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## REVIEW ARTICLE

# ATROPINE AND ATROPINE-LIKE SUBSTANCES USABLE IN WARFARE

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**Summary**

Plant tropane alkaloids atropine and scopolamine are very strong anticholinergic drugs used in medicine and also found their place in military medicine, in particular atropine as an antidote in case of poisonings by nerve gases. Atropine and scopolamine both easily penetrate the blood-brain barrier and may cause central nervous system toxicity. Its symptoms are delirium, restlessness, confusion, and impairment of mental capacities. Scopolamine is much more likely to produce sedation and amnesia than atropine. Synthetic atropine-like compounds are also strong anticholinergics, and found use as a modern type of chemical weapons that incapacitate enemy for some time, but do not kill him. They are so-called non-lethal weapons, which are able to temporarily disable personnel from combat action and to protect the environment without limiting desired negative consequences to the enemy's national economy. Such non-lethal weapons is Agent BZ.

*Key words: Tropane alkaloids; atropine; scopolamine; Agent BZ; non-lethal weapons*

## INTRODUCTION

Atropine (hyoscyamine) is plant alkaloide and together with scopolamine they are the predominant anticholinergic tropane alkaloids in the *Datura* genus, occurring in all plant organs. Atropine and related tropane alkaloids are widespread in the plant kingdom and their medicinal and recreational properties have been well known to many cultures for many centuries (Brighetti, 1966). Plants in the genus *Datura* (family *Solanaceae*), which produce the tropane alkaloids, have well deserved sinister reputations for being poisonous (Le Strange, 1977). Among the most important plants which produce tropane alkaloids, these are especially *Atropa belladonna* (Deadly nightshade), *Datura stramonium* (Jimson weed or thom apple), *Hyoscyamus niger* (henbane), and *Mandragora officinarum* (common mandrake).

## BOTANICS AND ETHNOBOTANCS OF THE TROPANE ALKALOIDS PRODUCING PLANTS OF THE FAMILY *SOLANACEAE*

Plants which produce tropane alkaloids are native to Europe, North Africa, and Western Asia. Its distribution extends from Great Britain in the west to western Ukraine and Iran in the east. It is also naturalised and/or

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introduced in some parts of Canada and the United States. These have a long history of use as medicine, cosmetic, and poison (Buess, 1952). All grow like weeds in nature and are easily accessible.

### *Atropa belladonna* (Deadly Nightshade)

*Atropa belladonna*, commonly known as deadly nightshade, is a perennial plant in the *Solanaceae* family whose leaves and berries are extremely toxic. The name Atropa comes from one of the three Fates of Greek mythology: Lachesis measured the thread of destiny at birth, Clotho spun it, controlling destiny and Atropos cut the thread of life, bringing death. This plant containing toxic tropane alkaloids such as atropine and scopolamine. These toxins cause hallucinations and delerium, which is why it has long been used as poison, however belladonna has been used medicinally since ancient times as a muscle relaxant and is also used to regulate the heart and pain (Ramoutsaki et al., 2002).

Deadly nightshade is an herbaceous perennial. It grows to a height of 1.5 m and has branched stem with oval shaped, pointed leaves on alternate sides. In the early summer it produces brownish, tubular flowers, which, over ensuing months, turn into hard green fruit that then ripes to dark purple and shiny black (Fig. 1). All parts of the plant are poisonous and are a potent source of atropine (Ylinen et al., 1986).

**Figure 1.** Flowering shrub of deadly nightshade (*Atropa belladonna*). Photo © Romana Jelinkova.

The plant was well known to the Ancient Greeks and it is a strong candidate for the potion that the sorceress Circe administered to the sailors on Odysseus' ship. This subsequently drove them mad and 'turned them into swine'. Odysseus resisted the poison by taking the antidote 'moli' which was probably either the snowdrop (*Galanthus nivalis*) or the snowflake (*Leucojum vernum*) (Lee, 1999). The deadly nightshade was also an important plant in the witches' pharmacopoeia and it was regarded as one of the Devil's favourite plants. Nightshade was a constituent of their flying ointments (sorcerors pomade). This was rubbed into the skin and genitals and the witch

would then experience delusions, hallucinations and sometimes sensations of levitation or flying. Sexual arousal could also ensue together with orgasm (Lee, 2007).

