
NATURAL STANDARD REVIEW

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An Evidence-Based Systematic Review of Belladonna by the Natural Standard Research Collaboration

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Synonyms/Common Names/Related Substances: Beladona, belladone, belladonnae herbae pulvis standardisatus, belladonna herbum, belladonna leaf, belladonna pulvis normatus, belladonnae folium, belladonna radix, belladonne, deadly nightshade, deadly nightshade leaf, devil's cherries, devil's herb, die

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belladonna, die tollkirsche, divale, dwale, dwayberry, galnebaer, great morel, herba belladonna, hoja de belladonna, naughty man's cherries, poison black cherries, powdered belladonna, Solanaceae (family), solanum mortale, solanum somniferum, stryshon, strygium, tollekirsche, tollkirschenblatter.

Selected Combination Products: Bellergal[®], Bellergal-S[®], Bellergil[®], Bel-Phen-Ergot S[®], B&O Suppettes[®], Cafergot-PB[®], Distovagal[®], Phenerbel-S[®], PMS-Opium & Beladonna[®].

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

Belladonna is an herb that has been used for centuries for a variety of indications, including headache, menstrual symptoms, peptic ulcer disease, inflammation, and motion sickness. Belladonna is known to contain active agents with anticholinergic properties, such as the tropane alkaloids atropine, hyoscyne (scopolamine) and hyoscyamine.


There are few available studies of belladonna monotherapy for any indication. Most research has evaluated belladonna in combination with other agents such as ergot alkaloids or barbiturates, or in homeopathic (diluted) preparations. Preliminary evidence suggests possible efficacy in combination with barbiturates for the management of symptoms associated with irritable bowel syndrome. However, there is currently insufficient scientific evidence regarding the use of belladonna for this or any other indication.

There is extensive literature on the adverse effects and toxicity of belladonna, related principally to its known anticholinergic actions. Common adverse effects include dry mouth, urinary retention, flushing, papillary dilation, constipation, confusion and delirium. Many of these effects may occur at therapeutic doses.



Scientific Evidence for Common/Studied Uses

TABLE 1

Indication	Evidence Grade	
Irritable bowel syndrome	C	
Airway obstruction	C	
Autonomic nervous system disturbances	C	
Headache	C	
Otitis media	C	
Premenstrual syndrome	C	
Radiodermatitis	C	
Menopausal symptoms	D	

See Table 2.

Historical or Theoretical Uses Which Lack Sufficient Evidence

Abnormal menstrual bleeding, acute inflammation, anesthetic, anti-spasmodic, anxiety,^{1,2} arthritis, asthma, chicken pox, colds, colitis, conjunctivitis, diarrhea, diuresis, diverticulitis, earache, encephalitis, fever, flu, gout, hay fever, hemorrhoids, hyperemesis gravidarum, hyperkinesia (excessive motor function), hyperhidrosis (excessive sweating), measles, menstrual irregularities,³ motion sickness, mumps, muscle and joint pain, mydriasis, nausea and vomiting during pregnancy, neuralgia, nocturnal enuresis, organophosphate poisoning, Parkinson’s disease, pancreatitis, peptic ulcer disease,⁴ rash, scarlet fever, sciatica, sedative, sore throat, teething, toothache, ulcerative colitis, urolithiasis, urinary retention,⁵ warts, whooping cough.

Expert Opinion and Historic Precedent

Belladonna was used during ancient times as a poison, and likely a medicinal, although knowledge of its therapeutic action dates to the 19th Century.⁶ A prominent 19th Century London physician, Charles Williams, studied belladonna as part of his investigations into the pathophysiology of

TABLE 2. **Natural Standard** evidence-based validated grading rationale™. Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication. Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each monograph (“Strength of Expert Opinion and Historic/Folkloric Precedent”). Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (Strong Scientific Evidence)	Statistically significant evidence of benefit from > 2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (Good Scientific Evidence)	Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from ≥ 1 properly conducted meta-analysis OR evidence of benefit from > 1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (Unclear or Conflicting Scientific Evidence)	Evidence of benefit from ≥ 1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥ 1 cohort/case-control/non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (Fair Negative Scientific Evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (Strong Negative Scientific Evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from ≥ 1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of Evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

* Objective criteria are derived from [validated instruments for evaluating study quality](#), including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; 17[1]:1-12).

† Listed separately in reviews in the “Historical or Theoretical Uses which Lack Sufficient Evidence” section.

asthma.⁷ In the same era in Paris, belladonna was introduced in the treatment of Parkinson's disease by Ordenstein, a pupil of Charcot.⁸

Belladonna was also prescribed by the founder of homeopathy, the German physician, Samuel Hahnemann. By the principle of homeopathy, that 'like cures like,' belladonna in homeopathic dilutions is said to be a remedy for inflammation characterized by the triad of redness, swelling, and pain. It is believed to act during the night, and to have an affinity for the head, throat, and ears.⁹

While studies in the late 1970s examined the effects of belladonna on irritable bowel syndrome, more recent placebo controlled trials have examined homeopathic prophylaxis of migraine,¹⁰ homeopathic treatment of radiodermatitis,¹¹ and the treatment of airway obstruction in infants.¹²

Brief Safety Summary

Possibly Safe: When taken by healthy individuals in recommended doses for a short duration, or when taken in homeopathic dilutions. Notably, there are numerous available preparations of belladonna alkaloids, the majority of which have not been evaluated for safety in controlled trials.

Possibly Unsafe: When taken by individuals with medical conditions such as congestive heart failure, hypertension, coronary artery disease, cardiac arrhythmias, constipation, partial or complete bowel obstruction, narrow-angle glaucoma, prostatic obstruction, myasthenia gravis, or urinary retention.

Likely Unsafe: When taken in large doses by children or adults. When taken by breast-feeding or pregnant women. When taken concurrently with other agents that possess anticholinergic properties.

DOSING/TOXICOLOGY

General

Recommended doses are based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Non-homeo-

pathic dilutions of belladonna should clearly state the quantity of tropane alkaloids contained.

Standardization

There is no current widely used standardized preparation of belladonna.

