# Evaluation of the pharmacoeconomics of drugs used for the treatment of long-term complications of sulfur mustard

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## ABSTRACT

Sulfur Mustard (SM), a cytotoxic vesicant chemical warfare agent, has powerful irritant and blistering effects on the skin, eyes and respiratory tract. Since during the Iraq-Iran war, many Iranian soldiers and civilians were exposed to SM, there are several victims still suffering from long-term cutaneous, ocular and pulmonary complications. Currently, there is no definite treatment for long-term complications of SM, and only supportive medical care is being taken to minimize the symptoms. In this study, we compared the cost-effectiveness of common drugs that are used against long-term SM-induced complications in Iranian patients. In this review article, electronic databases were checked using the following key words: sulfur mustard, lung, skin, eye, cost-effectiveness, pharmacoeconomics and treatment. Abstracts of non-English papers and proceedings of congresses on SM were also assessed. Among the studied drugs, high-dose oral N-acetyl cysteine and long-acting inhaled corticosteroids against respiratory complications, topical corticosteroids and oral antihistamines against cutaneous complications and non-steroidal anti-inflammatory drugs and corticosteroids ophthalmic drops against ocular complications were found to be cost-effective. Usage of different drugs in the treatment of SM injuries in Iran, have imposed a significant economic burden to patients and their families because many drugs that are effective against chemical injuries are not covered by insurance. In addition, the development of more effective drugs in this field is considered as an urgent demand that should be noticed by the pharmaceutical industry.

## Introduction

Sulfur Mustard (SM) is an alkylating agent widely used in chemical warfare. For the first time, SM was used by the German military forces at Ypresin in September 1917 during World War I. More recently, SM was used in the Iraq-Iran war (1980-1988). The world's first city in which civilians were attacked with chemical weapons was Sardasht which is located in the North West of Iran.[1]

When SM is released into the air, it can be transferred by wind affecting people over a vast area. SM can enter our body by inhalation, absorption from the skin or through the anterior surface of the eyes and also through the gastrointestinal tract from contaminated food or water. The effects depend on the severity and duration of the exposure and usually become apparent about 12 h after the exposure. SM-induced mortality is usually low and in severe cases, death can occur 4-5 weeks after the exposure. Only very high doses of SM (64 SM/kg dermal exposure or 1500 SM/min×m$^3$ inhalation) are acutely fatal in humans in a time interval as short as one hour. Fatality rates among the exposed soldiers during World War I and casualties of the Iran-Iraq war were about 2% and 3-4%, respectively.[2]

During the Iran-Iraq war, many Iranian military personnel and civilians were exposed to SM. There is no definite treatment for long-term complications of SM, and SM-poisoned individuals receive supportive medical care that minimizes the effects of the expo-

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sure. The aim of the current study was to compare a cost-effectiveness of drugs that are being commonly used against long-term complications of SM in Iranian patients.

## Methods of research

All studies published until June 2013 that focused on the treatment of lung, skin and eye injuries following SM exposure, were included. Publications were obtained from the following electronic databases: Medline/Pubmed, Scopus, Google Scholar, Embase, ISI Web of Knowledge, Biological Abstracts and Chemical Abstracts. To include all of the studies indexed in electronic databases, keywords such as sulfur mustard, lung, skin, eye, cost-effectiveness, treatment and pharmacoeconomics were used. Subsequently, therapeutic approaches for SM-induced pulmonary, skin and eye injuries were analyzed. Also, in this study, efficient prophylactic/therapeutic measures against acute and long-term SM-induced pulmonary damages are classified. To evaluate the cost-effectiveness of the drugs, the prices of medications that are being commonly used against SM-induced pulmonary, dermal and ocular complications were also studied. Parameters of clinical efficacy of common drugs were obtained from the literature and local standard costs, adverse events, and micro/macrovascular complications were considered in this regard. Drug prices were provided by the ministry of health and medical education of Islamic Republic of Iran (www.behdasht.gov.ir), Iran health insurance organization, Social security organization of Islamic Republic of Iran (www.tamin.ir) and Social organization of the armed forces of Islamic Republic of Iran. Prices (updated in June 2013) are reported in Rials.

## Lung injury

Respiratory system is an important target of SM and if it is injured by SM, higher morbidity and mortality will be expected.[1] The greatest discomfort produced by SM is the respiratory system injury.