### *Datura stramonium* (Jimson Weed, Devil's snare, Thorn Apple)

*Datura stramonium* is an extremely poisonous plant of the nightshade family (Urich et al., 1982). Currently growing everywhere from the tropics to the temperate zone. This plant is native to Central America but is found as a naturalised weed in entire Europe. In the Czech Republic it grows scattered from the lowlands to the foothills. It is a foul-smelling, erect, freely branching herb that forms a bush up to 60 to 150 cm tall.The leaves are pointed at the edges and yellowish at the base. The flowers are white trumpets, 10-cm long, and the fruits are green, spiny ovals, hence the name 'thorn apple'. These split to reveal numerous black seeds. Tropane alkaloids are concentrated in the seeds although all parts of the plant are poisonous (Friedman and Levin, 1989; Gaie et al., 2013). The name Jimson weed commemorates the event when settlers arrived to Jamestown Island, Virginia in 1607 and found the island overrun by this weed. Many of them ate the plant and died after experiencing delusions, convulsions and respiratory silure (Fowler, 2015).

Datura stramonium is attributed with both poisonous and medicinal values. It contains varieties of toxic tropane alkaloids such as atropine, hyoscamine, and scopolamine (Abdelouahab et al., 2011). In Ayurveda, it has been used for curing various ailments including wounds, inflammation, rheumatism, sciatica, swellings, fever, and asthma. A wide range of medicinal values has been attributed to this plant. Different studies reported safety and toxicity aspects while other studies reported analgesic, anti-inflammatory, anti-viral, anti-diarrheal, etc. activities of different extracts of the plant (Parveen et al., 2016).

### *Hyoscyamus Niger* (Henbane)

*Hyoscyamus niger* is an annual or biennial that grows to 75 cm and has a thick stem and toothed leaves. The plant is hairy and sticky and has an unpleasant smell. It produces flowers near the top of stems that are yellow with purple veins. The fruit hardens into spines and remains on the plant throughout winter. The whole plant is highly poisonous, containing a mixture of tropane alkaloids (Aparna et al., 2015).

*Hyoscyamus niger* is one of the drugs of Ayurvedic materia medica known as Parasika Yavani, which is mainly used for respiratory disorders. It is used in Ayurvedic system of medicine for treating insomnia, psychiatric disorders, epilepsy, swelling, pain, and breathlessness. Some of the chief constituents found in the drug are hyoscyamine, apoatropine, hyoscine, skimmianine, scopolamine, and belladonines. Various experiments proved antihistaminic, antipyretic, antimicrobial, antispasmodic, analgesic, antiinflammatory, antiallergic and sedative property of the drug (Begum et al., 2010; Aparna et al., 2015).

### *Mandragora officinarum* (Mandrake, Common Mandrake, Devil's Apples, Love Apple)

*Mandragora officinarum* is indigenous to Northern Italy, Western Balkans, Greece and Western Turkey, but can be cultivated in sheltered conditions in the United Kingdom. It is a perennial that produces a rosette of dark green leaves emerging from ground in spring, which are initially upright and then lie flat. It produces tubular bell shaped flowers in spring that are followed by spherical yellow fruit (Hawkes, 1972).

Mandrake has a long history of medicinal use, although superstition has played a large part in the uses to which it has been applied. The root is hallucinogenic and narcotic. In sufficient quantities, it induces a state of unconsciousness and was used as an anaesthetic for surgery in ancient times (Berry and Jackson, 1976). The special chemical properties of its root may have enhanced its reputation as highly desirable for its magical powers. The roots we so desirable that the rumours were spread abroad saying that when the root was pulled from the ground, a scream would be emitted that would kill any human who heard it. Thus it was that ingenious schemes were designed for a dog to be tied to the root and when called from a safe distance, pulled it up for its owner (Conway, 2016).

## TROPANE ALKALOIDS

Atropine and scopolamine lead the tropane alkaloids uses in medicine. Both alkaloids belong to a class of natural chemicals and secondary plant metabolites that contain a tropane ring in their chemical structure. Both tropane alkaloids have pharmacological properties and can act as anticholinergics or stimulants. Atropine and scopolamine are very strong anticholinergic drugs used in medicine (Tian et al., 2015).