Doses of belladonna are generally calculated by milligrams of total alkaloids. *Atropa belladonna* contains up to 20 different tropane alkaloid compounds. Those present in the largest concentration in leaves include hyoscyamine (68.7%), apoatropine (17.9%), 3 α -phenylacetoxytropane (2.8%), cuscohygrine (2.5%), and scopolamine (0.8%). Those present in the largest concentration in roots include hyoscyamine (36.7%), cuscohygrine (31.5%), 6-hydroxyhyoscyamine (8.9%), hygrine (6%), 6-hydroxyapoatropine (3.6%), scopolamine (2.9%), and apoatropine (1.7%).¹³

The commercial preparation Bellergal® contains 40 mg phenobarbital, 0.6 mg ergotamine tartrate, and 0.2 mg levorotatory alkaloids of belladonna.¹⁴⁻¹⁶

The commercial preparation Donnatal® contains 0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate, 0.0065 mg hyoscine hydrobromide, and 16.2 mg phenobarbital.¹⁷

Adult Dosing (18 Years and Older)

Oral

Traditional Dosing: Traditional doses of have included belladonna leaf powder 50-100 milligrams per dose with a maximum single dose of 200 mg (0.6 mg of total alkaloids, calculated as hyoscyamine) and a maximum daily dose of 600 mg (equivalent to 1.8 mg of total alkaloids calculated as hyoscyamine); or belladonna root 50 mg per dose with a maximum single dose of 100 mg (0.5 mg of total alkaloids, calculated as hyoscyamine) and a maximum with a maximum daily dose of 300 mg (equivalent to 1.5 milligrams of total alkaloids calculated as hyoscyamine); or belladonna extract 10 mg per dose with a maximum single dose of 100 mg (0.5 mg of total alkaloids, calculated as hyoscyamine), and a maximum daily dose of 150 milligrams (equivalent to 2.2 milligrams of total alkaloids calculated as hyoscyamine). These doses have been noted by the expert German panel, the Commission E, principally for the treatment of “gastrointestinal spasm.” Other

anecdotal reports have suggested a tincture of belladonna (27-33 mg of belladonna leaf alkaloids per 100 mL), at 1.5mg per day, divided into 3 doses per day with a double dose at bedtime or 0.6-1 mL (0.18 to 0.3 mg of belladonna leaf alkaloids) 3-4 times daily.

Irritable Bowel Syndrome: Placebo controlled trials during the 1960s and 1970s examined several doses and preparations of belladonna for irritable bowel, including *Hyoscine butylbromide* 10 mg taken four times daily or a combination preparation containing 0.25 mg levorotatory alkaloids of belladonna plus 50 mg phenobarbital.^{18,19} Donnatal® tablets (0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate, 0.0065 mg hyoscine hydrobromide, 16.2 mg phenobarbital) have also been used.¹⁷ A higher daily dose was used in one study, including 8 mg belladonna and 30 mg phenobarbital, although due to the known toxicity of belladonna, that dose may not be advisable.²⁰ Traditional doses are listed above.

Autonomic Nervous System Disturbances: Limited data are available in this area. One small clinical trial administered a combination formula including 15 mg belladonna, 60 mg ergot alkaloids, 15 mg propranolol, and 25 mg amobarbital, three times day for two weeks, and noted improvements in 72% of subjects with autonomic dysfunction (diseases poorly described).²¹

Headache: Studies in the 1960s and 1970s reported unimpressive effects on headache with the combination product Bellergal® (40 mg phenobarbital, 0.6 mg ergotamine tartrate, 0.2 mg levorotatory alkaloids of belladonna, taken twice daily).¹⁴⁻¹⁶

Premenstrual Syndrome: Bellergal® (40 mg phenobarbital, 0.6 mg ergotamine tartrate, 0.2 mg levorotatory alkaloids of belladonna) taken twice daily for 10 days prior to menses was evaluated in one poorly reported 1970s trial.²²

Menopausal Symptoms: A placebo controlled trial found no effects on menopausal symptoms with 4 weeks of Bellergal® Retard (total daily dose: 80 mg phenobarbital, 1.2 mg ergotamine tartrate, 0.4 mg levorotatory alkaloids of belladonna).²³

Homeopathic Dosing

Note: Homeopathic dosing is often dependent on the indication, presentation and philosophy of the practitioner, and dosing standards may range widely. In general, homeopathic preparations are initially diluted 1:10 or 1:100. Serial dilutions are continued until desired concentrations are achieved. When a 1:10 dilution is diluted 30 times, it is

said to be a 30X or 30D potency. When a 1:100 dilution is diluted 30 times, it is referred to as a 30C potency. 'Proving studies' have been conducted to investigate the effects of homeopathic belladonna in healthy volunteers, and have used preparations of Belladonna 30CH (Deutsche Homöopathie Union, Karlsruhe; Germany)⁹ and Belladonna C30 (Ainsworth's Homeopathic Pharmacy; UK) 1 tablet twice daily.²⁴

Radiodermatitis: Belladonna 7CH (Laboratoires Boiron; France), 3 granules sublingually twice daily has been used in a controlled trial in patients with breast cancer.¹¹

Topical

Musculoskeletal: The topical use of a belladonna plaster produced by Cuxson Gerrard (England) containing 0.25% belladonna alkaloids (hysoscine 2%, atropine 1%) has been described in a case report, and may be associated with contact dermatitis after prolonged use.²⁵

Pediatric Dosing (Younger Than 18 Years)

Oral

Traditional Dosing: Anecdotal use suggests a typical pediatric dose to be 0.03 mL/kg three times daily or 0.8 mL/square meter three times daily (27-33 mg of belladonna leaf alkaloids per 100 mL). Maximum dose has been reported as 3.5 mL per day. Safety and efficacy have not been clearly demonstrated.

Airway Obstruction: A poorly reported controlled trial administered a tincture of belladonna, in a dose equivalent to 0.01 mg/kg weight of atropine, at bedtime to infants.¹²

Note: Death in children may occur at 0.2 mg/kg of atropine.²⁶ Thus, 2 fruits may be lethal for a small child (2 mg atropine are often found in a fruit).²⁷

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Otitis Media: An observational study comparing homeopathic with conventional treatment for children with otitis media utilized Belladonna 30X globules (brand and dose not specified).²⁸ Favorable results were reported, although the study was poorly designed and described.

Toxicology

At a dose of up to 1.5 mg/day, belladonna is traditionally considered to be safe, although many people will experience anticholinergic side effects. The most common manifestations of belladonna overdose include anticholinergic symptoms such as dilated pupils, flushing, dry mouth, tachycardia, confusion, agitation, and hallucinations.^{6,29} The anticholinergic effects of belladonna can be dangerous at high doses, and may result in severe side effects or death. Death in children may occur at 0.2 mg/kg atropine.²⁶ Thus, 2 fruits may be lethal for a small child (2 mg atropine are often found in a fruit).²⁷

Cases of belladonna poisoning with plant ingestions have long been reported in the literature, including an early (1921) report of belladonna poisoning from eating rabbit that had been feeding on belladonna.³⁰ Case reports include anticholinergic poisoning symptoms in children and adults after ingestion of deadly nightshade berries.^{27,31,32} Several case reports exist of belladonna poisoning after ingestion of tomatoes grown from a plant grafted to jimson weed (*Datura stramonium*).³³ A case report describes a 68-year-old Italian man who presented with agitation, hallucinations, slurred speech, tachycardia, dilated pupils, hypertonia, and myoclonic jerks after ingestion of berries from deadly nightshade (*Atropa belladonna*).³⁴ A study of plant intoxications in Switzerland over 29 years revealed 152 severe cases, of which 62 were caused by *Atropa belladonna*, *Datura stramonium*, and *Hyoscyamus niger*.²⁹