### Acute lung injury

Few weeks after SM exposure, the common cause of discomfort and fatalities is respiratory system irritation and injury.[3] Respiratory effects are dose-dependent and can be seen in all parts of the respiratory system from the nasal mucosa to the terminal bronchioles. As SM has a high chemical activity, most of the acute injuries are limited to the upper respiratory tract.[4]

Recovery from the acute injury can be rapid but some irritation, cough, and huskiness may persist for about 6 weeks. However, a 1-2-month delay in recovery happens mostly after secondary infections and necrotic bronchopneumonia.[3]

### Chronic lung injury

Respiratory problems are the most common long-term consequences observed among patients with SM exposure. Three years after SM exposure, a triad of cough, expectoration and dyspnea was shown in most of Iranian victims.[5]

Chronic obstructive pulmonary disease is more common than restrictive patterns.[5] Chronic laryngitis, tracheobronchial stenosis, tracheobronchomalacia, chronic bronchitis, emphysema, bronchiectasis, pulmonary fibrosis, bronchiolitis obliterans and asthma are well-known chronic consequences of SM exposure among Iranian victims. However, alveolar microlithiasis, mediastinal emphysema and unilateral lung collapse may infrequently occur.[1,2]

Unlike other chronic effects of SM, pulmonary dysfunctions worsen over time.[2] Major causes of SM-induced morbidity and mortality are bronchial pneumonia and septicemia secondary to opportunistic infections of the injured respiratory tract.[3,6] Also, a single exposure to SM may increase the risk of lung cancer in some individuals.[7]

## Management of respiratory toxic effects and cost-effectiveness of drugs used in the treatment of sulfur mustard-induced respiratory complications

Lung injuries due to SM are associated with protease activation, oxidative injury and inflammatory responses. Previous studies on SM demonstrated the role of oxidative stress in SM toxicity and suggested antioxidant agents as effective treatments to decrease injuries. Chronic bronchitis is the most common chronic respiratory disease in SM-exposed Iranians.

Study of Ghanei *et al.* on SM-exposed patients who had chronic bronchitis and were not responsive to standard treatments in exacerbation occasions, showed that there was a significant improvement in spirometric indices of patients receiving short-term intravenous or oral corticosteroids.[8]

In another study, results revealed that a 6-month treatment with interferon-gamma-1b in combination with low-dose prednisolone improves lung function tests in SM-exposed patients who had bronchiolitis.[9] Ghanei *et al.* suggested that inhaled corticosteroids and long-acting β2-agonists are effective in the treatment of SM-exposed patients who had chronic bronchiolitis. Also, a medium dose of fluticasone/salmeterol had the same effects on the airways.[10]

As previous studies revealed, oxygen species and free radicals contribute to pulmonary damages caused

by SM. So, it will be useful to consider antioxidant drugs in the management of these injuries. N-acetyl cysteine (NAC) is a mucolytic drug with antioxidant activities. Prescription of NAC may be effective in the treatment of diseases caused by reactive oxygen species. Shohrati *et al*. showed that 4-month administration of NAC (1800 mg daily) can improve clinical outcomes and spirometric findings in SM-exposed patients.[11]

Ghanei *et al*. in a study on SM-induced bronchiolitis obliterans with normal pulmonary function test, revealed that a 4-month trial of oral NAC is effective against bronchitis and also bronchiolitis. They reported that NAC prevented SM-induced oxidative stress, and can be used in the treatment of pulmonary diseases in SM-exposed patients.[12]

Another study confirmed previous results and revealed that the instillation of liposomes containing reducing agents like NAC can significantly reduce acute lung injury even when instillation was delayed as long as 1 hour after the exposure of lungs to SM.[13] Dyspnea is one of the most important complaints of SM-exposed patients with chronic obstructive pulmonary disease. Shohrati *et al.* showed that nebulized morphine can improve dyspnea, coughing, respiratory rate, heart rate, night-time awaking secondary to dyspnea, night-time awaking due to coughing and peak expiratory flow rate without any important side effects.[14]

Also, it was shown that inhalation of furosemide is not different from placebo in improving dyspnea due to pulmonary diseases in SM-exposed patients. So, it was suggested that SM-exposed patients who had chronic bronchitis or bronchiolitis, may not benefit from furosemide to improve dyspnea.[15] Increased airway responsiveness to β-agonists is noted in asthmatics and smokers. Also, increased airway responsiveness to salbutamol in most subjects exposed to chemical warfare agents, was shown.[16]

In Table 1 we compared costs of the drugs that are being commonly used against respiratory complications of SM in Iran. Also, we compared the efficacy of drugs based on previous studies.[16]

As shown in Table 1, previous studies on the efficacy of NAC against respiratory complications of SM reported promising results as NAC could reduce the respiratory symptoms in SM-exposed patients. NAC is covered by health insurance of the armed forces of Iran and is of low price for veterans. For this reason, NAC has a high cost-effectiveness in Iranian SM-injured subjects. Inhaled corticosteroids are another group of drugs that have reasonable effects in this respect. β-agonists, despite the lower price, do not have significant effects on respiratory symptoms in SM-exposed subjects and many patients are resistant to the therapeutic effects of this class of drugs.