Atropine and scopolamine are among the most commonly used muscarinic antagonists in anethesia. Scopolamine and atropine both easily penetrate the blood-brain barrier and these two alkaloids have long been known to produce undesirable side effects ranging from stupor (scopolamine) to delirium (atropine). Scopolamine and atropine may cause central nervous system toxicity. Its symptoms are delirium, restlessness, confusion, and impairement of mental capacities. Scopolamine is much more likely to produce sedation and amnesia than atropine, but scopolamine doesn't produce amnesia in all patiens (Van Deuren and Missotten, 1979; Stone et al., 1988).

Tropane alcaloids (including calystegins) are present in many plant genera as *Anthocercis*, *Brugmansia*, *Datura*, *Hyoscyamus*, or *Solanaceae*, and today we have known for more than one hundreds of these alkaloids. However, atropine and scopolamine retain a privileged position, therefore this review article devoted primarily to these two natural substances and their synthetic derivatives with a similar pharmaceutical effect (Grynkiewicz and Gadzikowska, 2008)

### Atropine

Atropine (CAS Registry Number 51-55-8) is alkaloid which occurs naturally in a number of plants of the nightshade family including deadly nightshade, Jimson weed, and mandrake (Brust, 2004). It was first isolated in 1833 (Roberts, 1998). Atropine is used in medicine and is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system (WHO, 2014). Atropine is ester of bicyclic amine tropane-3α-ol and tropic acid. The asymmetric α-carbon of tropic acid allows the formation of two stereoisomers. It is racemat (the mixture of S- and D-enantiomer). In plant sources only S-enantiomer (S-hyoscyamine, Fig. 2) is present but during the isolation, alkaloid is subjected to racemization. Atropine is used in medicine usually in the form of salt with sulfuric acid (atropine sulfate). Atropine is a widely used drug in the form of eyedrops, solutions for intravenous administration, and auto-injectors for nerve agent intoxication.

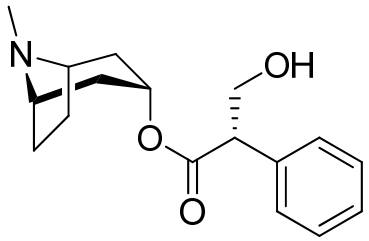


**Figure 2.** Chemical structure of hyosciamine.

### Atropine hypersensitivity

Atropine hypersensitivity is a rarely reported condition (Dundee and Mirakhur, 1978; Giala MM, Tzovairi-Tsakona, 1978; Economacos and Kanakis, 1981). However, in the military environment, such reactions are of significant concern given the threat of chemical warfare and the use of atropine as a nerve agent antidote. Upon deployment to regions where chemical attacks are a threat, each service member is issued three 2-mg intramuscular autoinjectors of atropine for self-treatment. Sensitivity testing revealed a significant reaction to <0.03 mg of intradermal atropine. This rarely reported reaction, in the military environment, poses a unique question regarding the suitability of deploying military members to areas where exposure to chemical warfare agents is possible (Hague and Derr, 2004).

**Atropine in treatment of organophosphate nerve agent intoxication**

Atropine is the drug of choice for treatment of organophosphate nerve agent and insecticide intoxication and has been used for this indication for several decades. Organophosphate nerve agents and insecticides are extremely toxic chemicals that exert their biological effects by inhibition of the enzyme acetylcholinesterase. The inhibited enzyme cannot hydrolyze mediator of cholinergic system – acetylcholine – resulting in the accumulation of this neurotransmitter in the muscarinic and nicotinic cholinergic synapses, and overstimulation of the cholinergic system (Geyer et al., 2009). Atropine is a competitive inhibitor of the muscarinic acetylcholine receptor. It blocks the effect of excess acetylcholine and protects the receptor from further stimulation. It has a minimal effect at nicotinic receptor site.

Exposure to organophosphorus (OP) chemicals has always been a potential poisoning threat to military personnel, however, this threat is now a growing concern for the civilian population today as well. Intoxication by OP chemicals can occur in instances of intentional and accidental release. OP chemicals are known inhibitors of acetylcholinesterase (AChE), resulting in increased acetylcholine levels in brain tissue and peripheral nerves that can lead to increased secretions, fasciculations, seizures, convulsions, respiratory distress, and death. Generally, OP chemical warfare nerve agents, such as sarin, soman, and VX, are much more toxic than bioactivated OP pesticides, such as paraoxon or chlorpyrifos-oxon, even though the mechanism of toxicosis via cholinolergic hyperstimulation of parasympathetic nerves is the same.