A case report from Chicago describes a four year-old girl with symptoms consistent with anticholinergic poisoning after ingestion of woody nightshade (*Solanum dulcamara*), a relative of belladonna that contains solanine, not generally thought to have anticholinergic effects. She was administered 0.2 mg (0.02 mg/kg) of physostigmine three times in an hour with complete resolution of symptoms. Despite the unusual plant exposure, this report serves as evidence of the efficacy of physostigmine as an antidote for anticholinergic poisoning.³⁵ How-

ever, a recent case report of two adults with belladonna poisoning reports supportive therapy, not physostigmine, to be efficacious.²⁷

Belladonna toxicity has been reported with various routes of administration, including topical plaster.³⁶ There are several case series of ingestion of approximately 0.5-1.5 teaspoons of Asthmadore powder (belladonna and stramonium alkaloids, 0.23-0.31%; R. Schiffman Co., Los Angeles) for the purpose of experiencing hallucinatory effects resulting in hallucinations, agitation, tachycardia, tachypnea, dilated pupils, blurred vision, and unsteady gait. After 7-24 hours of observation, the subjects in these case series fully recovered.³⁷⁻³⁹

Belladonna overdose should be considered serious and should be treated by qualified medical professionals. Due to the anticholinergic inhibitory effects on gastric emptying, delayed ingestion with resultant prolonged toxicity may occur.²⁶

PRECAUTIONS/CONTRAINDICATIONS

Allergy

Known allergy/hypersensitivity to belladonna and anticholinergic drugs.

Known allergy to other members of the Solanaceae (nightshade) family such as bell peppers, potatoes and eggplants.

Allergic contact dermatitis may develop with prolonged use of topical belladonna preparations, even at low concentrations.²⁵

Adverse Effects

General: Adverse reactions are common with belladonna alkaloid use. Doses of 0.5 mg or greater may cause anticholinergic side effects of varying severity. Anticholinergic effects may include dry mouth, urinary retention, flushing, pupillary dilation, constipation, and confusion. There is some evidence that in homeopathic (dilute) concentrations, oral belladonna may not elicit clinically relevant anticholinergic signs or symptoms.⁴⁰

Dermatologic: Case reports of toxicity have described redness of the skin, flushing, and dry skin. Allergic contact dermatitis has been reported with use of topical belladonna plaster, even at dilute concentrations.²⁵ Two incidences of rash and hives were noted with belladonna-phenobarbital-ergotamine treatment.¹⁶ Anecdotal reports have

mentioned such other adverse effects as fixed drug eruptions, Stevens Johnson Syndrome and photosensitivity.

Neurologic/CNS: Case reports have described headache, excitement, agitation, dizziness, lightheadedness, drowsiness, unsteadiness, confusion, hallucinations, slurred speech, sedation, hyperreflexia, convulsions, vertigo and coma.^{29,30,33,34,37-39,41}

Ocular/Otic: Ocular effects may include mydriasis, photophobia, blurred vision, and dilation of pupils.^{30,35,37-39,41,42} Belladonna splinters placed in the eye have been associated with fixed mydriasis.⁴³

Psychiatric: Hallucinations and acute psychosis have been documented in cases of toxicity.^{26,27,29,34,37-39}

Respiratory: Rapid respiration has been reported in cases of toxicity,³⁷ as well as coma with respiratory arrest requiring mechanical ventilation.²⁶

Cardiovascular: Tachycardia has been reported in cases of toxicity.^{26,30,37,38,41,44} Belladonna contains atropine, which is commonly used in hospitals to increase heart rate. In one case-report, infants who received hyoscyamine sulfate developed heart rates of 155-220 beats per minute when given 2-4 mL of hyoscyamine.⁴² Severe hypertension has been documented,⁴⁵ as have ventricular premature beats, among patients with belladonna poisoning.⁴⁶

Gastrointestinal: Case reports have noted dry mouth resulting from belladonna use or toxicity.^{30,33,37-39,41,44} Other anecdotal or theoretical effects include abdominal distention, and reduction in salivary flow.³³

Genitourinary: Urinary retention has been documented.^{38,44}

Endocrine: Case reports have documented decreased perspiration.³⁵ Anecdotal references note a possibility of decreased flow of breast milk.

Musculoskeletal: Anecdotal reports have noted muscle tremor, rigidity and crampy leg pains.^{27,33,36}

Precautions/Warnings/Contraindications

Avoid in elderly patients and in children, based on numerous case reports of serious effects of belladonna poisoning in these age groups.

Avoid in patients using other anticholinergic agents.

Use cautiously in patients with cardiac disease, including coronary heart disease, congestive heart failure, hypertension, cardiac arrhythmias, or unstable cardiovascular status, due to case reports of cardiac effects (hypertension, tachycardia, arrhythmias) with belladonna poisoning.

Use cautiously in patients with gastrointestinal tract disease such as ulcers, esophageal reflux, hiatal hernia, obstructive gastrointestinal disease, constipation, ileus or atony, colitis, ileostomy or colostomy. Belladonna's anticholinergic effects may delay gastric emptying and decrease esophageal pressure.

Use cautiously among patients with urinary retention, prostatic hypertrophy or obstruction, or obstructive uropathy. Due to belladonna's anticholinergic effects, these conditions may be aggravated.

Use cautiously among patients with narrow-angle glaucoma due to a theoretical increase in ocular tension.

Use cautiously in patients with Sjogrens syndrome, xerostomia or lachrymal problems due to belladonna's anticholinergic effects.

Use cautiously in patients with neuromuscular disorders such as myasthenia gravis, as belladonna may cause neuromuscular blockade resulting in weakness or paralysis.

Use cautiously among patients with fever.

Use cautiously among patients with Down's syndrome, as they may be particularly sensitive to anticholinergic effects of belladonna.

Pregnancy and Lactation

Not recommended due to the potential for toxicity and adverse outcomes.

Belladonna is listed under category C according to the U.S. Food and Drug Administration. Belladonna alkaloids are excreted in breast milk, thereby exposing infants to potential toxicity.

One small, case-control study of neonatal death and congenital malformations showed no increase in these outcomes in mothers ingesting belladonna alkaloids.⁴⁷ In another study, there was an increase in birth defects in the offspring of mothers who had taken belladonna, although no relationship between first trimester use of atropine and birth defects was found.⁴⁸

There have been anecdotal reports that use of belladonna during pregnancy may increase risk of respiratory abnormalities, hypospadias (penile urethral anomalies in males), and eye/ear malformations.

INTERACTIONS

Belladonna/Drug Interactions

Oral Medications: Belladonna may delay gastrointestinal transit time and thereby affect absorption of some medications.

