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The Bright Side and the Dark Side of Scopolamine (Pharmacology, Toxicology, Pharmacokinetics, and Clinical Use Review)

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ABSTRACT

Scopolamine is one of tropane alkaloids obtained from Solanaceae plants. This compound has been used for a long time by human for both good and bad cause, such as dilating pupil, analgesics, anaesthesia, and even poisoning or other criminal acts. Scopolamine possess many pharmacological activities due to its anticholinergic activity. It binds non-selectively to muscarinic receptors both peripherally and centrally.

At therapeutic dose, scopolamine may be beneficial for preventing motion sickness and Post Operative Nausea and Vomiting (PONV), treating sialorrhea in disabled patients, lowering depression, and preventing death rattle. However, its effect on anxiety level is still conflicting. Adverse effects commonly occurred at therapeutic dose is usually tolerable, such as sedation, dry mouth, skin reactions, blurred vision, mydriasis, and confusion.

At higher dose, scopolamine may generate harmful effects, such as amnesia, delirium, hallucination, hypertension, tachycardia, and arrythmia. For its effect on memory and sedative effect, scopolamine is frequently used in some countries, such as Columbia and Indonesia recently to incapacitating victims. Treatment for poisoning of scopolamine is usually supportive to treat symptoms. Antidote use, acetylcholinesterase inhibitor, such as physostigmine may be used in certain condition.

Keywords: *Scopolamine, pharmacology, toxicology, pharmacokinetics*

1. BACKGROUND

"All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison," Paracelsus said. Referring to that quote, one of alkaloid found in plant is more notorious for its harmful effects than its potentially beneficial effects, namely scopolamine. Scopolamine, or sometimes known as hyoscine, is an alkaloid tropane found in Solanaceae plants, such as *Datura stramonium*, *Datura metel* ("*kecubung*" in Indonesian), *and Atropa belladona* (deadly nightshade)[1]. Scopolamine has a chiral center located in tropic acid (Figure 1). It has molecular weight of 303.5 and pKa 7.55 – 7.81, thus it is considered as a weak base[2]. Since it has tertiary amine, scopolamine tends to lipophile with coefficient partition of octanol:water is 1.2 [3].

Historically, it has been used for various purpose for a long time, such as poison for killing people, hallucinogen, and recreational drug [4]. It has been researched as 'truth serum' by Central Intelligence Agency (CIA) as well since subjects exposed to scopolamine would answer question without remembering anything after recovered (amnesia anterograde)[4]. Scopolamine also has been used for criminal acts. In South America, it is called "Burundanga" and commonly used for robbery [1] . Recently, in Indonesia, the case of criminal acts using scopolamine rises.

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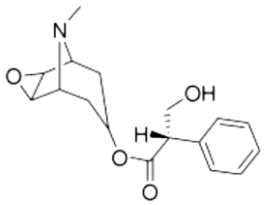

Scopolamine

Figure 1. The Structure of Scopolamine.

In biological system, scopolamine acts as an antagonist of muscarinic receptor. Despite its harmful effect, scopolamine is widely used for treating disease. In market, scopolamine is available in transdermal patch, eye drop, and infusion solution (as its salt, scopolamine hydrobromide) [3]. The most common usage of scopolamine is transdermal patch to treat nausea and vomiting. Other beneficial effects of scopolamine has also been studied, such as treating sialorrhea in disabled patients, lowering depression, and preventing death rattle. Therefore, this review aims to present both the beneficial and harmful effects of scopolamine. Besides, pharmacokinetics of scopolamine will be reviewed as well since it will affect clinical and toxicological aspects of scopolamine.

2. PHARMACOLOGICAL EFFECTS AND CLINICAL USES OF SCOPOLAMINE

Scopolamine acts as antagonist of muscarinic receptor. In our body, there are 5 subtypes of muscarinic receptors, M_1 – M_5. Distribution of each receptors in human body is presented on Table 1. Antagonist activity of scopolamine on M_1 - M_4 subtype muscarinic receptor is equal, whilst on M5 receptor tends to weak, hence scopolamine is considered as non-selective antimuscarinic [4]. Although in normal dose scopolamine only binds to muscarinic receptor, in higher dose it may inhibit nicotinic receptor as well [5].