Since the onset of toxic effects of OP is very quick, you must be submitted as soon as possible a suitable antidote. The primary components of the currently fielded therapies are (a) a competitive muscarinic receptor antagonist, atropine, to mitigate the excitotoxic effect at post-synaptic targets (Shutt and Bowes, 1979) and (b) an AChE oxime reactivator, to augment OP dissociation from and reactivation of inhibited AChE. The combination of these two therapeutic strategies aims to reduce the hyperstimulation of parasympathetic nerves that results from the over-accumulation of acetylcholine (Eyer, 2003). For use in emergency and pre-hospital settings, two-component autoinjector devices were developed (Bajgar, 2010).

During more than five decades, pyridinium oximes have been developed as therapeutic agents used in the medical treatment of poisoning with organophosphorus compounds (Jokanović and Prostran, 2009). Their mechanism of action is reactivation of AChE inhibited by OP agents. Presently, a combination of atropine, AChE reactivator such as one of the standard pyridinium oximes (pralidoxime, trimedoxime, obidoxime, HI-6) and diazepam has been used for the treatment of organophosphate poisoning in humans (Kuca et al., 2007).

**Atropine in autoinjector as a source of children poisoning**

It is unlikely that children are poisoned by atropine contained in an auto-injector, because this military material is or should be well guarded. Yet it happened. Automatic atropine injectors were distributed in Israel during the Persian Gulf Crisis as an antidote for chemical warfare agents. Over a period of 4 months, 268 cases of children poisoning after misuse of automatic atropine injectors were reported. The most common site of injection (75%) was the finger or palm. Doses were up to 17-fold higher than standard doses for age. In 116 children (48%), systemic effects of atropine were observed, and 20 (8%) had severe atropinization. Seizures and life-threatening arrhythmias were not reported, and there were no fatalities. Serum atropine levels (6.2 to 61.0 ng/mL) were much higher than those observed after administration of therapeutic doses (Amitai et al., 1992).

The article of Israel authors (Kozer et al., 2005) shows that the problem of atropine poisoning from automatic injectors in children still persists. Data collected from calls to the Israel Poison Information Center (IPIC) during a one-year period, and a cohort of children who were presented to pediatric emergency departments after unintentional injection of an automatic injector, summarized 142 patients. The median age was 8.5 years (range 1.25-18 years). The dose of atropine and TMB-4 was higher than the recommended dose for age in 22 (15.5%) cases. There were few side effects attributable to atropine: dilated pupils (26.7%), dryness of mucous membranes (24.6%), and tachycardia (22.5%). There were no side effects characteristic to oximes, and no specific medical intervention was required.

**Scopolamine (hyoscine)**

Scopolamine (CAS Registry Number 51-34-3) (1R,2R,4S,7S,9S)-9-methyl-3-oxa-9-azatricyklo[3.3.1.02,4]non-7-yl ester of tropic acid. Scopolamine was first isolated from *Scopola carniolica* in 1881 and later on identified also in *Hyoscyamus niger* (Soban et al., 1989). Scopolamine is main tropane alkaloid in *Datura* sp. Like (-)-hyoscyamine also (-)-scopolamine easily forms racemic mixtures when being extracted (Kitagawa et al., 2000).

Scopolamine is an anti-muscarinic agent with central and peripheral actions. It crosses the blood-brain barrier, and its central action differs from that of atropine in that it depresses the cerebral cortex, especially the motor areas, and produces drowsiness and amnesia. It is effective in prevention and control of motion sickness and has also been given as an anti-emetic in the prophylactic treatment of other forms of nausea (Reynolds, 1996). Scopolamine was used in medicinal products for a specific range of indications. Particularly its derivative n-butylscopolamine bromide is regularly used in the treatment of abdominal pain associated with cramps induced by gastrointestinal spasms (Tytgat, 2007).

