Schwarz Y, et al., J Pulm Med Respir Res 2019, 5: 021
DOI: 10.24966/PMRR-0177/100021

HSOA Journal of Pulmonary Medicine & Respiratory Research

Research Article

Safety Versus Toxicity of Inhaled Dextromethorphan in the Mice: Hematological, Biochemical and Histological Approaches

J Yehuda Schwarz[1], Alexander N Star[1], Amir Barshay[1], Silvia Marmor[2] and Avi A Weinbroum[3]*

[1]*Department of Pulmonary Medicine, Tel Aviv Sourasky Medical Center and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

[2]*Department of Pathology, Tel Aviv Sourasky Medical Center and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

[3]*Department of Animal Laboratory, Tel Aviv Sourasky Medical Center and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

Abstract

Background: Dextromethorphan (DM), an antitussive, was previously proven to effectively reduce cough when pre-medicating patients before bronchoscopy. The purpose of this study was to evaluate the safety vs. toxicity of inhaled DM in animals.

Methods: Female BALB/c mice were exposed to repeatedly administered aerosolized DM of 1 or 10mg/kg (safety phase) or 1, 60 or 360mg/kg (toxicological phase). Control animals were exposed to 0.9% NS-based aerosol. At the end of each series of treatments histological, hematological and toxicological analyses were performed on collected samples.

Results: Treatment-related microscopic lesions were observed only in the lungs, ranging from negligible to severe and diffused alveolar damage (DAD). These findings were detected 5 days after the end of 5-session trials of the 10mg/kg dose and 24 h after 15 inhalations of the toxic doses, respectively. The 1mg/kg dose was innocuous. No damage was detected after single sessions; nor were there biochemical or hematological pathologies detected in any of the groups.

Conclusion: A direct correlation may exist between DM dosing and the resulting severity of lung histopathological damage. Additional variables inducing it were multiplicity of inhalations and the time elapsing between the last session of inhalation and the pathological findings of DAD. The single dose of 1mg/kg DM, that is above the clinically accepted DM oral dose, proved safe in the tested animals.

Keywords: Dextromethorphan; Inhalation; Lung; Safety; Toxicity

***Corresponding author:** Avi A. Weinbroum, Department of Animal Laboratory, Tel Aviv Sourasky Medical Center and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, Tel: +972 35440904; Fax: +972 35440904; Email: draviw@tasmc.heatlh.gov.il

Citation: Schwarz Y, Star AN, Barshay A, Marmor S, Weinbroum AA (2019) Safety Versus Toxicity of Inhaled Dextromethorphan in the Mice: Hematological, Biochemical and Histological approaches. J Pulm Med Respir Res 5: 021.

Received: December 5, 2018; **Accepted:** February 12, 2019; **Published:** February 26, 2019

Introduction

Dextromethorphan (DM) is a noncompetitive N-Methyl-D-Aspartate Receptor Antagonist (NMDAR-A). DM has been used for many years as an antitussive; its exact pharmacological mode of action is not yet established. We have previously shown that DM improves the overall appreciation of both the patients and the interventionists during bronchoscopy when combined with midazolam vs. the latter alone; DM was effective in suppressing cough induced by bronchoscopy and in reducing lidocaine instillations in these patients [1]. Based on these results, we assumed that inhaled DM, if applied in patients immediately before bronchoscopy, especially when they are on NPO regimen, would equally benefit them. Following this rationale, we aimed at testing the effectiveness of inhaled DM, as could be obtained clinically in a fasting patient scheduled to undergo bronchoscopy.