Some of the mentioned drugs including interferon-gamma have high prices and are not affordable for patients despite excellent efficacy. Studies on the efficacy of macrolides (azithromycin, clarithromycin and erythromycin) showed that this group of drugs has good effects on inflammatory complications of SM and reduces symptoms but they (specially clarithromycin) have higher prices as compared to more common drugs and the insurance coverage does not compensate this difference. Prednisolone and similar drugs, despite their low cost and high effectiveness, have many side effects. Therefore, among the listed drugs, NAC appears to have the highest cost-effectiveness.

## Skin injury

### Acute skin injury

Several hours after SM exposure, dermal symptoms become visible. The intensity of lesions depends on the SM concentration. The characteristics of SM skin lesions are erythema and blisters (small vesicles). Rubbing these blisters can produce new blisters. Erythema and sometimes itching occur 2-8 h after exposure. Blisters appear 4-18 h after exposure. Gradually, blisters join together to form the characteristic pendulous blisters containing large volumes of a clear yellow fluid. Usually, blisters are not painful but they may be uncomfortable, feel tense and cause difficult movement and pain if they appear over the joints.[17,18]

These yellow liquid-filled blisters will merge together to form larger bullae. Rupture of the large blisters can cause full-thickness skin loss and ulceration followed by formation of a necrotic layer or scar on the skin surface about 72 h after the exposure.[19,20] Two weeks after milder SM exposure, the erythematous areas of skin become hyper-pigmented without other skin lesions. Also, hypo-pigmentation can occur during healing. The burns caused by high-dose exposures are very painful and the full-thickness of skin can be lost.[17,21]

SM-induced burns heal more slowly than a thermal burn wound. SM burns healing latency depends on the burnt surface area. In mild burnings, lesion may be only an erythema, which turns black in about 10-15 days.[22]

In Iranian SM victims, skin lesions were categorized as erythematous form, pigmentary exfoliation, superficial vesicular to bullous form, bullous necrotization, deep necrotizing non-bullous form, and allergic and toxic contact reactions of the skin. The most usual acute skin lesions in the Iraq-Iran war victims were erosions, erythema and hyperpigmentation.[23,24]

### Chronic skin injury

Chronic skin injury after SM exposure usually happens in those with a background of blister formation and skin necrosis. The injuries can be disfiguring and impair the quality of patient's life.[25]

**Table 1. Prices and efficacy of medications used in the treatment of respiratory complications of sulfur mustard.**

| Drug name | Dosage form(s) | Cost (Iran Rials)* | Dose | Design of study/ interventions/ participants | Clinical manifestation | Paraclinical test(s) | Time of survey | Result of study | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Sildenafil | Tablet 100 mg | 7500 | 50 mg daily | 20 patients with a history of mustard gas poisoning and PAH symptoms | PAH symptoms (presence of minimum pulmonary artery pressure of 30 mmHg) | TEE<br>6-MWT | 12 weeks | Effective | [16] |
| NAC | Effervescent tablet - 600 mg | 3150 | 1800 mg daily | 144 patients with bronchiolitis obliterans due to sulfur mustard in bronchiolitis obliterans syndrome (BOS) classes 1 and 2, randomly entered Group 1 (n=72, NAC) and Group 2 (n=72, placebo) | Dyspnea, wake-up dyspnea, cough, and sputum | Spirometry (FEV1, FVC, FEV1/FVC, PEF, MMEF)<br><br>Impaired PFT | 4 months | Effective | [16] |
| Cromolyn sodium<br>Prednisolone<br>Beclomethasone Dipropionate<br>Ipratropium bromide<br>Azithromycin<br>Prednisolone | Inhalant capsule<br>Tablet 50 mg<br>Spray 10 mg/cont<br><br>Inhaler 20 µg/dose<br><br>Capsule 250 mg<br>Tablet 5 mg | 30,000<br>6000<br>40,000<br><br>35,000<br><br>500<br>300 | Inhalation every 4 h<br>50 mg daily PO<br>9 puff every 8 h<br><br>7-8 puff every 8 h<br><br>250 mg daily<br>12.5 mg daily | 30 patients with bronchiolitis due to sulfur mustard in, treated with 2 protocol:<br>- Protocol 1: full dose corticosteroid (cromolyn sodium, prednisolone 50 mg, beclomethasone, ipratropium bromide)<br>- Protocol 2: azithromycin + prednisolone 12.5 mg | Dyspnea, wake-up dyspnea, cough, and sputum | Spirometry (FEV1, FVC, FEV1/FVC, PEF, MMEF)<br>HRCT | 8 weeks | Protocols 1 and 2 were ineffective | [16] |
| Clarithromycin<br><br>Acetylcysteine | Tablet 250 mg<br><br>Effervescent tablet - 600 mg | 3000<br><br>3150 | 500 mg QD<br><br>600 mg QD | 17 patients with bronchitis and bronchiolitis obliterans due to sulfur mustard treated with clarithromycin + acetylcysteine | Chronic cough, sputum | Spirometry (FEV1, FVC, FEV1/FVC, PEF, MMEF) | 6 months | Effective<br><br>Effective | [16] |
| Methyl prednisolone<br><br>Prednisolone | Vial IV<br><br>Tablet 5 mg | 15,000<br><br>300 | 500 mg daily<br><br>1 mg/kg daily | 65 mustard gas-exposed chronic bronchitis patients divided in 2 groups:<br>- Group 1: 26 patients treated with oral prednisolone<br>- Group 2: 39 patients treated with intravenous methylprednisolone | Exacerbation of chronic bronchitis | Spirometry (FEV1, FVC, FEV1/FVC, PEF, MMEF) | 8 days | Effective<br><br>Effective | [16] |