Scopolamine is used for premedication in anesthesia and for prevention of nausea and vomiting associated with motion sickness. Pharmacokinetics and pharmacodynamics of scopolamine depend on the dosage form. Scopolamine has a limited bioavailability if administered orally. Because of its short half-life in plasma and dose-dependent adverse effects (in particular hallucinations and the less serious reactions, eg, vertigo, dry mouth, drowsiness), the clinical use of scopolamine administered orally or parenterally is limited. To minimize the relatively high incidence of side effects, the transdermal dosage form has been developed (Wilkinson , 1987; Renner et al., 2005).

**Scopolamine in the treatment of soman intoxication**

Experiments in animal models suggest that scopolamine may be highly effective in the treatment of soman intoxications (Anderson et al., 1997; Philippens et al., 2005; Bonhange et al., 2009). Because soman intoxication is not treatable by conventional means antidotes, used in other OP intoxication (Bajgar, 1996), this finding is very signifiant (Koplovitz and Schulz, 2010). Scopolamine is also effective in the adjunctive treatment of poisoning by other OP agents (sarin) (Krivoy et al., 2004), and because it can be administered in aerosolized form, nasal drug delivery is a potential treatment option for mass casualty under field conditions (Che et al., 2011; Perkins et al., 2011).

**Scopolamine-induced memory impairments**

Memory impairment is a common symptom in patients with neurodegenerative disorders, and its suppression could be beneficial to improve the quality of life of those patients. Scopolamine as a nonselective centrally active muscarinic antagonist has been frequently used used to model aspects of the memory impairment of normal aging and of dementia (Molchan et al., 1990). Scopolamine is used as a memory impairment model to produce memory and cognitive dysfunctions (Jamialahmadi et al., 2013; Souza et al., 2013; Hosseini et al., 2915; Karimi et al., 2015; Mohammadpour et al., 2015).

## ATROPINE-LIKE CHEMICAL WARFARE AGENTS

Atropine-like drugs are pharmacologically classified as muscarinic receptor antagonists, which compete with acetylcholine for a common binding site on the muscarinic receptor. This binding prevents acetylcholine from binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, heart muscle, glands, peripheral ganglia and at centrally active antagonists mainly in the CNS (McDonough and Shih, 2007), where they act as psychotomimetics (Fusek et al., 2015).

**Psychotomimetic Chemical Weapons**

In the 1950s, a number of anticholinergic drugs with psychotomimetic effect, were investigated for potential industrial and military use. The research of these substances was attributed to the increasing interest of the US military in exploring chemical warfare agents which were non-lethal but incpacitating (Streda and Patocka, 2014).

Non-lethal weapons are weapons which are explicitly designed and developed to incapacitate or repell personnel, with a low probability of fatality or injury (NATO, 1999). Psychotomimetic chemical weapons are acting on the mind. These substances administered in low doses (<10 mg) cause conditions similar to psychotic disorders or other symptoms emanating from the CNS, for example loss of feeling, paralysis, rigidity, etc. These effects are transitory and cause inability to make decisions and incapacitation. Investigations in the USA have shown that an important group of substances with a psychotomimetic effect is the group of esters of glycolic acid (glycolates). Particular interest was paid to 3-quinuclidinyl benzilate, code-named Agent BZ. The effects of this group of substances are similar to those caused by atropine. BZ causes poisoning at doses of 0.5-5 mg. Peripheral symptoms such as distended pupils, deteriorated short-distance vision, dry mouth and palpitations occur after about 30 minutes (Misik, 2013).

**Agent BZ**

Agent BZ (CAS Registry Number 651-06-2, Agent Buzz, EA 2277, Ro 2-3308, QB, QNB, 3-quinuclidinyl benzilate, Fig. 3) is white, odorless crystalline solid which is absorbed mainly via oral route, or respiratory system when dispersed as aerosol. BZ was first synthesized by Hoffman-LaRoche as a possible ulcer remedy and originally as studies for the therapy of gastrointestinal diseases (Ketchum, 2006). But even in small doses, it produces unpleasant side effects (confusion a hallucination). BZ easily crosses the blood-brain barrier and interacts with all subtypes of muscarinic receptors responsible for various central effects. Onset of anti-cholinergic signs is rapid, observed immediately after subcutaneous injection of high doses or several min after low doses (Liu et al., 1984).