Nevertheless, it has been previously demonstrated that 10 and 20mg/kg of DM, when administered in rats who underwent superior mesenteric artery clamping-unclamping, attenuated the increase in peak ventilatory pressure by 85%, reduced the PO_2/FiO_2 ratio by 45%, allowed for 4-12-fold increase in bronchoalveolar lavage-retrieved volume, and bettered the polymorphonuclear leukocytes/bronchoalveolar cells ratio [2]. Ischemic-reperfused-40mg/kg DM-treated animals demonstrated worse lung parameters. The lung tissue total xanthine oxidase activity, the reduced glutathione, and the wet-to-dry weight ratio, also remained within normal ranges in the two lower dose-treated groups, as compared to the higher one. The former regimens were also associated with longer post-experimental animal survival vs. the latter, all suggesting DM dose-dependent lung DAD.

This study thus employed non-operated mice inhaling low and high doses of DM, and whose organs and blood samples were investigated after 1, 5 or 15 consecutive sessions.

Methods

Animals

Female BALB/c mice, 6-8 weeks old (Harlan Co., Jerusalem, Israel) were housed in polycarbonate cages with hardwood chip bedding. The animals' rooms were maintained at 20-22°C with relative humidity of 20-50%, and a 12-h light cycle, beginning at 06:00 AM. Rodent diet (Harlan Co., Jerusalem, Israel) and water were provided ad libitum, except during exposure to inhalation. The study protocol was approved by the Institutional Animal Care and Use Committee of the Tel Aviv Sourasky Medical Center, Israel.

Nebulization and Characterization of the Aerosol Particles

Aerosols were generated by Aeroneb Pro nebulizer (Galway, Ireland), applying high frequency vibration through the medication solution, thus creating waves that generate aerosol. Briefly, in 10-mL amounts of 0.9% NS, various doses of DM were loaded into the nebulizer that operated at an airflow rate of 10L/min. The amounts were calculated based on previous calculations of deposition indexes. The Aeroneb apparatus was connected to a filter-covered animal cage, so that the cage "saw" a specific and constant aerosolized solution throughout the exposure.

The sizes of the DM particles were characterized by Mass Median Aerodynamic Diameter (MMAD), their Geometric Standard Deviation (GSD), and the concentration of the aerosolized compound. These were determined using the Cis-100 Analyzer (Stanford Research Systems Inc., Sunnyvale, California, USA) and an analyzer's video channel (Ankersmid, Yokneam, Israel). The Ankersmid video analyzer was connected to the Cis-100 Analyzer, thus allowing to procure the MMAD and GSD characteristics. To determine the concentration of DM in each of the various solutions, aliquots were collected from the Aeroneb Pro apparatus at the end of each session, and were measured by the Cis-100 analyzer.

Study Design

DM aerosol dosing and phases of study: Since no DM-inhaled dose response cumulative safety and toxicity curves exist in the literature, the study consisted of two phases. The first phase looked into the results of inhaled DM at the dose of 1 and 10mg/kg body weight, administered at 1 and 5 consecutive days. All sessions lasted 30mins. The animals were euthanized and the organs were analyzed 5 days after the last session. This phase alluded to clinical use of DM for bronchoscopy. This phase also aimed at investigating the drug's effects several days after treatment, simulating common clinical follow-up. The doses were chosen alluding at clinical proven safety of daily DM's oral dose of approximately 1mg/kg [3].

The second phase consisted of toxicological investigations following DM given at doses of 1, 60, 360mg/kg. Each (30-min) session was repeated 15 times to each animal, 5 times/week. The analyses in this phase were undertaken 24h past the last session each animal underwent. Noteworthy, each phase of the study comprised a control group that was exposed to aerosolize NS only.

The estimated total deposited amounts (D) of the inhaled drug in the solutions were calculated by the following formula [4]:

$$D = C \times V \times DI \times T$$

where C is the concentration of the drug in the aerosol volume (e.g., for 1.0mg/mL concentration of the drug in the nebulizer, C = 15mg/L); V is the volume of air inspired by an animal during 1 min (for mice, V = 1L/min/kg); DI is the estimated deposition index (for mice, the known fraction of inhaled dose deposited throughout the respiratory tract is 0.3); T is the duration of treatment (min). Under the experimental conditions, the estimated total deposition dose of DM during a 30-min session, when prepared at a 1.0mg/mL concentration dose, was calculated to be approximately 0.45mg/kg/session once daily [5,6].