Generally, scopolamine inhibits the works of gastrointestinal symptoms. It inhibits salivary secretion and decrease tone of smooth muscle in gastrointestinal tract [3]. Scopolamine also decrease tone urethra and bladder contraction[3]. Since sweating is also innervated by muscarinic, scopolamine reduce the sweat gland activity, thus may increase body temperature and cause hyperthermia [3].

Table 1. Distribution of Muscarinic Receptors[6]

Receptor Muscarinic	Organs
M_1	Cerebral cortex, hippocampus, amygdala, basal ganglia, olfactory region, isocortex, prostate, salivary gland
M_2	Pons, medulla, heart, Gastrointestinal (GI) tissue (colon and stomach), gall bladder, urinary bladder
M_3	Cerebral cortex, Gl tissues (colon, esophagus, stomach) pancreas, urinary bladder, reproductive organs, eye
M_4	Basal ganglia, isocortex bangsal ganglia, spleen, testes
M_5	Basal ganglia (substania nigra, ventral tegmentum area), hypothalamus, CA2 hippocampus, cerebral vasculature endothelial cells

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2.1. Nausea and Vomiting

Regarding its antagonism on muscarinic receptor, scopolamine must be able to treat nausea and vomiting. In the form of transdermal patch, scopolamine is indicated in its label to prevent motion sickness. It has been approved by FDA since 1970 to treat motion sickness and Post Operative Nausea and Vomiting (PONV) since 2001 [2]. Motion sickness is induced by transmission from vestibular system, which detect a motion, to cerebellum. This process is mediated by histamine and muscarinic receptor. Signal from cerebellum then is transmitted to emetic center on medulla. Due to this process involve muscarinic receptor, thus inhibition on muscarinic receptor will interfere transmission to cerebellum and inhibit nausea induction [7]. Meta analyses conducted from 5 studies showed that transdermal scopolamine was able to prevent motion sickness, with risk ratio (RR) is 0.48 and 95% Confidence Interval is 0.32 to 0.73 [7].Application of transdermal patch scopolamine in patient undergoing cesarian delivery may decrease the need to use antiemetics post surgery. Moreover, scopolamine is superior than other class agent, ondansetron, in preventing PONV [2].

2.2. Drooling (Sialorrhea)

All salivary glands are innervated by parasympathetic nervous system, hence scopolamine which antagonize muscarinic receptor will decrease salivation[8]. Condition in which excessive salivation occurred is called sialorrhea. Clinical trial conducted on 30 patients with disability showed that transdermal scopolamine able to reduce drooling significantly, while placebo does not affect the drooling [9]. However, a randomized clinical study conducted by Odachi et al. on 10 patients of ALS showed that scopolamine treatment does not show significant difference compared to placebo in treating sialorrhea [10]

2.3. Depression

Scopolamine has long been investigated for antidepressant activity since the pathophysiology of depression is closely related to cholinergic activity. A randomized, clinical trial study was conducted on 19 depressive patients (both unipolar and bipolar). Patients administered with scopolamine in salt form, scopolamine hydrobromide, with dose of 4.0 μg/kg intravenous infusion exhibited a rapid reduction of depression symptoms, about 3 – 4 days following single dose of scopolamine [11]. This beneficial effect is superior than current existing antidepressant which usually takes longer time to show clinical effect. The duration activity of scopolamine effect is long despite its short half-life[3] , indicating that the effect does not only depend on direct antagonist muscarinic receptor activity [11]. Clinical response of scopolamine in bipolar patients is similar to unipolar patients, thus superior to conventional antidepressant which usually only work on one of depression type.