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**Table 1. Continued from previous page.**

| Drug name | Dosage form(s) | Cost (Iran Rials)* | Dose | Design of study/ interventions/ participants | Clinical manifestation | Paraclinical test(s) | Time of survey | Result of study | Reference |
|---|---|---|---|---|---|---|---|---|---|
| N-acetylcysteine | Effervescent tablet - 600 mg | 3150 | 1200 mg daily | 144 patients with bronchiolitis obliterans due to sulfur mustard and bronchiolitis bliterans syndrome class 0 randomly entered to group 1 (n=72, N-acetylcysteine) and group 2 (n=72, placebo) | Bronchiolitis obliterans (dyspnea, wake-up dyspnea, cough) | Spirometry (normal pulmonary function test) | 4 months | Effective | [16] |
| Interferon-gamma-1b | Vial IV | 500,000 | 200 mg subcutaneously three times per week<br>200 mg subcutaneously three times per week | 36 exposed to mustard gas:<br>- Group 1: 18 patients (interferon gamma-1b + prednisolone)<br>- Group2: 18 patients (previous conventional medications)<br>36 exposed to mustard gas:<br>- Group 1: 18 patients (interferon-gamma-1b + prednisolone)<br>- Group 2: 18 patients (prednisolone + salbutamol + beclomethasone) | Bronchiolitis<br>Bronchiolitis | Spirometry (FEV1, FVC)<br>Spirometry (FEV1, FVC) | 6 months<br>6 months | Effective<br>Effective | [16]<br>[16] |
| Air:oxygen<br>Helium:oxygen | 2 L portable oxygen capsule<br>2 L portable oxygen capsule | 1,450,000<br>1,980,000 | 79% air:21% oxygen<br>79% helium: 21% oxygen | 24 mustard gas-exposed patients:<br>- Group 1: 12 patients (air:oxygen)<br>- Group 2: 12 patients (helium:oxygen) | Acute respiratory failure (severe dyspnea) | Systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate, oxygen saturation | 45 min | Less effective<br>More effective | [16] |
| Fluticasone propionate<br>Salmeterol<br>Beclomethasone<br>Salbutamol | 0.05% nasal spray<br>Inhaler 50 mcg per dose<br>Inhaler 100 µg/dose<br>Inhaler 100 µg/dose | 167,000<br>80,000<br>70,000<br>66,000 | 500 µg daily<br>100 µg daily<br>1000 µg daily<br>800 µg dail | 105 mustard gas-exposed patients:<br>- Group 1: 52 patients (fluticasone propionate + salmeterol)<br>- Group 2: 52 patients (beclomethasone + salbutamol) | Dyspnea, night awakening due to dyspnea, cough | PFT: FEV1, FVC, FEV1/FVC%, and PEF | 12 weeks | Fluticasone propionate + salmeterol were more effective/ beclomethasone + salbutamol were less effective | [16] |
| Salbutamol | Inhaler 100 µg/dose | 66,000 | 800 µg daily | 22 exposed to chemical warfare (Group 1: 11 and Group 2: 15):<br>- Group 1: PC(20) salbutamol<br>- Group 2: PC(35) salbutamol | Airway hyper response | 20% change in FEV(1) as PC(20), or a 35% change in specific airway conductance (sGaw) as PC(35) | - | Effective | [16] |