Animal handling and execution: The animals were weighed every other day. While exposed to the aerosol, all mice were placed unrestrained in a sealed plastic cage. Following each exposure, the animals were returned to their original cages and observed for signs of misbehavior, anxiety, or sedation [7,8].

At due time, the animals were weighed, then anesthetized intraperitoneally with ketamine plus xylazine (100mg/kg, 10mg/kg, respectively), and autopsied. Blood samples for clinical chemistry and general hematology were obtained via a direct cardiac puncture. Then, all internal organs were removed, weighed, and were subjected to pathological examinations. Analyses were performed by skilled individuals who were blinded to the protocol the materials were related to.

Hematology and blood biochemistry: Blood cells were counted by an automatic blood cell counter available at the institutional hematology laboratory (Becton Dickinson, Franklin Lakes, NJ, USA) and blood serum ingredients (urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, total protein, albumin, and globulin) were analyzed using an appropriate automated analyzer (Roche Diagnostics Corporation, Indianapolis, IN, USA).

Gross and microscopic pathology: The organs were initially fixed in 10% neutral buffered formalin for histopathological evaluation. After the fixation, the tissues were embedded into paraffin and sections of 5-μm thickness and were stained with hematoxylin-eosin. Whenever organ microscopic lesions were identified, they were graded for severity and evaluated by the pathologists. All histopathological studies were performed by the same protocol-blinded observers.

Statistical Analysis

All numerical values were expressed as mean ± SD. The significance of differences was estimated using the unpaired, 2-tailed Student's t-test. A P value of ≤ 0.05 determined values as significant.

Results

Aerosol Characteristics

The MMAD and the geometric standard deviation (GSD) values of the aerosolized DM were 1.23μm and 3.75μm, respectively. The particles were distributed as expected in aerosolized drugs that pass through small airways [9].

Overall Animal Behavior, Gross Pathology and Blood Analyses Data

Aerosolized NS or any DM treatments were well tolerated by the animals; none succumbed during the period of inhalations or within 24h after it. Similarly, their clinical behavior, especially of the treated animals, did not appear abnormal, distressed or different in response to the increased doses of DM or as the number of sessions piled up.

No significant changes in the animals' and organs' weights were detected at the end of the study (Table 1). The hematological and biochemical analyses that followed both the safety and the toxicity phases of the study were similar among all the groups of animals. Table 2 and Table 3 reflect sampled data.

DM dose	Body	Lungs	Heart	Liver	Spleen	Kidney
NaCl 0.9%	21.9 (20-22.7)	0.25 (0.231-0.278)	0.141 (0.123-0.153)	1.12 (1.132-1.229)	0.111 (0.91-0.125)	0.157 (0.130-0.170)
60mg/kg	21.1 (20-23.3)	0.257 (0.230-0.280)	0.137 (0.120-0.160)	1.113 (1.100-1.380)	0.117 (0.90-0.130)	0.177 (0.150-0.200)
360mg/kg	23.7 (23.1-24.3)	0.267 (0.260-0.290)	0.16 (0.160-0.161)	1.333 (1.250-1.410)	0.127 (0.90-0.170)	0.177 (0.140-0.190)