Antidepressant activity of scopolamine is different to current standard treatment as well. Its work probably is associated with N-methyl-D-aspartate glutamatergic receptors (NMDARs). Patients with depression exhibited an increased of glutamatergic transmission, while scopolamine may decrease mRNA concentration of NMDAR in rat brain.[12] Female hormone, estrogen, contributes to enhance NMDAR activity which mediated by M2 muscarinic receptor [13,14]. This mechanism explained why the prevalence of depression is higher in female compared to male and response to scopolamine, a muscarinic antagonist, are greater in women than men patients. The antidepressant effect of scopolamine are different between man and woman, in which greater response are exhibited in women patients compared with men patients. In a randomized clinical study, 71% of female patients achieved a full response, while only 42% of male patients showed full response ($p < 0.05$) [12].

Other study concludes that antidepressant activity of scopolamine is mediated through inhibition of M1 muscarinic receptor on GABAergic interneuron in the medial Prefontral cortex (mPFC) which further stimulate pyramidal neuron activity and stimulate glutamate transmission [15]. Glutamate burst further increase the signalling of the mammalian target of rapamycin (mTOR) complex 1 (mTORC1). It is occurred at lower dose in mice (25 μg/kg), but does not happen in higher dose (100 μg/kg). Scopolamine cause induction of phospho-mTOR, phospho-Akt, and phospho-S6K 1 hour after treatment without affecting phospho-ERK [16]. Other additional mechanism involved in its antidepressant activity are reducing noradrenergic transmission, enhancing activity on dopamine receptor (D2/D3), blockade cholinergic activity on Ventral Tegmental Area (VTA) which further reduce dopamine release in the nucleus acccumbens, and elevate brain derived neurotrophic factor (BDNF) level [17–19].

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2.4. Anxiety

The effect of scopolamine on anxiety level somewhat confusing. In a randomized clinical trial involving depressed patient, scopolamine were successfully reducing anxiety level only in female patient. [12] Scopolamine transdermal patch is frequently used by cocaine addicts to lower their anxiety level during process of quitting since brain reward system is also influenced by cholinergic transmission. Acutely and chronically cocaine use may activate cholinergic interneurons in the nucleus accumbent (NAc) [20].

Study in animals also show conflicting results. Study in mice showed whilst scopolamine-treated rats showed lower freezing after context conditioning (anxiolytic effects), they exhibited shorter duration in center area in open field test, thus indicating anxiogenic effects [21]. Study in zebrafish result in anxiolytic activity at dose of 800 μM [22]. However, other studies in zebrafish conclude that scopolamine 120 mg/L (or equal to more or less 300 μM)[23] and 100 μM, [24] generate mild anxiogenic effect instead. Zebrafish treated with scopolamine exhibited reducing maximal acceleration [23].

2.5. Death Rattle

Death rattle is noisy breathing generally found in dying patient with terminally ill. It is caused by the presence of mucus in the upper respiratory tract [25]. It is usually occurred in patient with decreasing consciousness or the patient is too weak to expectorate [26]. Secretion of mucus in respiratory tract is regulated by cholinergic activities, hence antimuscarinic properties of scopolamine can be beneficial on this symptom. Scopolamine does not clear existing mucus, yet decrease its production, thus administration before death rattle occurred is more effective than to treat occurring death rattle.[27] A multicenter randomized clinial trial conducted on 162 patients resulted in decreasing the incidence of death rattle in patient treated with subcutaneous scopolamine hydrobromide 20 mg 4 times a day compared to placebo (p-value 0.02) [27]. Compared to other antimuscarinic agents such as atropine and hyoscine butylbromide, scopolamine exhibit equal activity in treating death rattle[26].

Other research reported the usage of scopolamine as antidote of sarin (nerve agent) and organophospate poisoning[28,29]. Sarin and organophosphate work by inhibiting acetylcholinesterase, an acetylcholine-degrading enzyme, thus increase the availability of acetylcholine. Therefore, anticholinergic activity of scopolamine is able to counteract their effect. Scopolamine may cross blood-brain barrier better than organophosphate, hence it has benefit on suppressing organophosphate effect on central nervous system [29].

