 (38%) patients, with the highest proportion of patients reporting improvement in the full combination group receiving HBB + lorazepam + psyllium (7/12, $p < 0.005$). Psyllium alone ($p < 0.05$), but not HBB or lorazepam alone had a significant improvement in IBS

Abbreviations: BID, twice daily; CI, confidence interval; HBB, hyoscine butylbromide; IBS, irritable bowel syndrome; NPRS, numerical pain rating scale; OR, odds ratio; PAR, paracetamol; QID, four times a day; TID, three times a day; VAS, visual analog scale; VRS, verbal rating scale.

TABLE 4 Summary of HBB effects

HBB is obtained by the addition of an N-group butylbromide to hyoscine or scopolamine to form a molecule that is poorly absorbed in the gut and does not pass the blood–brain barrier, resulting in a favorable safety profile
HBB blocks muscarinic M2 and M3 receptors, which are located on smooth muscle and epithelial cells where they induce smooth muscle contraction and secretion, respectively. In humans, these receptors are expressed more in the upper than in the lower GI tract, but HBB has a stronger effect on those located in the lower than in the upper GI tract
HBB also acts on nicotinic receptors that participate in synaptic transmission. However, this activity seems to be observed only when HBB is applied at high doses, and it is unclear whether this has any relevance in vivo
In in vitro animal studies, higher doses of HBB are necessary to obtain pharmacological responses when the drug is administered from the mucosal as opposed to the serosal side of the gut wall, but the effect is more persistent with the former than with the latter administration. This is probably related to the characteristics of a molecule that does not easily cross the GI epithelial cells
In in vitro studies on human colonic smooth muscle, HBB significantly reduces the on-contraction induced by EFS and the contraction induced by muscarinic agonists such as bethanechol. HBB partially reduces the off-contraction induced by EFS and the spontaneous contractions
In vivo, in healthy humans, oral HBB has no significant effect on gastric emptying time and small bowel motility either in fasting or postprandial conditions, while it reduces the visceral sensitivity to rectal distension in patients with IBS-D
In all the clinical trials, HBB is more effective than placebo in treating abdominal pain, even when administered as an as-needed treatment, without systemic anticholinergic side effects

Abbreviations: EFS, electrical field stimulation; GI, gastrointestinal; HBB, hyoscine butylbromide; IBS-D, irritable bowel syndrome with diarrhea.

Finally, another interesting pharmacological property of HBB is its effect as a nicotinic antagonist.[19] Nicotinic receptors are located in neurons of the ENS; hence, their blockage reduces the intrinsic reflexes associated with motility and secretion.[17,18] Therefore, the interest of the drug lies in low absorption; the combination of local action and muscarinic and nicotinic antagonistic effect probably reduces excessive muscle contraction and secretion (Table 4).

7 | WHAT INFORMATION SHOULD CLINICIANS CONSIDER IN THEIR CLINICAL PRACTICE?

HBB is not easily absorbed, which reduces its systemic side effects.[37] This results in HBB having a more favorable safety profile than other anticholinergic drugs, and effects such as tachycardia associated with blocking muscarinic receptors are rare.[3] In addition, HBB does not cross the blood–brain barrier, preventing it from having central effects.[11] These properties make HBB useful as first-line treatment for abdominal pain in functional disorders where antispasmodics are normally used.[7] Indeed, it has been shown that antispasmodics (otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine) provide symptomatic short-term relief in IBS.[1]

Clinicians should remember that oral HBB is expected to act on the lower GI tract, and particularly interesting is the observation of the action of this medication in reducing the sensitivity to rectal distension in patients with IBS-D.[45] This was not observed with the other antispasmodic tested in the study, drotaverine.[45] In the literature, IBS-D cases have been frequently reported to present with reduced rectal compliance to distension.[58] It would be useful to assess whether this effect on sensitivity is mediated by an activity of the drug on rectal compliance applying the rectal barostat. This information, combined with the in vitro observation of an effect of the medication on human gut secretion,[30] suggests it could be useful to consider restudying the possible application of HBB in the treatment of IBS-D.

The results of the clinical trials demonstrate the efficacy and safety of HBB in the short-term treatment of abdominal pain. Particularly interesting is that HBB is also effective when used as an as-needed treatment. Based on this, HBB could be taken on demand, but also as indicated in the summary of product characteristics. Nevertheless, it is important that clinicians follow local guidelines regarding the use of HBB. A recent study suggests that paracetamol has an antispasmodic effect on respiratory smooth muscle but with a different mechanism compared with HBB.[59] Ongoing studies will confirm whether this antispasmodic effect of paracetamol is also present in the human colon.

AUTHOR CONTRIBUTIONS

MC was involved in the clinical conception, MJ in the scientific conception and SF in the design of the review. MC and MJ contributed to writing sections of the review and shaping the manuscript. All authors were involved in critical manuscript review and approved the final version of the review for publication.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Not applicable.

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