Drugs that Interact with Anticholinergic Agents: Numerous drugs and drug classes may interact with anticholinergic agents. Examples include: acetophenazine, amantadine, amitriptyline, atropine, benztropine, bethanechol, biperiden, brompheniramine, carbinoxamine, chlorpromazine, clemastine, clindinium, clozapine, cyclopentolate, cyproheptadine, dicyclomine, diphenhydramine, dixyrazine, ethopropazine, fenotherol, fluphenazine, haloperidol, homatropine, hyosciamine, ipratropium, loxapine, mesoridazine, methdilazine, methotrimeprazine, olanzapine, oxybutynin, perazine, periciazine, perphenazine, pimozone, pipotiazine, prochlorperazine, procyclidine, promazine, promethazine, propiomazine, quinidine, scopolamine, thiethylperazine, thioridazine, thiothixene, trifluoperazine, trifluorpromazine, trihexyphenidyl, trimeprazine, triprolidine.

Drugs that Interact with Atropine: Atropine is a constituent of belladonna. Theoretically, drugs that interact with atropine may also interact with belladonna. Examples include: ambenonium, arbutamine, belladonna, cisapride, cromolyn, halothane, methacholine, procainamide.

Tricyclic Antidepressant Drugs: Due to the anticholinergic properties of belladonna, interactions may occur with tricyclic antidepressant drugs.

Cisapride: Atropine, a constituent of belladonna, has been reported to block the effects of cisapride on peristaltic contractions:⁴⁹ When atropine was administered before cisapride, the effects of cisapride on lower esophageal sphincter pressure were antagonized. The effect did not occur when atropine was administered after cisapride.

Antiarrhythmic Drugs: Administering belladonna with procainamide may result in additive anti-vagal effects on atrioventricular nodal conduction.

Alcohol: Concomitant use of alcohol with belladonna may theoretically result in additive CNS depression.

Tacrine (Cognex®): In mice, cognitive deficits associated with belladonna alkaloid administration are attenuated by tacrine.⁵⁰

Belladonna/Herb/Supplement Interactions

Oral Agents: Belladonna may delay gastrointestinal transit time and thereby affect absorption of some agents.

Anticholinergic Herbs and Supplements: Combination use of belladonna with anticholinergic agents may potentiate its therapeutic and adverse effects. Examples of anticholinergic herbs include bitterweet (*Solanum dulcamara*), henbane (*Hyoscyamus niger*), and Jimson weed (*Datura stramonium*).

Belladonna/Food Interactions

Insufficient available evidence.

Belladonna/Lab Interactions

Insufficient available evidence.

MECHANISM OF ACTION***Pharmacology***

Belladonna alkaloids are competitive inhibitors of the muscarinic actions of acetylcholine, acting at receptors located in exocrine glands, smooth and cardiac muscle, and intramural neurons.

The belladonna constituent scopolamine exerts greater effects on the CNS, eye, and secretory glands than the constituents atropine and hyoscyamine. Atropine exerts more activity on the heart, intestine, and bronchial muscle, and exhibits a more prolonged duration of action compared to scopolamine. Hyoscyamine exerts similar actions to atropine but has more potent central and peripheral nervous system effects.

A single-blind placebo controlled study was conducted to investigate the cardiorespiratory effects of belladonna, as a surrogate measure of vagal activity.⁵¹ Single doses of an oral belladonna tincture containing 0.1 mg/mL alkaloid concentration were administered, with a proportion of atropine to scopolamine of 20:1. In eight healthy young subjects, heart rate and noninvasive arterial finger blood pressure were recorded for 4 hours following oral application of 1 mL, 2 mL, or 5 mL of this belladonna tincture, or placebo. The authors reported that 1 hour after administration of 5 mL, mean respiratory rate, heart rate, and baroreflex sensitivity decreased significantly in six of eight subjects. In contrast, following administration of 1-2 mL, mean respiratory rate and heart rate increased compared to placebo.

Pharmacodynamics/Kinetics

The belladonna constituent atropine has a reported half-life of several hours and is rarely detectable in the plasma after 24 hours. Elimination half-life of atropine from raw or cooked belladonna berries was

reported to be approximately 120-140 minutes in a case report of toxic ingestion.²⁶

Atropine is primarily renally excreted. Renal clearance of atropine following ingestion of raw or cooked belladonna berries is variable, depending on the form ingested, but may be as high as 3.6 mg/24 hours.²⁶

HISTORY

The name belladonna means “beautiful woman” in Italian, and is derived from the use of this herb by 16th century Venetian women to self-induce dilated pupils and flushed cheeks in order to make them appear more attractive.

Possible references to the intoxicating properties of belladonna alkaloids appear throughout historical literature, including Homer’s *Iliad* and *Odyssey*. The poison used by Friar Lawrence to put Juliet to sleep in Shakespeare’s *Romeo and Juliet* may have been belladonna.

Belladonna has been used for centuries in the religious rites of Native North and South Americans, including the Algonquians and Incas. It was reported to be the agent in a poisoning of soldiers in Jamestown, Virginia in 1676, where *Datura stramonium* (a relative of *Atropa belladonna*) was known as “Jamestown weed.⁶”

EVIDENCE TABLE

Condition	Study Design	Author, Year	N	Statistically Significant?	Quality of Study 0-2 = poor 3-4 = good 5 = excellent	Magnitude of Benefit	ARR	NNT	Comments
Irritable bowel syndrome	Randomized controlled trial	Lichstein, 1959	75	Unclear	3	46%	2	NA	Combination formula Belladonal spacetabs studied (0.25mg belladonna alkaloids & 50mg phenobarbital).
Gastro-intestinal spasm	Randomized controlled trial	King, 1966	140	No	3	NA	NA	NA	Combination formula Donnatal studied (hyoscyamine, atropine, hyoscine plus phenobarbital) vs. Valpin (anisotropine +/- phenobarbital). Crossover design.
Irritable Bowel	Randomized controlled trial	Rhodes, 1978	16	Mixed	3	Small	NA	NA	No improvement in symptom index compared to placebo. 27% dropout.