Table 1: Median body and organ weights (gr) of sampled groups

DM dose	WBC	RBC	Hb	Hct	MCV	MCH	MCHC	RDW
NaCl 0.9%	4.9 (4.1-5.6)	8.8 (7.3-9.2)	12.3 (12.1-13.6)	40.2 (37.7-46.1)	51 (50.5-52.5)	16.1 (15.7-16.9)	32.3 (31.0-31.8)	16.5 (16.1-17.7)
60mg/kg	4.5 (4.4-4.6)	7.8 (7.3-8.2)	12.9 (12.1-13.6)	40.4 (37.7-46.1)	52 (51.7-52.3)	16.6 (16.0-17.2)	31.9 (31.7-32.0)	16.9 (16.7-17)
360mg/kg	5.1 (4.1-6.1)	6.9 (6.9-7.4)	11.3 (10.3-12.3)	35.2 (32.5-37.9)	50.1 (50.2-51.5)	16.3 (15.8-16.7)	32 (31.5-32.5)	16.5 (16.2-16.9)

Table 2: Median hematological parameters of sampled groups.

DM dose	WBC	RBC	Hb	Hct	MCV	MCH	MCHC	RDW
NaCl 0.9%	22.0 (20-26)	0.40 (0.39-0.51)	150 (149-151)	3.7 (3.3-3.5)	121 (118-122)	66.5 (52-92)	32 (24-51)	16.5 (16.1-17.7)
60mg/kg	21.3 (19-28)	0.42 (0.34-0.49)	151 (151-152)	3.4 (3.3-3.5)	123 (119-124)	66.5 (51-82)	34 (22-44)	16.9 (16.7-17)
360mg/kg	23 (20.1-26.3)	0.45 (6.9-7.4)	150.5 (150.3-152.3)	3.87 (3.8-3.9)	119 (117-119)	57 (49-65)	30.5 (27-34)	16.5 (16.2-16.9)

Table 3: Median blood biochemical values in sampled groups.

Histopathology

Gross examination of the internal organs, i.e., lungs, livers, kidneys, spleens, and hearts, resulted normal in all the control animals. Except for the lungs, none of the internal organs in any of the tested groups evidenced micro- or macroscopic changes attributable to DM in either phase of the study. The latter are specified below.

Safety Study Phase: The investigational phases focused on the potential effects of relatively low (safety) vs. high (toxicity) doses of DM. In the safety phase, the control mice (NS inhalation), and the 1mg/kg DM-treated ones, were of similar non-detectable lung lesions, independently of the number of the sessions the animals had undergone. Comparatively, the 10mg/kg animals that were autopsied 5 days after 5 inhalations developed barely detectable DAD (Figure 1), similar to those detected in the 1mg/kg animals that underwent 15 consecutive sessions and that were sacrificed and analyzed 24h after the last session of treatment (Figure 2). Single DM session, of either 1- or 10mg/kg dose, did not induce any lung damage whatsoever (data not shown).

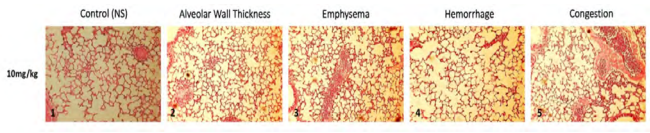

Figure 1: Lung histopathological findings following 5 consecutive DM 10 mg/kg inhalations.

Toxicology Study Phase: Lung damage that followed DM-60mg/kg treatments was characterized by mild thickening of the alveolar walls, appearance of peripheral emphysema, multiple limited intra-alveolar hemorrhagic spots, associated with occasional atelectasis areas, and mild-to-moderate congestion (Figure 2).

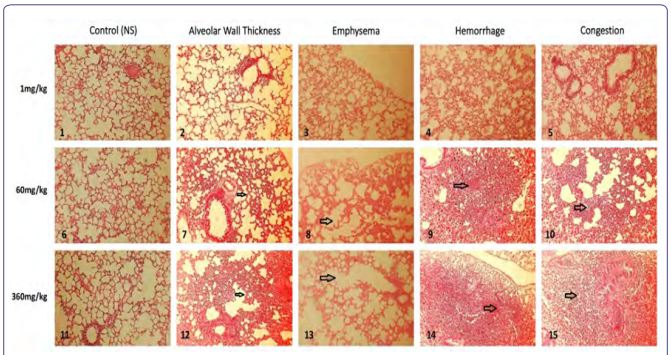

Figure 2: Lung histopathological findings following 15 consecutive inhalations.