Scopolamine administration also has benefit on treating severe tremor in Parkinson's Disease. Even before levodopa is used, scopolamine had been used [30]. The dose recommended by Perez et al. are 0.3–0.6 mg through the subcutaneous route every 4–6 hours [30].

3. TOXICOLOGICAL FINDINGS OF SCOPOLAMINE

The value of LD50 of scopolamine in rat is 3.8 g/kgBW subcutaneously, while lethal concentration has been reported to be ≥ 1890 ng/mL[3,31]. Overdose of scopolamine cause anticholinergic syndrome both peripherally (such as dry mouth, pupil dilation, urinary retention, hypertension, hyperthermia, tachycardia, arrythmia) and centrally (such as agitation, convulsion, hallucination, confusion, and even coma) [131]. Treatment of scopolamine overdose is usually supportive and intend to alleviate the symptoms, such as antipyretic to lower the temperature and benzodiazepine to reduce agitation and restless [5]. In any case in which antidote is needed, acetylcholinesterase inhibitor, such as physostigmine in dose of 0.5 – 1 mg may be administered intramuscularly, subcutaneously, or intravenously [32].

Since memory formation is facilitated by cholinergic activity, exposure of scopolamine as antagonist muscarinic to central nervous system (CNS) in high dose cause anterograde amnesia [1]. Research in animal showed that pre-training intradorsal hippocampal of scopolamine impair memory acquisition of rat [33]. Moreover, scopolamine also affects memory consolidation in rat training with context fear consolidation[21]. It turns out that acetylcholine is involved in both acquisition of new memory and consolidation of short-term memory to long-term memory. For its toxicity, scopolamine is often used in criminal act, such as robbery and sexual assault [31].

Besides its effect on memory, scopolamine in high dose may trigger delirium, a condition characterized as change in mental status and loss memory rapidly. Hyperactivity in Reticular Activating System (RAS)

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which located in brainstem may responsible to this [5]. Lethal dose of scopolamine is reported to be 2-4 mg.[34]

Long-term, high dose administration of scopolamine in rat can cause atrophy and degeneration of brain neurons, accumulation of protein Aβ in brain, APP mRNA expression in brain, and increase phosphorylated protein tau in brain, all of them are pathological characteristics of Alzheimer disease[35]. Therefore, scopolamine is commonly used to induce Alzheimer in laboratory animals, to evaluate the potential drug for treating Alzheimer's disease. The effect of scopolamine on fetus is not considered as teratogenic, however it may cause the newborn show tachycardia, fever, and lethargy[3].

4. PHARMACOKINETICS OF SCOPOLAMINE

The therapeutic blood level of scopolamine is around 0.3 to 19 ng/mL [31]. Scopolamine transdermal patch is available in dose of 1.5 mg and priming dose of 140 μg to quicken the onset. Rate of drug release from transdermal patch is 5 μg/hr [3]. Different skin location shows different permeability of scopolamine. The highest permeation rate is located on postauricular (mastoid process), whilst lowest permeation rate is found in the thigh [36]. Pharmacokinetic parameters of scopolamine transdermal patch which contain 1.5 mg is shown at Table I. Half-life of scopolamine oral is very short, limit its use for therapeutic purpose.

Table 2. Pharmacokinetic Parameters of Scopolamine [3]

Pharmacokinetic Parameters	Transdermal (dose 1.5 mg)	Oral (dose 0.5 mg)	Intravenous infusion (dose 0.5 mg)
Cmax (ng/mL)	0.1	0.54 ± 0.1	5.00 ± 0.43
Tmax	8 hours	23.5 ± 8.2 min	5.00 min
AUC (ng.min/mL)	N.A.	50.77 ± 1.76	369.4 ± 2.2
Half-life	2 – 4 hours	63.7 ± 1.3 min	68.7 ± 1.0 min
Bioavailability (%)	N.A.	13.0 ± 1	100
Steady-state plasma concentration	0.05 – 0.10 ng/mL	-	N.A.