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**Table 1. Continued from previous page.**

| Drug name | Dosage form(s) | Cost (Iran Rials)* | Dose | Design of study/ interventions/ participants | Clinical manifestation | Paraclinical test(s) | Time of survey | Result of study | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Erythromycin | Tablet 400 mg | 1200 | 400-600 mg daily | 43 patients with SM exposure were refractory to the bronchodilators and corticosteroids | Dyspnea, sleep disturbance, cough and hemoptysis | 5-point Likert-type scale, ranging from 0 to 4 | 6 months | Might be helpful in management of bronchiolitis obliterans | [16] |
| Morphine sulfate | Ampule 10 mg/mL | 3500 | 1 mg morphine sulfate diluted in 4 cc normal saline 0.5% using nebulizer once daily | 40 patients with SM exposure (G1: received morphine sulfate/ G2: received placebo) | Dyspnea | PEF using pick flow meter, VAS for dyspnea, cough, RR, night time awaking for dyspnea | 5 days | Effective | [16] |

*Prices are reported in Rials (the currency of Iran). PAH, pulmonary arterial hypertension; TEE, trans esophageal echocardiography; 6-MWT, 6-min walking test; NAC, N-acetyl cysteine; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory force; MMEF, maximum midexpiratory flow; HRCT, high resolution computed tomography; PFT, pulmonary function test; VAS, visual analysis scale; RR, respiratory rate.

Studies revealed that hyperpigmentation, hypopigmentation and dermal scar are the three most common late skin consequences of SM exposure. Also, local hair loss, eczema and chronic urticaria could be seen. Common skin complaints of these patients were itching, burning sensation and desquamation. These are because of dryness of the skin as they become worse in dry weather and after physical activity. Several years after exposure, pruritus was still the most common symptom.[2,19,26]

The most common skin conditions 16-20 years post-exposure to SM were hyperpigmentation, erythematous papular rash, dry skin, multiple cherry angiomas, atrophy, hypopigmentation, and hypertrophy.[19]

A higher incidence of vitiligo, psoriasis and discoid lupus erythematous was reported among SM-exposed patients.[27] SM has an adverse effect on immune system and these diseases have an immunological basis.[28] Also, it has been reported that injured sites are sensitive to mechanical stimuli.[2] The incidence of skin cancers after SM exposure is low and it is not clear whether skin malignancies are associated with SM carcinogenicity.[21]

## Management of skin complications of sulfur mustard and cost-effectiveness of drugs

Erythema, burning, and itching develop after dermal exposure to SM. Cooling these sites relieves the symptoms. Also, hypothermia may lessen the severity of SM-induced cutaneous lesions.[29]

Pain can be treated with analgesics, like acetaminophen and opioids. Anti-histamines and local corticosteroids are useful to reduce itching.[17] Small vesicles should not be opened; but, it is better to remove the top of larger blisters and apply a sterile dressing on them because of their susceptibility to rupture.[30]

In SM-exposed patients, chronic skin lesions are common and pruritus is the most common complaint, which affects the patients' quality of life. Panahi *et al.* showed that a combination of phenol and menthol has a significant therapeutic effect on pruritus in SM-exposed victims.[31]

Another study by Panahi *et al.* revealed that curcumin (a bioactive polyphenol from turmeric[32-49]) might be considered as a natural, safe and inexpensive treatment for SM-induced chronic pruritus. Also, they showed that curcumin could improve the quality of life of the victims.[36,50-52]

In another study, Shohrati *et al.* compared the effect of Unna's Boot cream and betamethasone on pruritus severity in SM-exposed subjects who had chronic cutaneous complications. They showed that there is no significant difference in the improvement of pruritus between the two drugs. Since long-term and widespread use of corticosteroids has restrictions and

because of limited adverse effects of Unna's Boot cream, Unna's boot seems to be a more reasonable agent for long-term treatment of SM-related pruritus as compared to betamethasone.[53]

Shohrati *et al.* also showed that hydroxyzine and doxepin had equal results on SM-induced pruritus but they had better effects in comparison with cetirizine in controlling the symptoms of chronic pruritus.[54,55]