Following the use of DM at 360mg/kg for 15 consecutive times, prominent findings of alveolar damage became obvious (Figure 2). These included intense lymphocytes infiltration into alveolar walls, peripherally and centrally-located areas of emphysema, appearance of multiple intra-alveolar hemorrhagic areas, extended atelectasis, and congestion. Noteworthy, the left-sided column, comprising pictures No. 1, 6, and 11, represent the controls for each of the study groups.

Discussion

Past reports have unveiled the usefulness of clinical DM; however, limited pre-clinical data indicate that DM at 40mg/kg IV may cause damage to the lung [1,3]. After this group has proven the usefulness of oral DM in patients undergoing bronchoscopy, we wondered if the drug may induce pulmonary toxicity if administered repeatedly, and if so, does dosage play a role in it [1]. This question was raised since such data neither exists pre-clinically nor clinically. The present results establish possible induction of toxicity following repeated

sessions of aerosolized DM at different dose concentrations in Balb/c mice. Pathological findings were detected in the only lungs, and depicted direct DM dose-time of exposure-reaction period curves. The higher were DM- dose exposures, the number of inhalational sessions (not a single or 5 ones), and the time lag before analyses were performed, the more severe was lung damage that consisted of various lesions that conform to Acute Lung Injury (ALI).

This is the first study of its kind showing tangible correlations between lung damage and three DM variables that appeared to affect it: (1) the higher was the concentration of DM that the animal inhaled, the more severe appeared the damage. The 10mg/kg dose, but not the 1mg/kg, generated minimal histopathological changes; (2) nevertheless, the 10mg/kg-induced changes could be detected only after 5 consecutive sessions but not after a single one; (3) the above traces of damage apparently developed slowly, requiring at least 5 days before their appearance. From the clinical and laboratory aspects of the data, animals did not demonstrate any abnormal behavior, even when the inhaled doses were as high as 60 or 360mg/kg [10]. The detection of lung pathological damage as soon as 24h after the 15-session-exposures, would support the authors' suggestion that both the concentration and the repetition of inhalation are relevant factors, since the 1mg/kg dose administered multiple times was innocuous as were the findings after 5-times inhalations of 10mg/kg.

Many drugs have been associated with pulmonary manifestations of interstitial inflammation and fibrosis, bronchospasm, pulmonary edema, and pleural effusion [11]. Among various medications, chemotherapeutic agents have been reported to exert toxicity-dependent interstitial lung disease (ILD) [12,13]. Drugs can virtually produce all histopathological patterns of interstitial pneumonia, including hypersensitivity pneumonitis, organizing pneumonia, diffused alveolar damage (DAD), eosinophilic pneumonia, pulmonary hemorrhage, and granulomatous pneumonitis [14,15]. The mechanisms by which they occur include both direct and indirect pulmonary toxicity, via inflammatory reactions of various lung components.

The herein presented pathological pattern of post-DM inhalation was consistent with acute interstitial pneumonia that is characterized by intra-alveoli and alveolar septal infiltration of small lymphocytes and varying numbers of plasma cells. The histological basis of acute interstitial pneumonia is the DAD, which is characterized by the appearance of hyaline membranes in the acute stage, and interstitial fibroblast proliferation in the late (organizing) stage. The latter histological feature illustrates the characteristic diffused interstitial thickening. Lung injury further results in sloughing of alveolar epithelial cells, causing the formation of protein-rich hyaline membranes. Neutrophils adhere to the activated capillary endothelium and then migrate into the alveolus and the septae [2]. Loss of alveolar capillary membrane barrier integrity induces the accumulation of a neutrophilic inflammatory exudate in the interstitium and air space.