As much as 30% scopolamine is plasma will be bound by albumin. Coadministration with contraceptives may reduce protein bound to 3 – 12% [3]. Due to its lipophilic character, scopolamine may penetrate blood brain barrier and placenta, thus its use in pregnant woman should be supervised closely. Scopolamine is metabolized in liver through various pathway, glucuronidation, hydrogenation, hydroxylation, methoxylation, hydrolysis, sulfation, dehydration, and oxidative demethylation. Of them, glucuronide and sulfate conjugation are the most metabolite of scopolamine[3]. Metabolism of scopolamine is inhibited by contraceptive agents. Demethylation of scopolamine is conducted by CYP3A subfamily [37].

5. ADVERSE EFFECTS OF SCOPOLAMINE

Adverse effects following use of scopolamine at therapeutic dose is usually mild and well tolerated. Adverse effects related to scopolamine use is showed at Table 1. The adverse effect of scopolamine is usually not correlated with its plasma concentration [5].

Table 3. Adverse Effects of Scopolamine in Therapeutic Dose

System	Adverse Effects [3,11,12,38]
Central Nervous System	Drowsiness, lightheadedness, dizziness, headache, confusion, hallucination, short term memory loss, restlessness, agitation, dreamless sleep, amnesia, vertigo, vestibular depression
Gastrointestinal system	Dry mouth, nausea
Eye	Blurred vision, mydriasis, eye pain, photophobia
Cardiovascular system	Hypotension, change in heart rate
Renal and urinary system	Difficulty in urination
Skin and subcutaneous system	Skin redness, sweating

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6. CONCLUSION

The potency of scopolamine in treating various disease still widely opened. Due to its mechanism in biological system is general, bind to muscarinic receptor which distribute in all over the body, its pharmacological activities should be vast too. It has both advantages and disadvantages, while its therapeutic benefits are wide, their side effects must be various too. However, in therapeutic dose, its side effects are usually tolerable. In higher dose, scopolamine may produce harmful effects which may be lethal. Therefore, clinical use of scopolamine must be monitored cautiously.

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CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this article.

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REFERENCES

1. Dufayet L, Alcaraz E, Dorol J, Rey-Salmon C, Alvarez JC. Attempt of scopolamine-facilitated robbery: an original case of poisoning by inhalation confirmed by LC–MS/MS and review of the literature. *Forensic Toxicol*. 2020;38(1):264-268. doi:10.1007/s11419-019-00492-z
2. Antor MA, Uribe AA, Erminy-Falcon N, et al. The effect of transdermal scopolamine for the prevention of postoperative nausea and vomiting. *Front Pharmacol*. 2014;5. doi:10.3389/fphar.2014.00055
3. Renner UD, Oertel R, Kirch W. *Pharmacokinetics and Pharmacodynamics in Clinical Use of Scopolamine*.
4. Lakstygal AM, Kolesnikova TO, Khatsko SL, et al. DARK Classics in Chemical Neuroscience: Atropine, Scopolamine, and Other Anticholinergic Deliriant Hallucinogens. *ACS Chem Neurosci*. 2019;10(5):2144-2159. doi:10.1021/acschemneuro.8b00615
5. Lin YG, Chen PH, Chang FY, Wu L Te, Liao KY, Wu TC. Delirium due to scopolamine patch in a 4-year-old boy. *Journal of the Formosan Medical Association*. 2011;110(3):208-211. doi:10.1016/S0929-6646(11)60031-4
6. Drevets WC, Bhattacharya A, Furey ML. The antidepressant efficacy of the muscarinic antagonist scopolamine: Past findings and future directions. In: *Advances in Pharmacology*. Vol 89. Academic Press Inc.; 2020:357-386. doi:10.1016/bs.apha.2020.04.002
7. Spinks A, Wasiak J. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database of Systematic Reviews*. Published online June 15, 2011. doi:10.1002/14651858.cd002851.pub4
8. Proctor GB, Carpenter GH. Regulation of salivary gland function by autonomic nerves. *Auton Neurosci*. 2007;133(1):3-18. doi:10.1016/j.autneu.2006.10.006
9. Mato A, Limeres J, Tomás I, et al. Management of drooling in disabled patients with scopolamine patches. *Br J Clin Pharmacol*. 2010;69(6):684-688. doi:10.1111/j.1365-2125.2010.03659.x