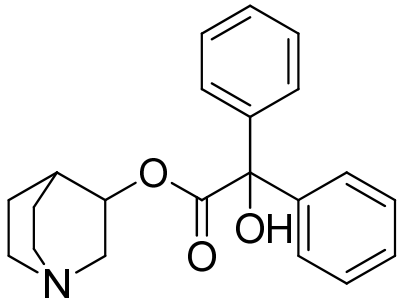


**Figure 3.** Chemical structure of Agent BZ (3-quinuclidinyl benzilate).

BZ is a non-selective, competitive agonist of cholinergic receptor. Similarly as atropine or scopolamine, BZ competes with neuromediator acetylcholine at muscarinic receptors in both, central and peripheral sites. A serious effect of poisoning with BZ, as also with other atropine-like substances, is increased body temperature. Central effects are connected with psychotomimetic incapacitating signs such as e.g. confusion, disorientation or delusions, and may result into unpredictable and irrational behaviour (Sidell, 1982). Therefore, BZ was withdrawn from com-mercial studies and turned over to the US army as a possible candidate for incapacitating agents (Hoenig, 2007). US Army begins experimenting with BZ as an incapacitant in 1958 (Lee and Shlain, 1985).

Action of BZ is expected to be long-lasting with significant behavioral effects within 24 hours in rats. A noticeable, but non-significant, behavioral effect was observed even 7 days after administration (Kunesova et al., 2008). The mean duration of incapacitation is considered to be about 70 hours in a man and may remain 1-3 weeks after the poisoning (Fusek et al., 2015). Since the effect of glycolates was found to be difficult to predict, interest in continued research into this type of substance gradually decreased.

Biphasic effect of BZ observed in animals (Liu et al., 1984) has the same course as in humans. The first stage, which lasts up to 4 hours in a man, is characterized by hyperactivity, muscle spasms, feelings of unrest and discomfort. The second stage, lasting up to 4 to 12 hours is connected with sedation and inactivity. Complex hallucinations continue 24 to 48 hours post exposure. Low effective dose (ED) expected to induce incapacitation in a man is 0.006 - 0.01mg.kg$^{-1}$ (i.m.) (Fusek et al., 2015).

**Analogues of BZ**

A number of analogues of BZ have been synthesized and their affinities to muscarinic receptor from rat or dog ventricular muscle were measured (Rzeszotarski et al., 1982). Their *in vitro* competition studies show that the affinities lie within a 270-fold range, from the highest affinity compound, 3-quinuclidinyl α-hydroxy-α-cyclopentylphenyl acetate, to the lowest affinity compound, 3-quinuclidinyl α-hydroxy-α-2-propargylphenyl acetate.

**N-Methyl-3-piperidyl benzilate** (CAS Registry Number 3321-80-0, JB-336, Fig. 4) is an anticholinergic drug related to the chemical warfare agent 3-quinuclidinyl benzilate (Rump et al., 1967). It is less potent and shorter acting than BZ and LSD (Bajgar et al., 1971; Kabes et al., 1971). Radiolabelled versions of this drug are used in scientific research to map the distribution of muscarinic acetylcholine receptors in the brain (Takahashi et al., 1999).

**N-Ethyl-3-piperidyl benzilate** (CAS Registry Number 3567-12-2, JB-318, Fig. 4) is an anticholinergic drug related to the chemical warfare agent 3-Quinuclidinyl benzilate (Ostfeld et al., 1959). This analogue of BZ is less potent and shorter acting than BZ, but like BZ its effects on the central nervous system predominate over peripheral effects (Lebovits et al., 1960; Ostfeld, 1961). It produces deliriant and hallucinogenic effects similar to those of plants such as datura and may be used recreationally at low doses; however, unpleasant side effects such as dysphoria, nausea and vomiting, dizziness and extreme dry mouth tend to make abuse of drugs of this kind uncommon (Menozzi and Scarlato, 1964; Nishiyama et al., 2001). Radiolabelled versions of this drug are used in scientific research to map the distribution of muscarinic acetylcholine receptors in the brain (Nishiyama et al., 2001). Both the N-methyl and N-ethyl analogues of 3-piperidyl benzilate are, however, Schedule I controlled drugs.