In addition to hyaline membranes and proliferation of interstitial fibroblasts, several other histological findings are variably present in DAD. These include alveolar collapse/atelectasis, edema within the alveolar septa, thrombi within small pulmonary arteries, mild interstitial chronic inflammation and Diffused Arterial Hemorrhage (DAH) [16-18]. Most of the above pathological features were variably present in the animals that were repeatedly treated with moderate-high aerosol DM concentrations. Contrarily, the lower dosages, as would be the case in clinical practice, did not induce lung damage, even allowing inflammatory reactions which evolve over a 5-day period.

It is yet unclear how DM directly induces a similar inflammatory reactions, unless an intermediary compound is involved, which requires time to recruit it and engineer its action, as demonstrated herein [19]. Overdose-related phenomena derive mostly from post-recreational systemically-used DM; they are related to mild-to-severe central stability and cognitive losses as the dose is acutely consumed [20,21].

Adverse effects associated with abnormally higher than the clinically-recommended antitussive doses, are also rare, but may induce unwanted effects as well, although of different receptor-induced symptomatology. The effects of mega dose (5-10 times the therapeutic dose) are ataxia, abnormal muscle movements, respiratory depression, and dissociative hallucination. Increase in heart rate, blood pressure and body temperature may lead to fatality.

While all the above symptoms were not identifiable in the investigated mice, neither signs of physical disturbances, nor damage to other organs in the body were noted, even after the mega dose (360mg/kg) repeatedly administered. Changes in blood components were neither identified. A limitation of this study may be the lack of long-term follow-up of the animals, although the finding that no damage was noted in any of the internal organs, and the absence of misbehavior of the animals, could minimize the limitation. However, this would be the next step in this dual-phase investigational study of DM.

Finally, a recent study evaluated the antitussive effectiveness of systemically-administered DM in healthy volunteers [22]. Dextromethorphan 30mg was found to attenuate cough sensitivity that was provoked by applying incremental capsaicin challenges, more effectively than four doses of butamirate. It is the opinion of the present authors that inhalational administration of DM would be as therapeutic as (if not superior to) the systemic administration before bronchoscopy, because of its direct effect in the airways. It also may obviate possible systemic bio-pharmacological untoward effects. This latter assertion awaits further confirmation by large-scale RCTs.

Conclusion

The use of dextromethorphan, when inhaled repeatedly in low concentrations, does not seem to induce pathological changes in the lungs, as well as in other organs or on blood components, or apparent clinical signs of animal distress. This provides the contingency that DM is safe inhalationally, before or during clinical bronchoscopy, even if administered more than once. The clinically recommended dose of DM for such purposes is yet to be determined.

Author Contributions

Dr. Yehuda Schwarz and Dr. Alexander N. Star contributed equally in conceiving the design of the study and in drafting of the manuscript. Dr. Amir Barshay was responsible for the analysis and interpretation of the data, provided critical suggestions and revised the manuscript's draft. Dr. Silvia Marmor and colleagues were the histopathologists who analyzed the animals' lesions, while Prof. Avi A. Weinbroum proposed the matter in question, handled the investigation as a whole, and finalized the manuscript.

All authors have read and approved the final version of the manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance With Ethical Standards

- All authors declare no conflict of interest.
- This study was not funded whatsoever.
- This research involved animals only.
- Informed consent: NR.

