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Belladonna Alkaloids and Phenobarbital Use in the Treatment of Irritable Bowel Syndrome: A Review

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Abstract

The etiology of irritable bowel syndrome (IBS) is still not well-understood even with recent advances in treatments for IBS with constipation (IBS-C) and IBS with diarrhea (IBS-D). Irritable bowel syndrome is a multifaceted condition characterized by abdominal pain and altered bowel habits. Consequently, no single treatment sufficiently manages IBS in a majority of patients. One option for treatment of IBS is to use a combination of different drugs or an all-in-one combination drug to help treat multiple aspects of the syndrome. Combination drugs which affect the brain-gut connection as well as an anticholinergic mechanism are standard-of-care for the treatment of IBS. They represent viable alternatives to newly approved agents. Even though drugs such as a combination of belladonna alkaloids/phenobarbital or Donnatal®, are used safely and effectively to manage IBS, their history of clinical investigation and results are not well-recognized by the field of gastroenterology given the lack of recent studies. This review is meant to update the field on the breadth of studies conducted on this combination drug for IBS.

Keywords: Atropine; Hyoscyamine; Scopolamine; Donnatal; IBS

Introduction

Irritable bowel syndrome (IBS) is a highly prevalent functional bowel condition affecting approximately 11% of the population worldwide, with a little over twice as many women experiencing IBS compared to men [1,2]. The exact etiology of IBS is largely still unknown, but a combination of genetic, environmental (i.e., infection, food intolerances and sensitivities, dysbiosis), inflammatory, and psychosocial interactions make some patients more susceptible to IBS [3].

The definition of IBS is a change in bowel habits associated with abdominal pain. To be diagnosed with IBS according to Rome IV criteria [4], patients must have recurrent abdominal pain for a minimum of 1 day per week for at least three months associated with defecation, change in daily stool frequency and/or a change in stool form (loose *vs.* hardened stool). It is crucial that two of three of these criteria be met. There are three basic types of IBS based on Bristol Stool Form Scale (BSFS): IBS with constipation (IBS-C) with patients having a BSFS of 1-2, 25% of the time; IBS with diarrhea (IBS-D) for patients with BSFS of 6-7, 25% of the time; and a mixture of constipation and diarrhea (IBS-A or -M) with BSFS of 1-2 and 6-7, each 25% of the time. Each subtype of this condition occurs in approximately 30% of the IBS population [4]. About 10% of the condition's overall population, however, cannot be characterized according to a change in bowel habits and are termed IBS unclassified or IBS-U. It was once thought defecation led to a lessening of abdominal pain, but the new Rome IV criteria states that there can be a worsening of abdominal pain as well [4]. Finally, the form of IBS is not static and can change over time,

although the association of abdominal pain linked to defecation remains constant.

There are two approved drugs for IBS-C, linaclotide and lubiprostone. Linaclotide is a peptide agonist of guanylate cyclase C on the luminal surface of intestinal enterocytes which activates a transmembrane conductance regulator leading to secretion of chloride and bicarbonate into the bowel [5]. Lubiprostone is a chloride channel type two activator that causes increased intestinal secretion of chloride into the lumen [6]. Water follows the chloride ions into the bowel relieving constipation in both cases. About one third of patients in clinical studies of linaclotide responded to the FDA-required composite endpoint for approval of ≥ 30% improvement in abdominal pain intensity and ≥ 1 complete spontaneous bowel movement per week from baseline in 6 of 12 study weeks [7,8]. Lubiprostone was approved with two studies prior to the FDA instituting a composite endpoint [9]. Chang et al. performed a post hoc analysis of these two clinical trials and found that between 25-27% of subjects could be considered responders using current FDA composite scoring [10]. This analysis was slightly biased, however, in that the original study measured spontaneous bowel movements compared to the FDA definition of complete spontaneous bowel movements per week. Even with these differences, the composite response rates were approximately one third in all patients treated with linaclotide and lubiprostone. Differences against placebo for lubiprostone and linaclotide when considering a composite endpoint were approximately 10% and 20%, respectively [7,8,10].

There are three FDA-approved treatments for IBS-D: alosetron, rifaximin and eluxadoline. Alosetron is a HT3-receptor antagonist active on intrinsic primary afferent neurons which mediate gastrointestinal (GI) motility and secretion [11]. Alosetron has increased efficacy in women compared to men [12]. Though the mechanism of rifaximin in the treatment of IBS-D is still controversial, it may act to modify the microbiota in the intestinal tract particularly by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase thereby blocking one of the steps in transcription [13]. In addition to its effect on specific bacteria in the intestine, rifaximin may also have an anti-inflammatory effect by reducing specific types of bacteria that increase cytokine expression in the gut and by reducing bacterial mucosal adherence [14]. The mechanism of action for eluxadoline involves the binding of three different opioid receptors acting both as agonists on the mu- and the kappa-receptors, but as an antagonist of the delta receptor [15,16]. The current FDA endpoint for approval of IBS-D drugs is a composite response of a decrease in abdominal pain and improvement in stool consistency, defined as patients reporting ≥ 50% of days with ≥ 30% reduction of mean baseline pain score for worst abdominal pain, and a stool consistency score <5 on the same days from weeks 1-12 [17]. Only eluxadoline has been approved using this guidance [18]. A recent review by Cash et al. attempts to compare response rates for eluxadoline, rifaximin, and alosetron using the available clinical data on each product with the composite FDA endpoint [19]. Based on their analysis, rifaximin has a 48% response rate (placebo 38%), but upon retreatment this drops to 25% (placebo 16%). Eluxadoline has a 27% response rate (placebo 17%) and alosetron has approximately a 61% response rate (placebo ~42%) averaged over three studies [19]. Though there appears to be a greater response rate for alosetron compared to rifaximin and eluxadoline, it is not approved for use or widely utilized in men.