Moreover, topical pimecrolimus and betamethasone were shown to be effective in controlling pruritus, burning sensation and also skin dryness but the severity of vesicle, erythema, fissure, lichenification, excoriation, hyperpigmentation and hypopigmentation did not decrease significantly following the administration of the afore-mentioned drugs. Also, they did not report any serious side effects during their study.[56] Panahi *et al*. reported equal efficacy for doxepin and betamethasone, and suggested that doxepin can be a potential alternative to betamethasone in controlling SM-induced pruritus.[57]

In a study conducted by Panahi *et al*., results revealed that *Aloe vera*/olive oil combination cream was as effective as betamethasone in the treatment of SM-induced chronic skin complications.[58]

In another study, the efficacy of immunotherapy using interferon-gamma (IFN-γ) in the treatment of SM-Induced chronic cutaneous complications was compared with topical betamethasone and the results showed that treatment with IFN-γ was associated with greater reductions in atopic dermatitis scores and improvements in life quality, as compared to betamethasone. The authors proposed that application of IFN-γ can be effective against SM-induced chronic skin complications.[59]

Additionally, the effects of capsaicin and betamethasone were compared and results revealed that both drugs can significantly decrease pruritus and skin dryness in SM-exposed patients but burning sensation was not improved in capsaicin-treated group. The results also showed that capsaicin topical cream was much less tolerated than betamethasone and also its effect on reducing chronic skin lesions was lesser than that of betamethasone.[60]

In a study done by Panahi *et al*., some of the patients who received capsaicin, reported a burning sensation and intolerable odor, but these effects were not serious enough to stop the treatment. Capsaicin topical cream 0.025% was much less tolerated than betamethasone and inferior to betamethasone in reducing SM-induced chronic skin lesions and related symptoms.[60]

Panahi *et al.* in another study on chronic pruritus in SM-exposed patients reported that curcumin may be regarded as a natural, safe, widely available and inexpensive treatment for the management of SM-induced chronic pruritus.[60]

As shown in Table 2,[60] antihistamines such as hydroxyzine and doxepin have lower prices and higher efficacies than Unna's Boot and capsaicin cream. Topical corticosteroids also have lower prices than Unna's Boot and capsaicin cream but it should be noted that the efficacies of these drugs are lower.

## Eye injury

### Acute eye injury

The most responsive organs to SM are eyes. It happens because of the high cellular turnover and intense metabolic activity of the corneal epithelial cells and also enhanced penetration through the aqueous-mucous surface of the cornea and conjunctiva. The latent period of initial signs and symptoms are shorter than those seen for skin effects and occur within minutes after attack.[61,62] Acute intoxication causes conjunctivitis, grittiness under the eyelid, tearing, local edema, blepharospasm, lacrimation, miosis, photophobia and severe eye pain. Conjunctivitis due to mild exposure to SM heals within a few days. At higher doses, full-thickness corneal injury, long-lasting chronic inflammation, delayed-onset lesions, chemical anterior uveitis, posterior synechiae, cataract and permanent blindness are probable (Table 3).[18,19,30,63,64]

### Chronic eye injury

Complaints during chronic phase include itching, burning sensation, photophobia, tearing, decreased vision, dry eye, red eye, ophthalmic pain and foreign body sensation.[19,63,65] An important ocular phenomenon known as delayed-type ulcerative keratitis may happen in some cases. It is characterized by corneal thinning, opacification, neovascularization and epithelial deficiency leading to photophobia, lacrimation, failing vision and late-onset blindness. Javadi *et al.* reported that delayed-type ulcerative keratitis usually develop in patients with multiple systemic injuries.[19,61,63] The pathogenesis of this chronic phenomenon is not clear, but formation of free radicals, by-products toxicity, necrotic changes, damage of the limbal vasculature and autoimmune reactions have been mentioned as possible causes and mechanisms.[62,63,66-68]

## Management of eye complications of sulfur mustard and cost-effectiveness of drugs

About 48 h after exposure to SM, spontaneous recovery occurs gradually even without treatment and the corneal epithelium is fully healed within a week. If the edema subsides by 1-2 weeks, usually recurrence does not occur.[19,64] The eyes should be washed immediately after exposure even for asymptomatic pa-