10. Odachi K, Narita Y, Machino Y, et al. Efficacy of transdermal scopolamine for sialorrhea in patients with amyotrophic lateral sclerosis. *Cogent Med*. 2017;4(1):1365401. doi:10.1080/2331205x.2017.1365401
11. Furey ML, Drevets WC. *Antidepressant Efficacy of the Antimuscarinic Drug Scopolamine A Randomized, Placebo-Controlled Clinical Trial*. Vol 63.; 2006.
12. Furey ML, Khanna A, Hoffman EM, Drevets WC. Scopolamine produces larger antidepressant and antianxiety effects in women than in men. *Neuropsychopharmacology*. 2010;35(12):2479-2488. doi:10.1038/npp.2010.131
13. Gibbs RB, Gabor R, Cox T, Johnson DA. Effects of raloxifene and estradiol on hippocampal acetylcholine release and spatial learning in the rat. *Psychoneuroendocrinology*. 2004;29(6):741-748. doi:10.1016/S0306-4530(03)00118-5
14. Daniel JM, Dohanich GP. *Acetylcholine Mediates the Estrogen-Induced Increase in NMDA Receptor Binding in CA1 of the Hippocampus and the Associated Improvement in Working Memory*.; 2001.
15. Wohleb ES, Wu M, Gerhard DM, et al. GABA interneurons mediate the rapid antidepressant-like effects of scopolamine. *Journal of Clinical Investigation*. 2016;126(7):2482-2494. doi:10.1172/JCI85033
16. Voleti B, Navarria A, Liu RJ, et al. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. *Biol Psychiatry*. 2013;74(10):742-749. doi:10.1016/j.biopsych.2013.04.025
17. Li Y, Zhu ZR, Ou BC, et al. Dopamine D2/D3 but not dopamine D1 receptors are involved in the rapid antidepressant-like effects of ketamine in the forced swim test. *Behavioural Brain Research*. 2015;279:100-105. doi:10.1016/j.bbr.2014.11.016
18. Addy NA, Nunes EJ, Wickham RJ. Ventral tegmental area cholinergic mechanisms mediate behavioral responses in the forced swim test. *Behavioural Brain Research*. 2015;288:54-62. doi:10.1016/j.bbr.2015.04.002
19. Yu H, Lv D, Shen M, et al. BDNF mediates the protective effects of scopolamine in reserpine-induced depression-like behaviors via up-regulation of 5-HTT and TPH1. *Psychiatry Res*. 2019;271:328-334. doi:10.1016/j.psychres.2018.12.015
20. Gambelunghe C, Bacci M, Aroni K, De Falco F, Ayroldi EM. Cocaine addiction treatment and home remedies: Use of the scopolamine transdermal patch. *Subst Use Misuse*. 2014;49(1-2):1-6. doi:10.3109/10826084.2013.824477
21. Luyten L, Nuyts S, Beckers T. Low-dose systemic scopolamine disrupts context conditioning in rats. *Journal of Psychopharmacology*. 2017;31(6):667-673. doi:10.1177/0269881117699614
22. Hamilton TJ, Morrill A, Lucas K, et al. Establishing zebrafish as a model to study the anxiolytic effects of scopolamine. *Sci Rep*. 2017;7(1). doi:10.1038/s41598-017-15374-w
23. Volgin AD, Yakovlev OA, Demin KA, Alekseeva PA, Kalueff A V. Acute behavioral effects of deliriant hallucinogens atropine and scopolamine in adult zebrafish. *Behavioural Brain Research*. 2019;359:274-280. doi:10.1016/j.bbr.2018.10.033
24. Cho H, Lee CJ, Choi J, Hwang J, Lee Y. Anxiolytic effects of an acetylcholinesterase inhibitor, physostigmine, in the adult zebrafish. *Anim Cells Syst (Seoul)*. 2012;16(3):198-206. doi:10.1080/19768354.2011.642084
25. Lokker ME, Van Zuylen L, Van Der Rijt CCD, Van Der Heide A. Prevalence, impact, and treatment of death rattle: A systematic review. *J Pain Symptom Manage*. 2014;47(1):105-122. doi:10.1016/j.jpainsymman.2013.03.011
26. Wildiers H, Dhaenekint C, Demeulenaere P, et al. Atropine, Hyoscine Butylbromide, or Scopolamine Are Equally Effective for the Treatment of Death Rattle in Terminal Care. *J Pain Symptom Manage*. 2009;38(1):124-133. doi:10.1016/j.jpainsymman.2008.07.007
27. Van Esch HJ, Van Zuylen L, Geijteman ECT, et al. Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life: The SILENCE Randomized Clinical Trial. *JAMA - Journal of the American Medical Association*. 2021;326(13):1268-1276. doi:10.1001/jama.2021.14785