Other therapies for both IBS-C and IBS-D, though not FDA-approved for these conditions are reviewed in the ACG monograph [20]. Antidepressant medications including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been found to be effective for global symptom and pain relief in IBS patients, although adverse effects have occurred that may limit their utility. Peppermint oil formulations also seem to improve pain in IBS [20,21]. In general, fiber is a bulking agent used to firm up stool for patients with IBS-D and to relieve constipation in IBS-C, providing overall relief in IBS [20]. Dietary manipulation has also been utilized in IBS (i.e., food exclusion diet, carbohydrate restricted diet, FODMAP diet, etc.) and has shown to relieve symptoms [20]. There are also other specific diet-related interventions with purified food components that have shown some promise in the management of IBS. Some probiotic formulations have also been shown to be useful in IBS-C for improving overall global symptoms, bloating, and flatulence [20,22,23]. Finally, an oral immunoglobulin, medical food formulation, has been shown to statistically improve IBS-D symptoms [24-26].

Certain drugs not specifically indicated for IBS-C or IBS-D are also widely utilized to treat these conditions. For example, the opioid agonist loperamide has been shown to improve stool frequency and consistency but not abdominal pain in IBS-D [27]. Polyethylene glycol (PEG) formulations are effective in treating constipation, but the data is mixed in the treatment of IBS-C. Only one study has shown PEG to relieve constipation symptoms but not abdominal pain [28]. Anticholinergic and antispasmodic agents, though not approved for IBS, are often first-line or add-on therapies in an empirical attempt to relieve symptoms. Ford et al.

reviewed individual anticholinergic/antispasmodic compounds and their clinical efficacy finding that individual compounds were effective for relieving IBS symptoms, but the variability in clinical studies performed, the size of the trials and the outdated clinical constructions made it hard to determine efficacy by today's standards [20].

Finally, multimodal approaches are often used in treatment of IBS which include a combination of medical and cognitive-behavioral therapy (i.e., identifying cognitive and behavioral stress triggers, developing strategies to deal with those triggers, mindfulness, desensitization strategies, etc.) as well as psychological treatments (mindfulness, hypnotherapy, etc.) [29]. A meta-analysis from 18 studies where IBS patients underwent cognitive-behavioral therapy found that it was superior to patients who did not undergo the same therapy and medical treatment but was inferior to psychological treatments [30].

Similarly, a meta-analysis of 7 different trials of hypnotherapy for IBS patients found that it was a highly effective technique to relieve abdominal pain over a three-month period [31]. These meta-analyses along with other data suggest that the brain-gut connection in IBS can be treated with both medical, cognitive-behavioral and psychological approaches. It is clear that no single therapy or multimodal approach works in all patients.

This review is intended to examine the clinical research in support of combination drugs composed of belladonna alkaloids (BAs) and phenobarbital (PB). The therapeutic uses of these agents will focus on IBS, their pharmacology and the clinical history.

Review

Belladonna Alkaloids

The anticholinergic/antispasmodic substances in the only currently marketed drug containing belladonna alkaloids (BA) (Donnatal®) are derived from the plant *Atropa belladonna*, colloquially known as nightshade. Belladonna belongs to the Solanaceae family of plants, which also includes tomatoes and potatoes; however, instead of being a foodstuff, this plant and its products have been known and used for centuries for cosmetic and medicinal applications, or even as poisons [32]. *Atropa belladonna* is versatile because it contains several pharmacologically active compounds, including atropine, hyoscyamine, and scopolamine, also known as hyoscine. These three compounds belong to the class of tropane alkaloids. Although some tropane alkaloids can possess stimulant properties (i.e., cocaine), the BAs are useful for gastroenterologists because of their anticholinergic and antispasmodic effects.

Therapeutic Uses

The BAs have several historical or theoretical uses, which include treatment of asthma, excessive motor function (i.e., acute dystonia), excessive sweating, motion sickness, nausea and vomiting experienced during pregnancy, organophosphate poisoning, toothache, and whooping cough. The rationale behind using the BAs for these purposes is equivocal. There are several uses for which the BAs have been studied which possess some, albeit not robust, clinical support. These uses include treatment of IBS, airway obstruction, autonomic nervous system disturbances, headache, otitis media, premenstrual syndrome, other menopausal symptoms, and radiodermatitis [32]. The remainder of this review of BAs in combination drugs is focused on the GI use, particularly functional bowel conditions like IBS.

Pharmacology of Belladonna Alkaloids

Of the three relevant BAs, atropine was the first to be isolated, in 1831 [33]. Atropine exists as a racemic mixture of d- and l-hyoscyamine. In clinical practice, the word hyoscyamine typically refers to the l-isomer, as l-hyoscyamine has more anticholinergic activity than d-hyoscyamine [34,35]. Hyoscine, also known as scopolamine, is closely related to l-hyoscyamine, differing only by the inclusion of an extra oxygen atom within the tropane ring (Figure 1).