**Table 2. Pharmacoeconomic evaluation of the medications used in the treatment of skin complications of sulfur mustard.**

| Drug name | Dosage form(s) | Cost (Iran Rials)* | Dose | Design of study interventions/ Participants | Clinical manifestation | Clinical or paraclinical test | Period of survey | Result of study | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Menthol | Bulk | 9600 | 1% solution, twice a day | 80 mustard gas (mg) exposed patients with chronic skin lesion<br>Group 1: phenol+menthol<br>Group 2: placebo | Pruritus<br>Skin dryness<br>Burning sensation | Pruritus score (1-48 points)/VAS | 6 weeks | Effective | 60 |
| Phenol | Bulk | 14,000 | 1% solution, twice a day | | | | | Effective | |
| Doxepin | Capsule 10 mg | 900 | 10 mg daily | 75 MG exposed patients with chronic skin lesion<br>Group 1: doxepin (25 patients)<br>Group 2: hydroxyzine (25 patients)<br>Group 3: cetirizine (25 patients) | Refractory chronic pruritus | Pruritus score (1-48 points)/VAS | 4 weeks | More effective than hydroxyzine and cetirizine | 60 |
| Hydroxyzine | Coated tablet 10 mg | 100 | 25 mg daily | | | | | Effective | |
| Cetirizine | FC tablet 10 mg | 400 | 10 mg daily | | | | | Effective | |
| Unna's boot | Topical cream | 300,000 | 1 fingertip (equal to 0.47 g in males and 0.42 g in females) every night | 75 MG exposed patients with chronic skin lesion divided in 3 groups:<br>- Group 1: betamethasone<br>- Group 2: Unna's boot<br>- Group 3: placebo | Refractory chronic pruritus | Pruritus score (1-48 points)/VAS | 3 weeks | Effective | 60 |
| Betamethasone | Topical cream 1% | 7000 | 1 fingertip each night | | | | | Effective | |
| Pimecrolimus | Topical cream 1% | 400,000 | 1 fingertip BID | 70 MG exposed patients with chronic skin lesion:<br>- Group 1: betamethasone (35 patients)<br>- Group 2: pimecrolimus (35 patients) | Pruritus/skin dryness/ burning sensation/ hypo-hyper pigmentation/vesicle/ erythema/ fissure/ lichenification/ excoriation | Pruritus score (1-48 points)/VAS | 6 weeks | Effective on pruritus/ skin dryness/burning sensation<br>Non effective on hypo-hyper pigmentation/ vesicle/erythema/ fissure/ lichenification | 60 |
| Betamethasone | Topical cream 1% | 7000 | 1 fingertip BID | | | | | Effective on pruritus /skin dryness/burning sensation | |
| Doxepin | Capsule 10 mg | 900 | 10 mg/d | 50 SM exposed patients with chronic pruritus | Chronic pruritus (1-48 points) | Pruritus score | 4 weeks | Effective | 60 |
| Hydroxyzine | Coated tablet 10 mg | 100 | 25 mg/d | | | | | Effective | |
| Capsaicin | Topical cream 0.025% | 300,000 | 2 times a day | 64 SM exposed patients (32 applied capsaicin/32 betamethasone) | Chronic pruritus | Pruritus score (1-48 points)/VAS | 6 weeks | Effective on pruritis/ non effective on burning sensation | 60 |

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**Table 2. Continued from previous page.**

| Drug name | Dosage form(s) | Cost (Iran Rials)* | Dose | Design of study interventions/ Participants | Clinical manifestation | Clinical or paraclinical test | Period of survey | Result of study | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Doxepin hydrochloride | Topical cream 5% | 600,000 | Twice a day | 75 SM exposed patients (40 applied doxepin topical cream/35 applied betamethasone topical cream 0.1%) | Chronic pruritus, burning sensation, dryness, skin scaling | Pruritus score (1-48 points)/VAS | 6 weeks | Equal efficacy of doxepin topical cream and betamethasone | 60 |
| Aloe vera/olive oil | Topical cream | 300,000 | Twice a day | 67 SM exposed patients (31 applied aloe vera-olive oil/32 applied betamethasone 0.1%) | Chronic pruritus | Pruritus score (1-48 points)/VAS | 6 weeks | Aloe vera/olive oil topical cream was effective as betamethasone 0.1% | 60 |
| Curcumin | Capsule | 10,000 | 1 g/d | 96 SM exposed patients (Group 1: 46 curcumin/ Group 2: 50 placebo) | Chronic pruritus | Pruritus score, VAS and SCORAD index/serum concentrations of substance P and activities of antioxidant enzymes | 4 weeks | Effective | 60 |

*Prices are reported in Rials (the currency of Iran). VAS, visual analysis scale; MG, mustard gas; SM, sulfur mustard; SCORAD, scoring atopic dermatitis.