EVIDENCE TABLE (continued)

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Irritable Bowel	Randomized controlled trial	Ritchie, 1979	96	No	3	NA	NA	NA	Of three therapies, only ispaghula husk significantly improved symptoms.
Airway obstruction prevention	Randomized controlled trial	Kahn, 1991	20	Yes	4	Medium	30%	3.3	Tincture of belladonna studied (contained ethanol) in infants with breath-holding spells.
Autonomic nervous system dysfunction	Equivalence trial, non-randomized.	Dobrescu, 1970	36	Yes	0	Medium	36%	2.8	Two combination formulas containing barbiturates compared; superior results with formula containing higher concentration of belladonna and propranolol. No placebo control.
Vagal response	Randomized controlled dosing study	Bettermann, 2001	8	Unclear	3	Medium	NA	NA	Belladonna tincture higher dose associated with respiratory and heart rate. Tinctures contain ethanol.
Headache prophylaxis (homeopathic treatment)	Randomized controlled trial	Whitmarsh, 1997	63	No	4	None	NA	NA	Homeopathic migraine prophylaxis administered for 4 months.
Headache	Randomized controlled trial	Stieg, 1977	76	Mixed	3	Variable	NA	NA	Combination formula BEP (belladonna, ergotamine, phenobarbital) associated with benefits in one study arm but not another. 28% dropout.
Headache	Randomized controlled trial	Lance, 1977	110	No	0	None	NA	NA	Combination formula Bellergal compared to other therapies or placebo. Poorly described study.
Otitis media (homeopathic treatment)	Observational study	Friese, 1997	131	Yes	0	Medium	14.2%	7	Various homeopathic remedies studied including belladonna preparation. Benefits reported vs. antibiotics.

Condition	Study Design	Author, Year	N	Statistically Significant?	Quality of Study 0-2 = poor 3-4 = good 5 = excellent	Magnitude of Benefit	ARR	NNT	Comments
Pre-menstrual syndrome	Randomized controlled trial	Robinson, 1977	32	Yes	4	Medium	NA	NA	Combination formula Bellergal studied over 3 menstrual cycles. Reduced symptoms reported. 23% dropout.
Radio-dermatitis (homeopathic treatment)	Randomized controlled trial	Balzarini, 2000	66	Yes	5	Small	NA	NA	Homeopathic belladonna dilution studied for 8 weeks. Significant effects in total severity score only.
Meno-pausal symptoms	Randomized controlled trial	Bergmans, 1987	71	No	4	None	None	NA	Combination formula including belladonna studied. Trend towards improvement at 2-4 weeks, but no effect at 8 weeks.

In the late 1960s, several reports appeared that Asthmador, a compound of belladonna and stramonium alkaloids, was being used in a number of different communities in the United States as a hallucinogen. There are case reports in the medical literature describing overdoses of Asthmador taken for this effect.⁵²

Condition

Refers to the medical condition or disease targeted by a therapy.

Study Design

Common Types Include

Randomized Controlled Trial (RCT): An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.

Equivalence Trial: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.

Before and After Comparison: A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.

Case Series: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.

Case-Control Study: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary & alternative medicine literature.

Cohort Study: A study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary & alternative medicine literature.

Meta-Analysis: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.

Review: An author's description of his or her opinion based on personal, non-systematic review of the evidence.

Systematic Review: A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, Year

Identifies the study being described in a row of the table.

N

The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as N. N includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of drop-outs that are not

included in the analysis are considered to be weaker evidence for efficacy. (For systematic reviews the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.)

Statistically Significant

Results are noted as being statistically significant if a study’s authors report statistical significance, or if quantitative evidence of significance is present (such as p values).

Quality of Study

A numerical score between 0-5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (*Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996;17[1]:1-12*). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the “Evidence Discussion” sections of reviews).

A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate

Jaded Score Calculation	
Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?	0/1
Was the study described as double blind?	0/1
Was the method of double binding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)	0/-1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/-1

poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Magnitude of Benefit

This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant “NA” for “not applicable” is entered. In order to be consistent in defining small, medium, and large benefits across different studies and monographs, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:

- Large: if >1 SD
- Medium: if 0.5 to 0.9 SD
- Small: if 0.2 to 0.4 SD

In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation (Effect size = $[\text{Mean Treatment} - \text{Mean Placebo}]/\text{SD}_p$).

Absolute Risk Reduction

This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, Absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ($[\text{control event rate} - \text{experimental event rate}]/\text{control event rate}$). Many studies do not include adequate data to calculate the ARR, in which cases “NA” is entered into this column.

Number Needed to Treat

This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order

for one person to experience the specified benefit. It is calculated by dividing the Absolute Risk Reduction into 1 (1/ARR).

Comments

When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/sub-groups (age, gender, etc). More detailed description of studies is found in the “Evidence Discussion” section that follows the “Evidence Table” in Natural Standard reviews.

EVIDENCE DISCUSSION

Irritable Bowel Syndrome

Summary: Anticholinergic medications have been used for years in the treatment of irritable bowel syndrome. Patients with this disorder are thought to have abnormal colonic motility, and their symptoms may be replicated with a cholinergic agonist. Although the mechanism of action provides a compelling case for the use of belladonna, there have only been limited controlled trials of belladonna in combination with phenobarbital in heterogeneous samples, and one study showing a trend toward improved symptoms in patients treated with the belladonna constituent hyoscine (scopolamine). Therefore, there is currently insufficient evidence to recommend belladonna as a monotherapy for the treatment of irritable bowel syndrome.

Evidence: An early (1959) contribution to the literature was a 15-month double-blind trial of 75 patients with “irritable colon,” treated with Belladenal[®] spacetabs (0.25 mg levorotatory alkaloids of belladonna plus 50 mg phenobarbital), placebo, or both (18). The percentage of patients that improved was 70% with Belladenal[®] treatment, compared to a 24% placebo response. The study provides limited detail, and methods, outcome measurement techniques, and statistical analysis were not adequately described.

A 1966 double-blind, crossover trial of 140 patients with gastrointestinal spasm compared Donnatal[®] tablets (belladonna [0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate, 0.0065 mg hyoscine hydrobromide]

plus 16.2mg phenobarbital) with Valpin® (anisotropine, with or without phenobarbital).¹⁷ Baseline diagnoses of subjects were heterogeneous, including spastic colon and peptic ulcer disease. The authors reported “excellent” or “good” results in 96% of subjects treated with anisotropine with phenobarbital, 86% of subjects treated with anisotropine alone, and 70% of subjects treated with belladonna plus phenobarbital. However, inconsistent results were noted depending on the order of crossover, suggesting a possible lack of adequate washout period. In addition, greater variability was observed in the results for belladonna than for the other medications. This study was poorly designed and reported, and evaluated outcomes subjectively. It is therefore of limited clinical value.

In a randomized, double-blind trial, Rhodes et al., compared five different sedative-anticholinergic medications with placebo in 22 patients with irritable bowel syndrome.²⁰ Treatments were administered serially, and effects were measured via a patient questionnaire. Each treatment was given four times daily for one month. The dose of belladonna administered was 8 mg, combined with 30 mg phenobarbital. The symptom index questionnaire revealed no significant effect of any of the treatments vs. placebo. However, a significant number of patients (7/15) “preferred” the belladonna/phenobarbital combination to the other treatments. This study was limited by a small sample size, lack of use of a validated outcomes measure, inadequate descriptions of blinding, randomization, or statistical analysis, and a high dropout rate (27%).