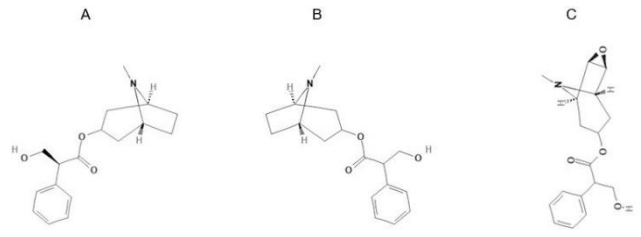

Figure 1: Structure of belladonna alkaloids: (A) Hyoscyamine; (B) Atropine; and (C) Scopolamine.

Belladonna alkaloids are competitive muscarinic acetylcholine receptor antagonists [36]. Acetylcholine functions as a neurotransmitter within the body. It is stored in several motor neurons. Upon stimulation of these neurons, acetylcholine is released to stimulate muscles by binding to acetylcholine receptors [37].

There are two types of acetylcholine receptors, those that are more sensitive to muscarine, which are called muscarinic acetylcholine receptors, and those that are

more sensitive to nicotine, called nicotinic acetylcholine receptors. They are competitive inhibitors of the acetylcholine receptor, which means their effects are dose-dependent, and can be overcome by increasing the concentration of acetylcholine present at the receptor.

Peristalsis describes the normal movement of materials throughout the intestines via rhythmic contractions. Aberrant spasms of the intestines disrupt peristalsis and can lead to abdominal pain and hyperactive peristalsis. Abdominal pain and altered bowel habits are hallmarks of IBS. The antispasmodic properties of the BAs stem from their antagonism of acetylcholine receptors (muscarinic receptors) within the smooth muscle of the GI tract. By binding to these acetylcholine receptors, BAs relax smooth muscles to reduce motility [38]. In summary, the rationale behind including the BAs in an IBS regimen is to reduce aberrant intestinal spasm and smooth muscle associated motility, which in theory reduces symptoms of IBS.

Belladonna alkaloids are absorbed in the upper part of the digestive tract. For example, over 90% of atropine is absorbed in the small intestine with a peak plasma concentration reached within about 1 hour [39]. The half-life of atropine is ~4 hours with hepatic metabolism accounting for the elimination of approximately half of the compound and the rest through urinary excretion. Being the levorotatory optical isomer of atropine, hyoscyamine peak plasma levels are similarly reached at about the same time as that of atropine, primarily metabolized in the liver with about half excreted in urine [39]. Peak plasma levels for scopolamine of oral doses in healthy subjects occurs within about 0.75 to 1 hour [40]. The elimination half-life was found to be 4.5 ± 1.7 hours [41]. Bioavailability tends to be variable from ~11-50% with oral dosing of scopolamine.

Adverse Effects

Over time, a colloquial expression, or minor variations of it, has arisen as a common mnemonic to remember consequences of BA overdose, and that expression is "hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hen" [33]. These adverse effects that can commonly occur with the BAs are perhaps better described as pyrexia, dilation of the pupils, dry mouth and trouble swallowing due to suppression of salivation, vasodilation of the skin causing flushing, and symptoms resembling delirium.

Individuals may also experience sinus tachycardia and leukocytosis. Other known adverse effects include constipation, confusion, and retention of urine. Several of these adverse reactions can occur at therapeutic doses used to treat GI conditions.

Warnings and Contraindications

The anticholinergic effects of the BAs may delay gastric emptying and decrease esophageal pressure. Belladonna alkaloids can aggravate the condition of urinary retention, xerostomia, and neuromuscular disorders, such as myasthenia gravis. Concomitant use with other anticholinergic agents should also be avoided, as combined use may augment anticholinergic activity. The typical side effects of anticholinergic agents in younger age patients can be more severe in elderly patients. Dry mouth in the elderly, for example, can lead to difficulty in speech. Blurred vision in older patients may lead to an increased risk of falls. Symptoms relating to delirium can lead to increased anxiety necessitating administration of anxiolytic agents in the elderly.

Finally, there can also be worsening urinary disorders necessitating catherization [42]. Care should be also taken in patients with cardiac comorbidities, gastric ulcers, esophageal reflux, hiatal hernia, GI obstructions, constipation, ileus, ileostomy, or colostomy. Children administered BAs can be more susceptible to rapid body temperature increases especially in warm weather. Unusual excitement, nervousness, irritability and restlessness may also occur in children. Belladonna alkaloids are excreted in breast milk and are listed as pregnancy category C; accordingly, BAs are not recommended for individuals who are pregnant or lactating.

Dosing

There is no standardized dosing protocol for the BAs, but over time, general practice has included typical doses used in combination with PB. A typical formulation of BAs and PB contains 0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate and 0.0065 mg scopolamine hydrobromide [43]. The usual dosage of this drug, both tablet and elixir, should be adjusted to individual patients for symptomatic control with minimum adverse reactions. In general, this formulation is dosed at one or two tablets three or four times daily depending on the patient's condition and severity of symptoms. In children, dosing of the elixir is based on body weight [44].

Toxicology

Atropine is generally considered safe up to 1.5 mg/day, although adverse effects can be experienced at this dose [32]. At high doses, the anticholinergic properties of BAs can be life-threatening, and severe adverse effects may occur. The LD_{50} in humans is approximately 900 μg/kg [45]. In children, doses as low as 0.2 mg/kg may

be lethal, and multiple reports of accidental overdose have been recorded throughout time after children have ingested berries of the plant, frequently mistaking them for blueberries or other similar fruit [32].

