# بسم الله الرحمن الرحيم


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# شبكة المعلومات الجامعية

# التوثيق الالكتروني والميكروفيلم

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# جامعة عين شمس

# التوثيق الإلكتروني والميكروفيلم

# قسم

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# "Evaluation of The Effect of N-Acetyl cysteine in the Prevention of Paclitaxel-Induced Peripheral Neuropathy in Cancer Patients"

A Thesis submitted for fulfillment of Master's Degree in Pharmaceutical Sciences (Clinical Pharmacy)

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بسم الله الرحمن الرحيم

قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ"
مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ
" الْحَكِيمُ

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# List of abbreviations

| | |
|---|---|
| **ESBC** | **Early stage breast cancer** |
| **CIPN** | **Chemotherapy induced peripheral neuropathy** |
| **ROS** | **Reactive oxygen species** |
| **PIPN** | **Paclitaxel induced peripheral neuropathy** |
| **NAC** | **N-acetyl cysteine** |
| **GSH** | **Glutathione** |
| **QOL** | **Quality of life** |
| **ER** | **Estrogen receptor** |
| **PR** | **Progesterone receptor** |
| **HER** | **Human epidermal growth factor** |
| **BCS** | **Breast conservative surgery** |
| **DRG** | **Dorsal root ganglia** |
| **NCI-CTACE** | **National common terminology criteria for adverse effect** |
| **mTNS** | **Modified total neuropathy score** |
| **FACT-GOG-NTX** | **The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity** |
| **NGF** | **Nerve growth factor** |
| **MDA** | **Malondialdehyde** |
| **RT** | **Radiotherapy** |
| **BSA** | **Body surface area** |

# Abstract

# Abstract

## Background:

Breast cancer is the most common cancer in women. Currently, the average risk of breast cancer in the United States is about 13% indicating that, one for every eight women has the chance to develop breast cancer. There are different treatment modalities for breast cancer including surgery, radiotherapy, endocrine therapy and chemotherapy. Paclitaxel is a microtubule stabilizing agent that is most commonly used in the treatment of early stage breast cancer patients (ESBC).Paclitaxel can cause painful sensory neuropathy which is a dose-dependent cumulative side effect. Paclitaxel induced peripheral neuropathy (PIPN) occurs in about 60-70% of patients and adversely affect their quality of life (QOL). One of the main pathophysiological mechanism of PIPN is oxidative stress which causes neuronal damage. N-acetyl cysteine (NAC), a powerful antioxidant which might have a protective role against PIPN through oxidative stress reduction and free radical elimination. The aim of the current study was to evaluate the effect of NAC on the incidence and severity of PIPN in ESBC.

## Methods:

A prospective, randomized, controlled, open-label study was conducted on75 early stage breast cancer patients receiving adjuvant paclitaxel 80 mg/m2 weekly for 12 weeks. Patients were included if they were adults >18 years old with adequate bone marrow, kidney, and liver function. Exclusion criteria included clinical and diabetic neuropathy or receiving vitamin supplementations including vitamin B complex. Eligible patients were randomized to either the low dose group who received 1200mg NAC daily, the high dose group who received 1200mg NAC twice daily and the control group who received paclitaxel only. The primary outcome was the incidence of PIPN using the National Cancer Institute's common terminology criteria for adverse event (NCI-CTCAE) while secondary outcomes were the severity of PIPN using modified total neuropathy score (mTNS), QOL using Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-GOG-NTX) subscale, time to develop grade 2,3 peripheral neuropathy, serum nerve growth factor (NGF) and serum malondialdehyde (MDA).

## Results

Final analysis was done on 65 patients. At the end of the 12-week-period, the incidence of grade (2, 3) peripheral neuropathy was significantly lower in the high dose group (28.6%) compared to the low dose group (61.9%) and the control group (100%), *p* value < 0.001.

After 6 and 12 weeks, the total mTNS was significantly lower in the low dose and the high dose group compared to the control group (*p* value < 0.001). Comparisons of mTNS within groups were statistically significant in the three study groups (*p* value < 0.001).The QOL score was statistically different between the three groups after 6 and 12 weeks (*p* value < 0.001). Comparisons of the QOL within groups revealed statistically higher scores of QOL in the three groups (*p* value < 0.001). Serum NGF was significantly higher in the high dose group and serum MDA was lower in the high and the low dose groups.Comparing the low dose group to the control group, the HR was found to be 0.123 (95% confidence interval: 0.055–0.275) while when comparing the high dose group with the control group the hazard ratio was 0.047 (95% confidence interval: 0.017–0.131).

The high dose was considered protective by 95.3% and the low dose by 87.7% as compared to the control group.Only one patient in the high dose group was withdrawn from the study because of acute watery diarrhea with a frequency of 5–7 times per day and abdominal pain. Two patients were withdrawn from the low dose group because of a hypersensitivity reaction with skin rash that necessitated treatment with oral and topical antihistaminic. Other adverse effects reported were tolerable including nausea and vomiting (11 patients), diarrhea (3 patients), constipation (5 patients), and transient skin rash (5 patients).

**Conclusion**

Oral NAC at doses of 1200mg once and twice daily were found to be effective in decreasing the incidence and severity of PIPN in ESBC with improvement in their QOL. Oral NAC was tolerable with minimal side effect.

# Introduction

Breast cancer is the second most common cancer in women with an incidence of 1.5 million cases each year **(Barnard et al., 2015)**. It accounts for 32 % of cancer in Egyptian women **(Ibrahim et al., 2014)**.Treatment of early stage breast cancer (ESBC) includes surgery followed by adjuvant chemotherapy **(Chew, 2001)**. Chemotherapeutic agents, despite being effective in arresting the progression of cancer by targeting and eliminating rapidly dividing cancer cells, they are associated with various side effects with 20-100% of patients develop chemotherapy-induced peripheral neuropathy (CIPN)**(Zhang et al., 2017a)**.

Chemotherapy-induced peripheral neuropathy can be defined as a disturbance of the structure and function of peripheral motor, sensory, and autonomic nerves due to chemotherapy causing peripheral neuropathic symptoms and signs **(Kieffer et al., 2017).** It is a common and dose limiting side effect of several chemotherapy agents, including paclitaxel, one of the adjuvant chemotherapeutic agents used in management of early stage breast cancer **(Kottschade et al., 2011).**

The majority of signs and symptoms of CIPN arise from damage to dorsal root ganglion neurons or their axons, leading to sensory loss, and sometimes sensory ataxia **(Staff et al., 2017).** Sensory disturbances range from a mild tingling sensation to spontaneous burning pain and hypersensitivity to stimuli. These symptoms often affect both hands and feet and may spread into a "glove/stocking "distribution **(Park, 2014)**.Motor symptoms include foot drop, wrist drop and difficulty with fine motor skills, such as buttoning a shirt or holding a pen **(Fernandez et al., 2014).**For some individuals, severe and disabling CIPN symptoms become chronic, impairing their daily function and diminishing their quality of life, this can lead to chemotherapy dosage reductions and/or treatment delays, resulting in sub-therapeutic cancer treatment **(Ellen etal., 2013)**. The most common clinical neurotoxicity associated with paclitaxel is a predominantly sensory peripheral neuropathy which is dose- and infusion-duration related (**Scripture et al., 2006)**.