References

1. Schwarz Y, Greif J, Lurie O, Tarrasch R, Weinbroum AA (2007) Dextromethorphan premedication reduces midazolam requirement: objective and subjective parameters in peribronchoscopy. Respiration 74: 314-319.
2. Ben-Abraham R, Guttman M, Flaishon R, Marouani N, Niv D, et al. (2006) Mesenteric artery clamping/unclamping-induced acute lung injury is attenuated by N-methyl-D-aspartate antagonist dextromethorphan. Lung 184: 309-317.
3. Ben Abraham R, Marouani N, Weinbroum AA (2003) Dextromethorphan mitigates phantom pain in cancer amputees. Ann Surg Oncol 10: 268-274.
4. Koshkina NV, Kleinerman ES (2005) Aerosol gemcitabine inhibits the growth of primary osteosarcoma and osteosarcoma lung metastases. Int J Cancer 116: 458-463.
5. Phalen RF, Mannix RC, Drew RT (1984) Inhalation exposure methodology. Environ Health Perspect 56: 23-34.
6. Koshkina NV, Giovanells B, Roberts LE, Gilbert GE, Knight V (2004) Cyclosporin A aerosol improves the anticancer effect of Paclitaxel aerosol in mice. J Aerosol Med 17: 7-14.
7. Masneuf S, Lowery-Gionta E, Colacicco G, Pleil KE, Li C, et al (2014) Glutamatergic mechanisms associated with stress-induced amygdala excitability and anxiety-related behavior. Neuropharmacology 85: 190-197.
8. Marinho EA, Oliveira-Lima AJ, Santos R, Hollais AW, Baldaia MA, et al (2015) Effects of rimonabant on the development of single dose-induced behavioral sensitization to ethanol, morphine and cocaine in mice. Prog Neuropsychopharmacol Biol Psychiatry 58: 22-31.
9. Imai Y, Miki T, Ishikawa T, Aoki T, Yamaguchi T (2012) Deposition of micrometer particles in pulmonary airways during inhalation and breath holding. J Biomech 45: 1809-1815.
10. Ben Abraham R, Marouani N, Kollender Y, Meller I, Weinbroum AA (2002) Dextromethorphan for phantom pain attenuation in cancer amputees: a double-blind crossover trial involving three patients. Clin J Pain 18: 282-285.
11. Muller NL, White DA, Jiang H, Gemma A, et al. (2004) Diagnosis and management of drug-associated interstitial lung disease. Br J Cancer 91: S24-S30.
12. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, et al. (2003) Severe acute interstitial pneumonia and gefitinib. Lancet 361: 137-139.
13. Okamoto I, Fujii K, Matsumoto M, Terasaki Y, Kihara N, et al. (2003) Diffuse alveolar damage after ZD1839 therapy in a patient with non-small cell lung cancer. Lung Cancer 40: 339-342.
14. Flieder D, Travis W (2004) Pathologic characteristics of drug-induced lung disease. Clin Chest Med 25: 37-45.
15. Nemery B, Bast A, Behr J, Borm PJA, Bourke SJ, et al. (2001) Interstitial lung disease induced by exogenous agents: factors governing susceptibility. Eur Respir J 18: 30S-42S.
16. Ieki R, Saitoh E, Shibuya M (2003) Acute lung injury as a possible adverse drug reaction related to gefitinib. Eur Respir J 22: 179-181.
17. Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, et al. (2006) Predictive factors for interstitial lung disease, antitumor response, and survival in non–small-cell lung cancer patients treated with gefitinib. J Clin Oncol 24: 2549-2556.
18. Higenbottam T, Kuwano K, Nemery B, Fujita Y (2004) Understanding the mechanisms of drug-associated interstitial lung disease. Br J Cancer 91: S31-S37.
19. Yang HH, Hou CC, Lin MT, Chang VP (2012) Attenuating heat-induced acute lung inflammation and injury by dextromethorphan in rats. Am J Respir Cell Mol Biol 46: 407-413.
20. Stanciu CN, Penders TM, Rouse EM (2016) Recreational use of dextromethorphan, "Robotripping"-A brief review. Am J Addict 25: 374-377.
21. Zajac M, Andrzejczyk A, Kuich A, Tyrańska-Fobke A, Waldman W, et al. (2013) Recreational usage of dextromethorphan--analysis based on internet users experiences. Przegl Lek70: 525-527.
22. Faruqi S, Wright C, Thompson R, Morice AH (2014) A randomized placebo controlled trial to evaluate the effects of butamirate and dextromethorphan on capsaicin induced cough in healthy volunteers. Br J Clin Pharmacol 78: 1272-1280.