Relative Strength and Potency of the Individual Belladonna Alkaloids

The literature regarding the relative strength of each individual BA is also equivocal. Several studies have been conducted with varying methodologies, test subjects, and outcomes. An early study performed on men enlisted in the armed forces compared the ED_{50} of atropine and scopolamine in multiple studies. It was reported that scopolamine was 7.5-8.8 times more potent than atropine [46]. This observation was supported by another study performed in Swiss mice [47]. A study comparing the spasmolytic potency of atropine sulfate to n-butyl hyoscine bromide in dogs found that atropine was only slightly more potent than hyoscine [48]. In one of perhaps the most directly relevant comparisons, one source reported that at comparable doses, atropine is the strongest of the BAs, and that hyoscyamine possesses 98% of the anticholinergic efficacy of atropine, while scopolamine possesses 92% [49]. This may be due in part to scopolamine exerting more effects on the CNS than atropine and hyoscyamine, whereas atropine exerts more effects on smooth muscle, such as within the GI tract [32,50].

Phenobarbital

For over 100 years, PB has been safely utilized in both inpatient and outpatient settings. Phenobarbital was first synthesized from barbital in 1911 by von Hörlein and marketed as Luminal® by Bayer in 1912 [51]. The World Health Organization has added PB to its 'List of Essential Medicines' and recommends this agent for first-line treatment for convulsive seizures [52].

Therapeutic Uses

The discovery of PB's anticonvulsive activity occurred immediately after marketing began on the drug. Hauptmann in 1912 discovered that PB decreased the number of epileptic seizures and lessened their severity [53]. Phenobarbital allowed thousands of patients who were previously institutionalized to live normal lives. Even into the 21st Century, PB is considered the most effective drug for epilepsy in the world [54]. In addition to its anticonvulsant properties, PB is used for sedation and anxiety [55], alcohol detoxification [56,57] and benzodiazepine detoxification [58]. Since the 1950s, PB has also been combined with BAs for use in patients with spastic colon, IBS, mucous colitis, and acute enterocolitis. The clinical testing history of these combination agents for spastic colon and IBS is summarized below.

Pharmacology of Phenobarbital

Phenobarbital is a derivative of barbituric acid. It acts as a non-selective central nervous system depressant via potentiation of gamma-aminobutyric acid (GABA) on $GABA_A$ receptors by modulating chloride currents through receptor channels essentially mimicking the action of GABA in the brain [59] (Figure 2).

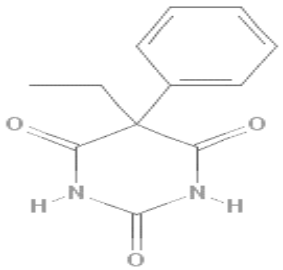

Figure 2: Structure of phenobarbital.

Phenobarbital is highly absorbed (>95%), has a rapid onset of action and a long half-life, approximately 3-5 days in adults and 1.5 days in children [60]. Peak plasma concentration and time to peak concentration tend to occur earlier from elixir versus tablet formulations [61].

Adverse Effects

Phenobarbital can produce sedative, behavioral, and mood effects. Poor tolerability at higher doses has also been observed. In a double-blind Veteran's Administration study comparing PB with other anti-seizure medications [62], approximately half of the patients randomized to PB dropped out of the study mainly due to side effects. A recent meta-analysis of PB studies contradicts this, however, finding no evidence of an association between PB and a higher rate of adverse effects [63]. A recent controlled study of 144 patients with epilepsy in China looked at sedation and cognitive testing in patients receiving PB for a year compared to 144 healthy controls [64]. The study found that in 136 PB administered patients where cognitive test scores and mood ratings were available had virtually identical outcomes to 137 age, sex, and education-matched healthy controls [64]. In this study, doses of PB were lower when compared to the earlier VA study. There was no major negative impact on

cognitive function or sedation on these patients with convulsive seizures. In a Nigerian hospital study, 90% of 344 children with epilepsy were treated with PB. Only 2 of the 344 patients stopped the drug because of intolerable side effects; 50.6% achieved complete seizure control [65]. Goldenberg published an overview of adverse events for drugs used for epilepsy and seizure [66]. In this review, PB was found to cause in alphabetical order the following: agitation/irritability, anxiety, apnea, ataxia, bradycardia, central nervous system reactions/depression, abnormal cognition, confusion, constipation, dizziness, fever chills, hallucinations, headache, hepatic failure/dysfunction/damage, hyperkinesia, hypersensitivity reactions, hypotension, hypoventilation, insomnia, megaloblastic anemia, nausea, nervousness, night terrors/nightmares, psychiatric disorder, syncope, and vomiting [66]. Some of these observed side effects are very rare and tend to be dose-dependent. Side effects with chronic PB use are rare.

Warnings and Contraindications

Phenobarbital can be habit forming [66]. Phenobarbital should not be taken by pregnant women as there is a potential for fetal damage. Withdrawal symptoms and seizure can occur once PB is discontinued. Phenobarbital also has a synergistic effect with alcohol and central nervous system depressants which can result in severe sedation and it is contraindicated in patients with a history of sensitivity [66]. A lower dose of PB is recommended in patients with poor liver or kidney function, as well as in elderly patients.