The effects of hyoscine butylbromide 10 mg four times a daily, lorazepam, and ispaghula husk were studied in a sample of 96 patients with irritable bowel syndrome.¹⁹ Eight groups of 12 patients were randomized to all possible combinations of these three therapies and placebo. Each therapy demonstrated a trend towards improved symptoms over the three-month trial, although results were only significant for ispaghula husk. Methods and statistical analysis were not well described.

Prevention of Airway Obstruction

Summary: Anticholinergic agents such as belladonna cause relaxation of smooth muscles of the airway and a reduction in production of mucus. Although the known mechanism of belladonna is compelling for this use, there is only limited human research in this area. One study

looking at treatment of airway obstruction during sleep in infants demonstrated a beneficial effect of belladonna. However, due to a lack of other controlled trials, there is currently insufficient evidence to recommend belladonna for the prevention of airway obstruction.

Evidence: Kahn et al., studied obstructed breathing in the sleep of 20 infants (average age 12-weeks-old) with a history of breath-holding spells.¹² This randomized, double-blind, crossover trial lasted for 14 days, with each infant spending one night undergoing polysomnography with each treatment (placebo or belladonna). Tincture of belladonna was administered in a dose equivalent to 0.01 mg/kg weight of atropine at bedtime. The authors reported a significant reduction in obstructed breathing events, with response noted in 50% (10/20) of infants receiving belladonna and in 20% (4/20) of infants in the placebo group. Differences between groups were statistically significant. No significant adverse effects were observed, although decreased “water evaporation rates” were noted in the belladonna-treated patients. It is unclear if a history of breath-holding spells correlates clearly with physiological airway obstruction. The authors recognized that belladonna overdose in infants and children can be deadly, and that the long-term effects of belladonna treatment are unknown. In addition, tinctures contain ethanol, which may have elicited effects in subjects.

Autonomic Nervous System Disturbances

Summary: Literature review reveals limited evidence regarding the use of belladonna for treatment of symptoms associated with autonomic nervous system dysfunction. Therefore, there is currently insufficient evidence to support the use of belladonna for symptoms of autonomic nervous system dysfunction.

Evidence: In a 1970 trial, Dobrescu compared two different combination formulas, each taken three times daily by patients with disturbances of the autonomic nervous system:²¹ “Formula I” contained a low concentration of belladonna (0.25 mg belladonna, 0.3 mg alkaloids of ergot, 30 mg phenobarbital) and “Formula II” contained a higher concentration of belladonna (15 mg belladonna extract, 60 mg ergot extract, 15 mg propranolol, 25 mg amobarbital). A total of 36 subjects were enrolled in this single-blind, crossover trial and received treatment for one week, followed by crossover to the alternate therapy for one week. “Very good” results were noted in 72% of subjects receiving Formula II (higher belladonna concentration), compared with 36% treated with Formula I. Limitations of this study include the small sample size,

lack of adequate randomization, use of subjective outcome measures, and failure to report the dropout rate. In addition, due to multiple variations between the two formulas, it is not clear which constituent(s) might be responsible for the differing effects.

A single-blind placebo controlled study was conducted to investigate the cardiorespiratory effects of belladonna, as a surrogate measure of vagal activity.⁵¹ Single doses of an oral belladonna tincture containing 0.1 mg/mL alkaloid concentration were administered, with a proportion of atropine to scopolamine of 20:1. In eight healthy young subjects, heart rate and noninvasive arterial finger blood pressure were recorded for 4 hours following oral application of 1 mL, 2 mL, or 5 mL of this belladonna tincture, or placebo. The authors reported that 1 hour after administration of 5 mL, mean respiratory rate, heart rate, and baroreflex sensitivity decreased significantly in six of eight subjects. In contrast, following administration of 1-2 mL, mean respiratory rate and heart rate increased compared to placebo.

Headache

Summary: Studies comparing belladonna-containing compounds with placebo have been small and have reported limited or no benefits. However, this research has been poor-quality and has examined combination products containing other agents such as ergotamine or phenobarbital (which may be efficacious in the absence of belladonna), or used homeopathic (dilute) belladonna preparations. There is currently insufficient evidence to support the use of belladonna for the treatment or prophylaxis of headache.

Evidence: A study conducted by Stieg compared a combination formula belladonna-ergotamine-phenobarbital (BEP) to placebo in a randomized crossover and parallel group design trial.¹⁶ BEP is equivalent to the commercially available product Bellergal-S®, which contains 40 mg phenobarbital, 0.6 mg ergotamine tartrate, and 0.2 mg levorotatory alkaloids of belladonna. The trial enrolled 76 patients with recurrent throbbing headaches at least once a week. No other prophylactic headache medication was allowed, but the use of medications for symptomatic relief was allowed during the study period. BEP or placebo was administered twice daily to subjects during the trial. The authors reported that over a four-week period, there was no difference in drug effectiveness or headache severity between groups. A modest significant decrease in headache severity and increase in days without headache medication was noted in a crossover sub-study. Problems with this trial

include the use of subjective measures of effect, small sample size and 28% dropout with no intention-to-treat analysis, and lack of description of randomization.

In a poorly described 1965 study by Lance et al., Bellergal® was compared to methysergide, cyproheptadine, and placebo in the treatment of 110 subjects with migraine headache.¹⁴ Compared with placebo, Bellergal® was reported to elicit no significant effect. No randomization or blinding was described, no dropout rate was reported, and the methods of the study were not described.

Whitmarsh et al., conducted a randomized, placebo controlled study in 63 outpatients with migraine headache diagnosed by International Headache Society criteria.¹⁰ Subjects received either a belladonna-containing homeopathic remedy or placebo for 4 months. No significant differences were detected between groups, and overall, headache frequency was 19% in the homeopathy group, and 16% with placebo. The sample size may have been too small to detect significant between-group differences, and the groups were dissimilar at baseline.

A 1965 placebo controlled trial compared methysergide, cyproheptadine, Bellergal® (40 mg phenobarbital). Uncontrolled studies have been reported, reporting small benefits from belladonna-containing compounds. Steele et al., reported a 1954 case series in which administration of Bellergal® for headache yielded “satisfactory results” in 73.3% of patients.¹⁵

Otitis Media

Summary: There is currently insufficient evidence to support the use of belladonna for the treatment of otitis media.

Evidence: A German homeopath and four otolaryngologists performed an observational study comparing homeopathic with conventional treatment for children with otitis media.²⁸ The homeopathic practitioner chose from among 12 remedies for otitis, including belladonna 30X globules (brand not specified). The homeopathic treatment group was reported to experience significantly fewer recurrences of otitis (29.3% vs. 43.5%), a shorter treatment duration, and a shorter duration of symptoms than the otolaryngologist-treated group (which received antibiotics). However, the frequency with which belladonna was used from among the 12 remedies was not specified, and there was no randomization or blinding in this trial (allowing for the possible introduction of bias or confounding). Therefore, although these results are compelling, they cannot be considered conclusive.