**Table 3. Pharmacoeconomic evaluation of the medications used in the treatment of eye complications of sulfur mustard.**

| Drug name | Dosage form(s) | Cost (Rials of Iran)* | Dose | Authors, year | Design of study/ interventions/ participants | Clinical manifestation | Clinical or paraclinical test | Treatment duration | Main findings | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| Dexamethasone | Strile ophthalmic /optic drop 0.1% | 5000 | Q6h 1 drop | Amir *et al.*, 2000 | Rabbit eyes were exposed to SM vapor (390 μg $L^{-1}$ for 2 min) and were treated with a topical commercial ophthalmic solution | Neovascularization, recurrent erosions and recurrent edema of the cornea | PGE in anterior chamber/ Light microscopy evaluation (epithelial denudation, edema, stroma cellular infiltration) | Starting 1 h post-exposure | No therapeutic effect on corneal erosions/short delay in epithelial regeneration/ potential candidates for the treatment of ocular lesions | 19 |
| Diclofenac sodium | Strile ophthalmic drop 0.1% | 7000 | Q6h 1 drop | | | | | | | |
| Betamethasone | Strile ophthalmic drop 0.1% | 6500 | Q6h 1 drop | Naderi *et al.*, 2009 | 25 New Zealand white rabbits were divided into 4 groups of normal (Group 1: not exposed to SM or solution/ Group 2: exposed to solution/ Group 3: exposed to SM/ Group 4: received eye solution of betamethazone) | Eye closure, eyelid swelling, conjunctival hyperemia, corneal erosions and inflammation | Ocular morphometric characteristics/light microscopy erosion | 2 weeks | Decrease in changes in number of keratocyte thickness of cornea and corneal epithelium, changes in Meibomian gland's palpebral conjunctival epithelium and palpebral skin (μm), and number of goblet cells in conjunctival sac | 19 |

*Prices are reported in Rials (the currency of Iran). PGE, prostaglandin E; SM, sulfur mustard.

tients. As SM has a rapid and irreversible reaction with ocular tissue components, it may be useless to start washing after 10-15 min post-exposure.[2,19] Mild ocular injury could be treated with soothing eye solution used several times a day. Vaseline can prevent sticking of the eyelids together and is also useful to maintain drainage of ocular fluid. Topical antibiotics and mydriatics can prevent formation of synechiae.[2,19,30] According to Kadar *et al*., only topical anti-inflammatory drugs have the criteria of an efficient post-exposure ocular treatment for SM injuries.[69]

In a study conducted by Gordon *et al.* on the effect of doxycycline on the injury of rabbit corneal organ cultures, results showed that eyes treated with doxycycline had better results than those received no therapy. Additionally, corneal thickness decreased somewhat faster using doxycycline drops, but the administration hydrogel formulation of doxycycline decreased the neovascularization.[70] In another study, results showed that silibinin, a non-toxic natural flavanone, and a combination of doxycycline and dexamethasone are effective, more than doxycycline or dexamethasone alone, on SM analogue-induced ocular injuries by reversing epithelial thickening, microbullae formation and apoptotic cell death. Their results also showed strong multifunctional efficacy of silibinin in reversing SM-induced ocular injuries, which make it an effective and safe treatment for ocular injuries due to SM exposure.[71] Another study on the effect of polyethylene glycol (PEG)-based doxycycline hydrogels on wound healing efficacy of doxycycline in SM analogues-exposed rabbit corneas in organ culture showed that doxycycline-PEG hydrogels accelerate corneal wound healing after vesicant injury.[72]

To date, there has been no definite treatment for SM-induced delayed keratopathy. However, artificial tears, therapeutic contact lenses, local/systemic corticosteroids and other immunosuppressive drugs such as azathioprin may be used according to keratitis severity.[19]

## Conclusions

Reasonable prescription of drugs for respiratory, skin and ocular complications of SM needs awareness of the economic conditions of patients and cost-effectiveness of medications. Since patients have poor compliance with expensive drugs, it is not recommended to use costly and less effective medications for the treatment of SM complications. Unfortunately, many of the effective medications are not covered by the social insurance of armed forces especially for chemical injuries and these patients are not able to afford the necessary medications such as interferon-gamma and some of the effective topical creams. Health Policy should pay more attention to provide subsidized medications for chronic diseases like chronic complications of SM. For this reason, it is recommended that future studies evaluate the efficacies and costs of different brand name and generic drugs in relieving chronic complications of SM-exposed subjects. Finally, it is worth noting that the current available evidence is not strong enough to allow judgment on the efficacy of drugs in reducing the occurrence of hard outcomes in patients suffering from chronic respiratory complications of SM. Hence, future outcome trials are warranted to enable a better cost-effectiveness and pharmacoeconomic evaluation.

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