Dosing

Phenobarbital oral tablets for seizure typically come in several sizes: 15 mg, 30 mg, 60 mg and 100 mg. Suggested pediatric dosage, as recommended by the American Academy of Pediatrics for preoperative applications is 1 to 3 mg/kg [67]. In adults, daytime sedative dosages range from 30-120 mg in 2 to 3 divided doses. If used as a bedtime hypnotic for sleep, the dosage range is 100 to 320 mg. For anticonvulsant use in adults, the dose range is 50-100 mg, 2 to 3 times daily [67].

Toxicology

The primary route of elimination of PB is through hepatic detoxification with 25% via renal excretion. Due to PB being processed in the liver, there are drug interactions which can result. Sodium valproate, for example, inhibits hydroxylation and glucosidation of PB [68,69]. This can result in a prolonged half-life due to reduced clearance of the drug [70]. Phenobarbital can also induce the CYP enzymes which can increase the clearance and reduce the plasma concentrations of many other antiepileptic drugs [71]. Neurotoxicity for PB is fairly common especially at higher doses. This typical involves sedation as well as changes in behavior, cognition, mood and affect [72]. There is some suggestion in animal models of brain deposition of PB [73], but the data are inconclusive. Other toxic effects are possible propylene glycol toxicity from intravenous formulations of PB used for status epilepticus [74]. This type of toxicity not directly related to the action of PB can induce seizures as well as respiratory and cardiovascular depression. Fatality associated with PB overdose is rare.

IBS-Related Clinical Research Experience with Belladonna Alkaloids and Phenobarbital

Belladonna alkaloids and PB in various formulations have been tested clinically and used to treat GI disorders since the 1940s. During this time there have been a variety of studies including clinical trials, comparative studies and case series to investigate the safety and efficacy of these agents in combination (Table 1) [75-85].

Table 1: Summary of various studies investigating belladonna alkaloids and phenobarbital.

Study Type	N	Result	Reference
RCT	204	BAs/PB treatment significantly reduced night pain in patients with IBS and was judged by clinicians to result in higher global improvement.	Turner [75]
RCT	22	Patients significantly preferred BAs/PB over placebo and performed better than other anticholinergic agents (heteronium, propantheline) and another barbiturate (amobarbital) in terms of symptom responses.	Rhodes [76]

Case Series	42	69% of patients reported a good response to treatment and 19% reported fair response. Only 12% reported poor or no response.	Maly [77]
RCT/CO	140	Anisotropine methylbromide, anisotropine methylbromide/PB, and BAs/PB gave a possible excellent response of 75%, 83% and 70%, respectively. There were 98 patients that crossed over to another treatment. The proportion of patients reporting a better response after crossing over compared to the prior therapy was anisotropine methylbromide (31%), anisotropine methylbromide/PB (37%), and BAs/PB (27%).	King [78]
RCT/CO	75	BAs/PB treated patients responded 2.5- to 3-fold better than placebo for symptom improvement. In patients who crossed over (n=12) from placebo to BAs/PB, there was a 5-fold improvement in symptoms. For patients with diarrhea, 100% reported an improvement while 53.2% of those with constipation reported an improvement.	Lichstein [79]
Case Series	33	18 reported good response with complete relief of symptoms and 13 reported fair response with partial relief. In both groups, relief was noted within 24 hours. Only 2 IBS patients reported no response to BAs/PB.	Steigmann [80]
Case Series	82	65 patients reported an improvement in symptoms with 33 reporting at least a 50%-75% improvement and 20 reporting a 75%-100% improvement. While there were improvements in pain, patients who experienced either constipation or diarrhea reported significant improvement in their bowel habits.	Hock [81]
Case Series	64	A complete and sustained response was reported by 43 (67%) patients. Insufficient or limited response was found in 15 (24%) patients and 6 (9%) patients could not be assessed.	Backenstoe [82]
Case Series	20	14 patients reported an excellent or good response and 6 reported no change.	Ezzo [83]
Case Series /CO	25	4 of 12 patients responded to placebo. When the placebo patients crossed over to BAs/ PB, 11 of 12 patients reported a response. 12 of 13 patients responded to BAs/PB in the original treatment group. Overall, 23 of 25 patients reported complete or significant relief of symptoms.	Santor [84]
Case Series	66	Good response with complete relief was found in 53% of male patients and 58% of female patients. Fair response with partial improvement was noted in 37% of male patients and 34% of female patients. No response was reported in a small number of IBS patients with 10% of male and 8% of female BAs/PB.	Steigmann [85]

BAs: Belladonna Alkaloids; CO: Crossover Design; IBS: Irritable Bowel Syndrome; PB: Phenobarbital; RCT: Randomized Placebo-controlled Trial.

Though research still has not definitively proven the cause of IBS, recent scientific and clinical studies point to an organic etiology linking abdominal pain to a brain-gut connection [29,30,86] and to the changing luminal environment within the bowel leading to changes in stool form [87-89].