Premenstrual Syndrome

Summary: Bellergal®, a combination formula containing 40 mg phenobarbital, 0.6 mg ergotamine tartrate, and 0.2 mg levorotatory alkaloids of belladonna, has been reported in one controlled human trial to decrease symptoms associated with premenstrual syndrome, including fatigue, breast tenderness, and irritability. Further study is warranted before an evidence-based recommendation can be made.

Evidence: Robinson et al., performed a randomized, double-blind, placebo controlled trial in 32 patients experiencing symptoms associated with premenstrual syndrome.²² Patients were administered oral Bellergal® or placebo three times daily, beginning 10 days prior to menses. The primary outcome assessed was presence of any of nine “typical symptoms” of premenstrual syndrome over three menstrual cycles. The authors reported significantly less fatigue, breast tenderness, and lethargy in the treatment group vs. placebo. Although these results are suggestive, limitations of this study included its short duration, small sample size, 23% dropout, and unclear reporting of results or statistical analysis. The use of a combination formula leaves open the question of belladonna’s efficacy.

Radiodermatitis

Summary: Homeopathic application of belladonna for the management of radiodermatitis has been proposed based on the observed similarities between symptoms of radiodermatitis and the effects of belladonna (based on the dictum that “like cures like”). One randomized trial has reported modest benefits of a homeopathic (dilute) oral belladonna preparation for this indication, although there is no known biochemical basis for this use. There is currently insufficient evidence to support the use of belladonna for the management of radiodermatitis.

Evidence: A randomized, double-blind, placebo controlled trial was conducted in 66 patients undergoing radiation therapy following surgery for breast cancer.¹¹ Subjects were assigned to receive either the homeopathic dilution Belladonna 7CH (3 granules sublingually twice daily), the homeopathic preparation X-ray 15CH (3 granules sublingually once daily), or placebo. The authors reported that after 8 weeks, there was a small significant improvement measured by a subjective index of severity in the two treated groups vs. placebo. This study was properly

randomized and blinded, although dosing regimens varied by therapy, which may have revealed group assignments. The study was limited by the use of a non-standard outcomes measurement scale. Further study may be warranted in this area.

Menopausal Symptoms

Summary: Bellergal[®], a combination formula containing 40 mg phenobarbital, 0.6 mg ergotamine tartrate, and 0.2 mg levorotatory alkaloids of belladonna, has been used historically and reported anecdotally to reduce the incidence of hot flashes. One randomized control trial has reported negative results. There is currently insufficient evidence to recommend for or against the use of belladonna for the alleviation of menopausal symptoms.

Evidence: Bergmans et al., conducted a randomized, double-blind, placebo controlled trial in 71 patients experiencing menopausal symptoms.²³ After 8 weeks of follow-up, no benefit of Bellergal[®] was observed vs. placebo. Notably, a trend towards improved symptoms was seen at 2-4 weeks. These results cannot be considered conclusive due to limitations, including a 46% dropout rate.

PRODUCTS STUDIED

Brands Used in Statistically Significant Clinical Trials

Bellergal[®] (40 mg phenobarbital, 0.6 mg ergotamine tartrate, and 0.2 mg levorotatory alkaloids of belladonna).¹⁴⁻¹⁶ Also available: Bellergal-R[®], Bellergal-S[®].

International Brand Names

Astrobel[®], Belladonnysat Burger[®], Bellafolin[®], Bellafolina[®], Bellanorm[®], Tremoforat[®].

REFERENCE

1. Samet CM. The evaluation of Bellergal Tablets compared to librium and placebo in the treatment of symptoms of anxiety tension states associated with functional gastrointestinal disorders. *Psychosomatics* 1976;17(4):202-209. *View Abstract*

2. Steadman HE. Treatment of psychosomatic disorders with bellergal. *J Med Assoc Ga* 1968;57(8):384-386. *View Abstract*
3. Reichenberg-Ullman J. Homeopathy for women: menstrual discomfort and abnormal bleeding; relieved with Belladonna. *Resonance (Magazine Internat Foundation Homeop)* 1991;13(2):12-13.
4. Sodeman WA, Augur NA, Pollard HM. Physiology and pharmacology of belladonna therapy in acid-peptic disease. *Med Clin North Am* 1969;53(6):1379-1388. *View Abstract*
5. Tita B, Bolle P, Martinoli L, et al. A comparative study of Atropa belladonna and atropine on an animal model of urinary retention. *Pharmacol Res Commun* 1988;20 Suppl 5:55-58. *View Abstract*
6. Shader RI, Greenblatt DJ. Uses and toxicity of belladonna alkaloids and synthetic anticholinergics. *Seminars in Psychiatry* 1971;3(4):449-476. *View Abstract*
7. Lotvall J. Contractility of lungs and air-tubes: experiments performed in 1840 by Charles J.B. Williams. *Eur Respir J* 1994;7(3):592-595. *View Abstract*
8. Kapp W. The history of drugs for the treatment of Parkinson's disease. *J Neural Transm Suppl* 1992;38(Suppl):1-6. *View Abstract*
9. Walach H. Does a highly diluted homeopathic drug act as a placebo in healthy volunteers? Experimental study of belladonna 30C in double-blind crossover design—a pilot study. *Journal of Psychosomatic Research* 1993;37(8):851-860. *View Abstract*
10. Whitmarsh TE, Coleston-Shields DM, Steiner TJ. Double-blind randomized placebo-controlled study of homeopathic prophylaxis of migraine. *Cephalalgia* 1997;17(5):600-604. *View Abstract*
11. Balzarini A, Felisi E, Martini A, et al. Efficacy of homeopathic treatment of skin reactions during radiotherapy for breast cancer: a randomised, double-blind clinical trial. *Br Homeopath J* 2000;89(1):8-12. *View Abstract*
12. Kahn A, Rebuffat E, Sottiaux M, et al. Prevention of airway obstructions during sleep in infants with breath-holding spells by means of oral belladonna: a prospective double-blind crossover evaluation. *Sleep* 1991;14(5):432-438. *View Abstract*
13. Hartmann T, Witte L, Oprach F, et al. Reinvestigation of the alkaloid composition of Atropa belladonna plants, root cultures, and cell suspension cultures. *Planta Med* 1986;5:390-395.
14. Lance JW, Curran DA, Anthony M. Investigations into the mechanism and treatment of chronic headache. *Med J Aust* 1965;2(22):909-914. *View Abstract*
15. Steele CH. The use of Bellergal in the prophylactic treatment of some types of headaches. *Ann Allergy* 1954;42-46.
16. Stieg RL. Double-blind study of belladonna-ergotamine-phenobarbital for interval treatment of recurrent throbbing headache. *Headache* 1977;17(3):120-124. *View Abstract*
17. King JC. Anisotropine methylbromide for relief of gastrointestinal spasm: double-blind crossover comparison study with belladonna alkaloids and phenobarbital. *Curr Ther Res Clin Exp* 1966;8(11):535-541. *View Abstract*
18. Lichstein J, Mayer JD. Drug therapy in the unstable bowel (irritable colon). A 15-month double-blind clinical study in 75 cases of response to a prolonged-acting belladonna alkaloid-phenobarbital mixture or placebo. *J Chron Dis* 1959;9(4):394-404.
19. Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *Br Med J* 1979;1(6160):376-378. *View Abstract*