Journal of Anesthesia & Clinical Care

Journal of Addiction & Addictive Disorders

Advances in Microbiology Research

Advances in Industrial Biotechnology

Journal of Agronomy & Agricultural Science

Journal of AIDS Clinical Research & STDs

Journal of Alcoholism, Drug Abuse & Substance Dependence

Journal of Allergy Disorders & Therapy

Journal of Alternative, Complementary & Integrative Medicine

Journal of Alzheimer's & Neurodegenerative Diseases

Journal of Angiology & Vascular Surgery

Journal of Animal Research & Veterinary Science

Archives of Zoological Studies

Archives of Urology

Journal of Atmospheric & Earth-Sciences

Journal of Aquaculture & Fisheries

Journal of Biotech Research & Biochemistry

Journal of Brain & Neuroscience Research

Journal of Cancer Biology & Treatment

Journal of Cardiology: Study & Research

Journal of Cell Biology & Cell Metabolism

Journal of Clinical Dermatology & Therapy

Journal of Clinical Immunology & Immunotherapy

Journal of Clinical Studies & Medical Case Reports

Journal of Community Medicine & Public Health Care

Current Trends: Medical & Biological Engineering

Journal of Cytology & Tissue Biology

Journal of Dentistry: Oral Health & Cosmesis

Journal of Diabetes & Metabolic Disorders

Journal of Dairy Research & Technology

Journal of Emergency Medicine Trauma & Surgical Care

Journal of Environmental Science: Current Research

Journal of Food Science & Nutrition

Journal of Forensic, Legal & Investigative Sciences

Journal of Gastroenterology & Hepatology Research

Journal of Gerontology & Geriatric Medicine

Journal of Genetics & Genomic Sciences

Journal of Hematology, Blood Transfusion & Disorders

Journal of Human Endocrinology

Journal of Hospice & Palliative Medical Care

Journal of Internal Medicine & Primary Healthcare

Journal of Infectious & Non Infectious Diseases

Journal of Light & Laser: Current Trends

Journal of Modern Chemical Sciences

Journal of Medicine: Study & Research

Journal of Nanotechnology: Nanomedicine & Nanobiotechnology

Journal of Neonatology & Clinical Pediatrics

Journal of Nephrology & Renal Therapy

Journal of Non Invasive Vascular Investigation

Journal of Nuclear Medicine, Radiology & Radiation Therapy

Journal of Obesity & Weight Loss

Journal of Orthopedic Research & Physiotherapy

Journal of Otolaryngology, Head & Neck Surgery

Journal of Protein Research & Bioinformatics

Journal of Pathology Clinical & Medical Research

Journal of Pharmacology, Pharmaceutics & Pharmacovigilance

Journal of Physical Medicine, Rehabilitation & Disabilities

Journal of Plant Science: Current Research

Journal of Psychiatry, Depression & Anxiety

Journal of Pulmonary Medicine & Respiratory Research

Journal of Practical & Professional Nursing

Journal of Reproductive Medicine, Gynaecology & Obstetrics

Journal of Stem Cells Research, Development & Therapy

Journal of Surgery: Current Trends & Innovations

Journal of Toxicology: Current Research

Journal of Translational Science and Research

Trends in Anatomy & Physiology

Journal of Vaccines Research & Vaccination

Journal of Virology & Antivirals

Archives of Surgery and Surgical Education

Sports Medicine and Injury Care Journal

International Journal of Case Reports and Therapeutic Studies

Submit Your Manuscript: http://www.heraldopenaccess.us/Online-Submission.php

Herald Scholarly Open Access, 2561 Cornelia Rd, #205, Herndon, VA 20171, USA.
Tel: +1-646-661-6626; E-mail: info@heraldsopenaccess.us
http://www.heraldopenaccess.us/