Randomized Clinical Research

Research in the combination of BAs and PB for the treatment of IBS or spastic colon dates back to the 1940s. In the most recent 4-week study of BAs and PB, a multicenter (6) randomized placebo-controlled trial by Turner et al. compared Donnatal® tablets (hyoscyamine sulfate, 0.1037 mg; atropine sulfate, 0.0194 mg; scopolamine hydrobromide, 0.0065 mg and PB, 16.2 mg) to BAs alone (hyoscyamine sulfate, 0.1037 mg; atropine sulfate, 0.0194 mg; scopolamine hydrobromide, 0.0065 mg), PB alone (PB, 16.2 mg) and placebo [75]. The intent-to-treat population of 204 IBS patients was evaluated for pain (cramping), night-time and daytime pain severity, bowel movement frequency and with a clinician global evaluation of improvement in response to treatment. The response for improvement of pain was mixed for all groups after 1 day. After 1 day, patients exhibited significant improvement in day and night pain as well as clinician global evaluation when taking Donnatal® tablets and BAs, but the PB group was also statistically better for day and night pain and the placebo for day pain [75]. Females taking Donnatal® tablets were 4-times more likely to experience weeks free of daytime pain compared to PB alone and 2-times as likely to experience weeks free of nighttime pain compared to BAs [75]. Only the PB group demonstrated a significant change in "pain type" at the end of the study compared to baseline with an approximate 48% response rate. Patients on Donnatal® tablets, BAs, and placebo all had non-significant ($p > 0.149$) shifts to dull pain, 39.5%, 52.3%, and 40.4%, respectively compared to baseline [75]. Males also showed a greater response for pain free weeks on PB in comparison to Donnatal® tablets. All groups demonstrated an improvement in bowel movement frequency [75].

A small study in 1978 by Rhodes et al. used a randomized controlled double-blind crossover study design investigating 30 mg of PB in combination with 8 mg of BAs, 4 other sedative-anticholinergic product combinations (15 mg amobarbital + 1.5 mg heteronium; 30 mg amobarbital + 1.5 mg heteronium; 15 mg amobarbital + 0.75 mg heteronium; 15 mg PB + 15 mg propantheline), and placebo in IBS patients [76]. As a crossover design, 16 patients were included in this study with each treatment phase lasting 1 month. The key measures were patient drug preference, patient indicated global improvement, numerical summation of 10 symptoms, and a combination symptom index. It was found that BAs and PB combination resulted in a significant improvement in patient-indicated symptoms with 10 of 15 patients reporting some or a lot of improvement [76]. It was also significant that 7 of 15 patients preferred BAs and PB combination to the other treatments. While there were improvements found in the other factor analysis methods, the difference was not significant compared to placebo. The authors noted that the simpler patient subjective analysis methods found significant improvements and preferences while the factor analysis found a strong placebo response which has been a challenge for many IBS studies [76].

One of the earliest randomized double-blind clinical trials of BAs and PB combination was in 1959 by Lichstein et al. [79]. The study involved 75 patients with unstable bowel (whose symptoms are typical or similar to a current diagnosis of IBS) to investigate the combination therapy of an anticholinergic with the addition of PB against placebo over 15 months. Response was assessed using no change, worsening symptoms or improvement and a rank score of 0 to +5 was used for each category. Of these patients, 20 were treated with placebo, 43 were treated with 50 mg PB in combination with 0.25 mg BAs, and 12 received both therapies (patients who lacked a response were switched therapy) [79]. Of patients receiving the BAs and PB combination, 75.6% reported a mean improvement (2+ or better) in all symptoms measured including abdominal pain, constipation, and diarrhea. Among the placebo patients, only 29.8% reported mean improvement in symptoms. When improvement was clinically assessed, 69% of the patients on the BAs and PB combination reported improvement compared to 24% of patients receiving placebo. For patients who exhibited a lack of response to placebo (11.1% reported a mean improvement), 55.5% reported mean improvement after the switch to treatment therapy [79]. The authors noted that among patients with diarrhea, 100% reported an improvement while 53.2% of those with constipation reported an improvement. In several patients with constipation, fiber and laxatives were also provided which may be a confounding factor in this population. In patients where constipation was the chief complaint, the authors noted that they failed to respond [79].

Comparative and Practical Experience Research

Over the years, the combination of BAs and PB has been studied in a "real world", observational setting by physicians treating patients with GI disorders. Steigmann et al. evaluated 93 patients with GI distress using a combination of 0.25 mg BAs and 50 mg PB [80]. All 93 patients were tested for relief of clinical complaints. Among the patients reporting IBS (n=33), 18 reported good response with complete relief of symptoms and 13 reported fair response with partial relief, all reporting relief within 24 hours. Only 2 IBS patients reported no response [80]. Of the 93 patients,

12 patients reported the following side effects: dry mouth, metallic taste, and heartburn. Seven patients discontinued treatment due to adverse effects [80]. A second study by Steigmann and Kaminski looked at 176 patients with GI disorders of which 66 were diagnosed with IBS [85]. The focus of the study examined the antisecretory effect of 0.1296 mg BAs and 16.2 mg PB (Donnatal®) in peptic ulcer patients, motility in a subgroup of patients and clinical effects in all patients. Of the IBS patients, a reported good response with complete relief was found in 53% of male patients and 58% of female patients [85]. Fair response with partial improvement was noted in 37% of male patients and 34% of female patients. No response was reported in 10% of male and 8% of female IBS patients. There were few side effects noted with 8% reporting dry mouth. Dosages were reduced in patients who reported drowsiness (10%) as well as 1 patient who reported visual disturbance. Otherwise, the BAs and PB formulation was well-tolerated [85]. This case series supports the findings reported by Bargen in 20 patients evaluated with abdominal pain including 5 IBS patients who found that BAs and PB provided marked response in relief of symptoms [90].