**Ditran** (CAS Registry Number 8015-54-1, JB-329, Fig. 4) is an anticholinergic drug mixture, related to the chemical warfare agent BZ (Gershon and Olariu, 1960). Ditran is an anticholinergic drug with hallucinogenic properties causing intense mental confusion. It is composed of a mixture of 70% 1-ethyl-2-pyrrolidinylmethyl-α-phenylcyclopentyl glycolate and 30% 1-ethyl-3-piperidyl-α-phenylcyclopentyl glycolate (Hollister et al., 1960). These compounds are structural isomers and have very similar pharmacological properties. The piperidine compound is the more potent of the two and the reason the mixture was used was because of ease of manufacture, however it is also possible to make the piperidine compound in its pure form, so there were ultimately two forms of Ditran used in research, the original 70/30 mix, and "Ditran-B", the pure piperidine compound (Burchard, 1962; Davis et al., 1964). Ditran was developed during chemical weapons research in an attempt to produce non-lethal incapacitating agents, similar to BZ itself. The ditran mixture is more potent as an anticholinergic than the piperidyl benzilate drugs such as N-methyl-3-piperidyl benzilate, but is less potent than BZ (Baryshnikov et al., 1968).

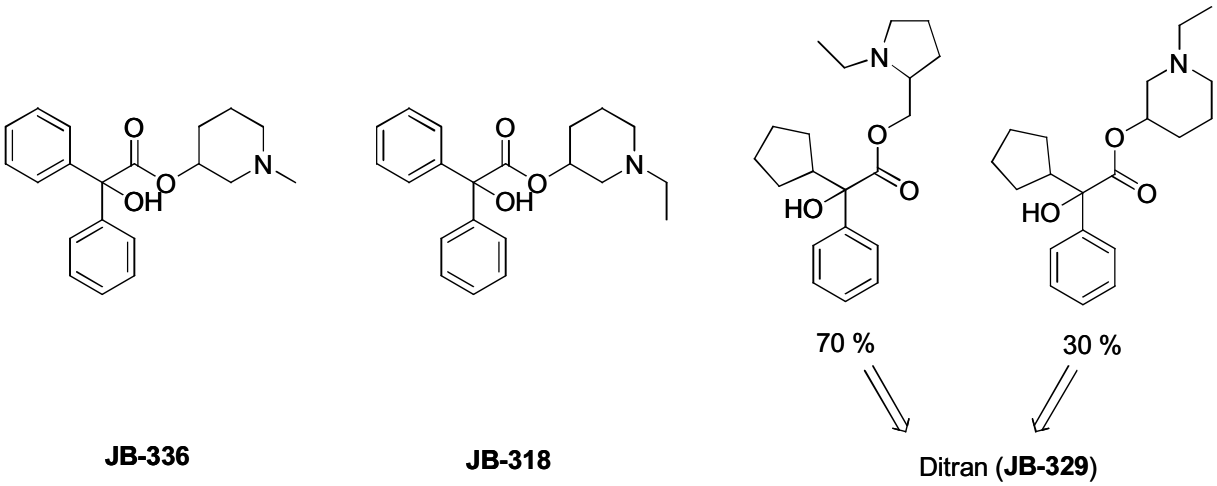


**Figure 4.** Chemical structures of JB-336, JB-318 and JB-329.

## CONCLUSIONS

Atropine and similar substances will still have its place in the general medicine and they are also in military medicine. Anticholinergics are also playing an increasingly important place in psychiatry. Problematic issue remains the possible misuse of centrally acting anticholinergics as psychologically debilitating substances. These could be exploited in war and in terrorist activities.

## DISCLOSURE STATEMENT

The authors proclaim that they have no competing interests.

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## ABBREVIATIONS

HI-6 (1-[[[4-(aminocarbonyl)pyridinio]methoxymethyl]-2-[(hydroxyimino)methyl]-pyridinium dichloride)

LSD Lysergyl diethylamide, (6aR,9R)- N,N-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-fg]chinolin-9-karboxamid

TMB-4 Trimedoxime, 1,3-bis-(4-hydroxyiminomethylpyridinium)propane dibromide

VX Ethyl ({2-[bis(propan-2-yl)amino]ethyl}sulfanyl)(methyl)phosphinate

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