20. Rhodes JB, Abrams JH, Manning RT. Controlled clinical trial of sedative-anticholinergic drugs in patients with the irritable bowel syndrome. *J Clin Pharmacol* 1978;18(7):340-345. *View Abstract*
21. Dobrescu DI. Propranolol in the treatment of disturbances of the autonomic nervous system. *Curr Ther Res Clin Exp* 1971;13(1):69-73. *View Abstract*
22. Robinson K, Huntington KM, Wallace MG. Treatment of the premenstrual syndrome. *Br J Obstet Gynaecol* 1977;84(10):784-788. *View Abstract*
23. Bergmans M, Merkus J, Corbey R, et al. Effect of Bellergal Retard on climacteric complaints: a double-blind, placebo-controlled study. *Maturitas* 1987;9:227-234.
24. Goodyear K, Lewith G, Low JL. Randomized double-blind placebo-controlled trial of homoeopathic 'proving' for Belladonna C30. *J R Soc Med* 1998;91(11):579-582. *View Abstract*
25. Williams HC, du Vivier A. Belladonna plaster—not as bella as it seems. *Contact Dermatitis* 1990;23(2):119-120. *View Abstract*
26. Schneider F, Lutun P, Kintz P, et al. Plasma and urine concentrations of atropine after the ingestion of cooked deadly nightshade berries. *J Toxicol Clin Toxicol* 1996;34(1):113-117. *View Abstract*
27. Southgate HJ, Egerton M, Dauncey EA. Lessons to be learned: a case study approach. Unseasonal severe poisoning of two adults by deadly nightshade (*Atropa belladonna*). *Journal of the Royal Society of Health* 2000;120(2):127-130. *View Abstract*
28. Friese KH, Kruse S, Ludtke R, et al. The homoeopathic treatment of otitis media in children—comparisons with conventional therapy. *International Journal of Clinical Pharmacology and Therapeutics* 1997;35(7):296-301. *View Abstract*
29. Jaspersen-Schib R, Theus L, Guirguis-Oeschger M, et al. [Serious plant poisonings in Switzerland 1966-1994. Case analysis from the Swiss Toxicology Information Center]. *Schweiz Med Wochenschr* 1996;126(25):1085-1098. *View Abstract*
30. Firth D, Bentley JR. Belladonna poisoning from eating rabbit. *Lancet* 1921;2:901.
31. Joll ME. Three cases of belladonna poisoning. *Lancet* 1916;2:647.
32. Minors EH. Five cases of belladonna poisoning. *Br Med J* 1948;2:518-519.
33. Eichner ER, Gunsolus JM, Powers JF. "Belladonna" poisoning confused with botulism. *Jama* 1967;201(9):695-696. *View Abstract*
34. Trabattoni G, Visintini D, Terzano GM, et al. Accidental poisoning with deadly nightshade berries: a case report. *Human Toxicol* 1984;3(6):513-516. *View Abstract*
35. Ceha LJ, Presperin C, Young E, et al. Anticholinergic toxicity from nightshade berry poisoning responsive to physostigmine. *The Journal of Emergency Medicine* 1997;15(1):65-69. *View Abstract*
36. Sims SR. Poisoning due to belladonna plasters. *Br Med J* 1954;1531.
37. Gabel MC. Purposeful ingestion of belladonna for hallucinatory effects. *J Pediatr* 1968;72(6):864-866. *View Abstract*
38. Goldsmith SR, Frank I, Ungerleider JT. Poisoning from ingestion of a stramonium-belladonna mixture: flower power gone sour. *J A M A* 1968;204(2):169-170. *View Abstract*
39. Cummins BM, Obetz SW, Wilson MR, et al. Belladonna poisoning as a facet of psychodelia. *Jama* 1968;204(11):153.
40. Walach H, Koster H, Hennig T, et al. The effects of homeopathic belladonna 30CH in healthy volunteers—a randomized, double-blind experiment. *J Psychosom Res* 2001;50(3):155-160. *View Abstract*
41. Hamilton M, Sclare AB. Belladonna poisoning. *Br Med J* 1947;611-612.

42. Myers JH, Moro-Sutherland D, Shook JE. Anticholinergic poisoning in colicky infants treated with hyoscyamine sulfate. *Am J Emerg Med* 1997;15(5):532-535. *View Abstract*
43. Berney C, Wolfensberger TJ. [Mydriasis induced by splinter from belladonna bush]. *Klin Monatsbl Augenheilkd* 2000;216(5):346-347. *View Abstract*
44. Heindl S, Binder C, Desel H, et al. [Etiology of initially unexplained confusion of excitability in deadly nightshade poisoning with suicidal intent. Symptoms, differential diagnosis, toxicology and physostigmine therapy of anticholinergic syndrome]. *Dtsch Med Wochenschr* 2000;125(45):1361-1365. *View Abstract*
45. Pentel P, Mikell F. Reaction to phenylpropalamine/chlorpheniramine/belladonna compound in a women with unrecognised autonomic dysfunction. *Lancet* 1982;2(8292):274. *View Abstract*
46. Golwalla A. Multiple extrasystoles: an unusual manifestation of belladonna poisoning. *Dis Chest* 1965;48:83-84.
47. Mellin GW. Drugs in the first trimester of pregnancy and the fetal life of Homo sapiens. *Am J Obst Gynec* 1964;90(7):1169-1180.
48. Diaz DM, Diaz SF, Marx GF. Cardiovascular effects of glycopyrrolate and belladonna derivatives in obstetric patients. *Bull N Y Acad Med* 1980;56(2):245-248. *View Abstract*
49. Corazziari E, Bontempo I, Anzini F. Effects of cisapride on distal esophageal motility in humans. *Dig Dis Sci* 1989;34(10):1600-1605. *View Abstract*
50. Pan SY, Han YF. Learning deficits induced by 4 belladonna alkaloids are preferentially attenuated by tacrine. *Acta Pharmacol Sin* 2000;21(2):124-130. *View Abstract*
51. Bettermann H, Cysarz D, Portsteffen A, et al. Bimodal dose-dependent effect on autonomic, cardiac control after oral administration of Atropa belladonna. *Auton Neurosci* 2001;90(1-2):132-137. *View Abstract*
52. Jacobs KW. Asthmador: a legal hallucinogen. *Int J Addict* 1974;9(4):503-512. *View Abstract*

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