A small assessment of sustained release of 0.4 mg BAs and ~60 mg PB (1 grain) was studied by Santor in patients with functional GI disorders (i.e., gastric hyperacidity, dyspepsia, pyrosis, gas pains and epigastric distress) [84]. Overall, 23 of 25 patients reported complete or significant relief of symptoms. Additionally, 13 of 25 patients reported some mild side effects (mainly dry mouth), but it was not significant enough to discontinue the medication [84]. Hock also examined the effect of 0.25 mg BAs and 50 mg PB sustained release formulation in 82 clinical practice patients with GI disturbances over 27 months [81]. Seventy-one of these patients were diagnosed as having "functional bowel distress." Of the 82 total patients, 65 reported an improvement in symptoms with 33 patients reporting at least a 50%-75% improvement and 20 reporting a 75%-100% improvement [81]. While there were improvements in pain, patients who experienced either constipation (n=44) or diarrhea (n=16), reported significant improvement in their bowel habits. Side effects were reported by 7 of 85 patients with dry mouth and drowsiness the primary events and 12 patients were removed from the study for psychoneurotic element or poor cooperation [81].

Several small office-based case series also examined the effect of BAs and PB formulations in patients with a variety of GI disorders. Maly et al. published observations on 49 patients with either functional disorders (n=35) or gastric/duodenal ulcers (n=14) that were treated with BAs and PB in a sustained released formulation for at least 4 weeks [77]. Forty-two of these patients described their condition as severe or very severe prior to treatment. After 4 weeks, 34 (69%) patients reported a good response to treatment and 9 (19%) reported fair response. Only 6 (12%) reported poor or no response [77]. In another study, a sustained release formulation of 0.4 mg BAs and ~60 mg PB (1 grain) was administered to 64 patients with a variety of cardiovascular and GI disorders for an average of 11 months [82]. There were 10 patients diagnosed with ulcers and 13 with "other GI dysfunction" whose chart history could be evaluated. In 10 ulcer patients, 6 reported "excellent" response, 3 had a "good" or "fair" response with one not characterized. In the GI dysfunction cohort, 8 out of 13 had an "excellent" response with 5 reporting a "poor" response. Out of the 64 patients observed on treatment, there were 4 reported side effects with dizziness and drowsiness noted for 2 of these [82]. Ezzo evaluated the effect of a sustained release 0.15 mg 1-hyoscamine and 50 mg PB formulation in 58 patients with a variety of GI conditions [83].

There were 23 patients with peptic ulcer, 20 cases of GI disturbances characterized by complaints of belching, cramping, constipation, and anorexia, 10 patients with hiatal hernia, and 5 diagnosed with cholelithiasis, gastritis and diverticulitis [83]. Of the 58 total patients, 43 (74%) reported an excellent or good response and 15 (26%) reported no change. Also, 14 out of 20 patients with functional disorders reported an excellent or good response and 6 reported no change [83]. In another analysis, 60 patients with various GI disorders were compared after being administered either 0.25 mg BAs and 50 mg PB in a sustained (given 1 tablet twice daily) and standard release formulation (given three times daily), alternating days of each treatment with the placebo [91]. The results were similar between the sustained release and standard release formulations of BAs and PB with 58 patients in both groups reporting excellent or good response on the days administered the treatments. On the days that these patients took placebo, only 22 patients reported a good response while none reported an excellent response. In a third phase of the study, 50 patients took the sustained release formulation at night and alternated days with placebo [91]. The sustained release BAs and PB dosing resulted in 36 patient reporting excellent results and 14 with a good response. On the nights that placebo was administered, 10 patients reported a good outcome while 40 reported a poor response. Side effects were minimal with dry mouth or visual disturbance the primary events [91].

Finally, a private practice physician also reported his broad experience in treating 700 patients with irritable colon and basic observations regarding available treatment options from change in diet to fiber usage to antispasmodic therapies [92]. While not a scientific assessment, Miskimon determined, based upon clinical experience that BAs and PB, seem to provide the greatest benefit among these patients without creating significant side effects [92].

Discussion

Anticholinergic/antispasmodic therapies have long been known to provide benefit for GI disorders. Kramer and Ingelfinger summarized the antispasmodic effects of BAs in balloon kymograph studies finding that atropine, hyoscyamine and scopolamine were the most effective in reducing intestinal tone and peristalsis compared to other antispasmodics like amethone, homatropine, pavatrine, and profenil [93]. An early review of anticholinergic drugs suggested their potential benefit as antimotility and antisecretory agents as well as beneficial effects on clinical symptoms and low side effect profile [94]. Belladonna alkaloids have known side effects such as dry mouth, mydriasis and heart palpitation. Hardin et al. evaluated a variety of anticholinergic products on GI distress and side effects [95]. While they concluded there was a general similarity in response, BAs and dicyclomine hydrochloride had fewer side effects than the other anticholinergics.

Phenobarbital's anticonvulsive activity has been known for over 100 years [53] and is still widely used today for epileptic seizures [54] as well as for its sedative and anxiolytic effects [55], alcohol detoxification [56,57], and benzodiazepine detoxification [58]. The doses typically used for epileptic seizures tend to be 100 mg to 300 mg and total accumulated doses of greater than 1 g delivered intravenously until the seizure is under control have been administered [96]. The side effect profile for PB even at high doses is well-known and considered manageable. The primary side effects are related to PB's sedation effect including drowsiness, dizziness, temporary memory loss, poor concentration, loss of coordination, and drowsiness the day after administration [66]. There are minor side effects which include aggression, confusion, excitability, irritability, nausea, headache and constipation. The rationale in combining BAs with PB was due to perceived benefit of combining both anticholinergic and anxiolytic effects in one medication.