28. Cornelissen AS, Klaassen SD, van Groningen T, Bohnert S, Joosen MJA. Comparative physiology and efficacy of atropine and scopolamine in sarin nerve agent poisoning. *Toxicol Appl Pharmacol*. 2020;396. doi:10.1016/j.taap.2020.114994
29. Kventsel I, Berkovitch M, Reiss A, Bulkowstein M, Kozer E. Scopolamine treatment for severe extra-pyramidal signs following organophosphate (chlorpyrifos) ingestion. *Clin Toxicol*. 2005;43(7):877-879. doi:10.1080/15563650500357636
30. Pérez LM, Farriols C, Puente V, Planas J, Ruiz I. The use of subcutaneous scopolamine as a palliative treatment in Parkinson's disease. *Palliat Med*. 2011;25(1):92-93. doi:10.1177/0269216310381662
31. Le Garff E, Delannoy Y, Mesli V, Hédouin V, Tournel G. Forensic features of a fatal Datura poisoning case during a robbery. *Forensic Sci Int*. 2016;261:e17-e21. doi:10.1016/j.forsciint.2016.02.028
32. Sandia S I, Ramírez V J, Piñero A J, Baptista T T. Treating 'Devil's Breath' intoxication: Use of rivastigmine in six patients with toxic psychoses due to non pharmaceutical scopolamine. *European Neuropsychopharmacology*. 2017;27(8):833-834. doi:10.1016/j.euroneuro.2017.05.006
33. Khakpai F, Nasehi M, Haeri-Rohani A, Eidi A, Zarrindast MR. Scopolamine induced memory impairment; possible involvement of NMDA receptor mechanisms of dorsal hippocampus and/or septum. *Behavioural Brain Research*. 2012;231(1):1-10. doi:10.1016/j.bbr.2012.02.049
34. Centers for Disease Control and Prevention. Jimson weed poisoning--Texas, New York, and California, 1994. *JAMA*. 1995;273:523-533.
35. Tang KS. The cellular and molecular processes associated with scopolamine-induced memory deficit: A model of Alzheimer's biomarkers. *Life Sci*. 2019;233. doi:10.1016/j.lfs.2019.116695
36. Pergolizzi J V., Philip BK, Leslie JB, Taylor R, Raffa RB. Perspectives on transdermal scopolamine for the treatment of postoperative nausea and vomiting. *J Clin Anesth*. 2012;24(4):334-345. doi:10.1016/j.jclinane.2011.07.019
37. Ebert U, Oertel R, Kirch W. Influence of grapefruit juice on scopolamine pharmacokinetics and pharmacodynamics in healthy male and female subjects. *Int J Clin Pharmacol Ther*. 2000;38(11):523-531.
38. Gan TJ. *Postoperative Nausea and Vomiting-Can It Be Eliminated?* http://jama.jamanetwork.com/