Irritable bowel syndrome, known originally as spastic or irritable colon, was first recognized in the 1950s as a functional disorder of unknown etiology [97]. Though the "brain-gut" connection was recently formally recognized as part of the etiology of IBS in the Rome IV criteria [4], the role of emotional state in disease was discussed over 80 years ago [98]. Almy et al. first suggested emotional status could lead to diarrhea due to the hypotonicity present in the sigmoid colon [99]. Bachrach et al. then summarized data on emotional stress and its effect on motility even suggesting the attitude of the patient to the person conducting a clinical study could lead to constipation and/or diarrhea in certain patients diagnosed with functional GI disease [94]. Based on this early research, it seemed perfectly reasonable at the time to combine anticholinergic/antispasmodic agents with an anxiolytic compound like PB.

Donnatal®, as well as a couple of other formulations with varying levels of BAs and PB, were marketed beginning in the 1950s. These included sustained release formulations like Spacetab® (0.25 mg BAs and 50 mg PB) and a non-sustained release formulation Belladenal® with the same active ingredients. In addition to BAs and PB formulations, a combination of chlordiazepoxide and clidinium bromide (Librax®) was tested in IBS [100]. Chlordiazepoxide is a benzodiazepine and clidinium bromide is an anticholinergic agent with a similar mechanism of action to BAs. In a double-blind, crossover clinical trial, a 2.5 mg of clidinium bromide and 5 mg of chlordiazepoxide formulation (up to 4 capsules daily) was compared to a matched placebo over 4 weeks in 42 patients diagnosed with functional indigestion (22), irritable colon (4), pyrosis (2), pylorospasm (2), mixed diagnoses of patients with the preceding as well as symptoms of flatulence, GI neurosis, post-cholecystectomy, hiatal hernia and gastroesophageal reflux (12) [101]. Seventeen of 23 patients administered clidinium bromide and chlordiazepoxide exhibited a good to excellent response. The most common complaints in recruited patients for the study were insomnia, anxiety, heartburn, nausea, emesis, flatulence, abdominal pain, and diarrhea [101]. One patient discontinued taking the formulation. When these patients crossed over to placebo, 7 of 22 patients taking the formulation demonstrated the same response. Initially, 8 of 18 patients on placebo reported good to excellent responses. One patient dropped out prior to crossing over. After crossing over to the combination of clidinium bromide and chlordiazepoxide, 10 of 17 patients originally on placebo reported a good to excellent response. The greatest symptomatic improvement was noted for insomnia, anxiety-tension, abdominal pain and nausea. Side effects associated with

clidinium bromide and chlordiazepoxide administration were dry mouth and drowsiness [101]. The contraindications and common side effects for Librax® are similar to those of Donnatal® [43,102].

Contraindications include a recommendation not to use in patients with glaucoma, in patients with hypertrophy of the prostate and those with benign bladder neck obstruction. Common side effects include dryness of the mouth, blurring of vision, urinary hesitancy, drowsiness, ataxia and confusion, especially in the elderly, as well as rare skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido [102]. There are also changes in electroencephalograms, blood dyscrasias, including agranulocytosis, jaundice and hepatic dysfunction. When comparing the addiction potential for PB and chlordiazepoxide, one study in methadone patients found that they had a similar low addiction and abuse potential and that both were less risky than lorazepam [103]. In 2016, the FDA issued a warning for the use of benzodiazepines with opioids listing multiple therapeutics for many different diseases and conditions [104]. The list included Librax® but not Donnatal®.

In a randomized placebo-controlled trial conducted by Ritchie et al., a combination of 10 mg hyoscine butylbromide four times daily and 1 mg lorazepam (another benzodiazepine) twice daily + ispaghula husk (psyllium fiber) from a sachet twice daily either individually or in combination was dosed over a three-month period in patients with IBS [105]. All treatments had matched placebos. While the individual components showed improvement over placebo, the combinations of therapies (2 and 3 active substances together) showed improvements over just the single agents. It was a triple combination therapy of hyoscine + lorazepam + ispaghula husk that demonstrated the greatest benefit [105]. Lorazepam is not, however, currently marketed in combination with an anticholinergic agent for IBS.

Conclusion

The combination of BAs and PB has been clinically researched over the last 60 years for functional bowel disorders including IBS. While the standards for research have changed over these 60 years, the findings summarized in this review are consistent in that BAs in combination with PB relieve the symptoms of IBS, particularly abdominal pain. The most recent study of Donnatal® by Turner et al. suggests that there may be a differential effect in women compared to men for the relief of abdominal pain in the management of IBS [75]. Sex differences have been noted with regard to abdominal pain sensitivity in general and in patients with IBS [106-109]. Indeed, a study of Librax® also found sex differences in men versus women which may determine visceral pain responses to this therapy [110]. Since no one therapy manages a majority of symptoms in IBS patients, Donnatal® and other combination drugs, though older, are still viable alternatives for the treatment of this difficult condition with safety which has been proven over decades of use.

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Conflict of Interest

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