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Safety profile of Paclitaxel

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Abstract

Pharmacovigilance is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. It heavily focuses on adverse drug reactions (ADRs), serious adverse drug reactions and unexpected adverse drug reactions. Pharmacovigilance is used to establish the safety profile of drugs in humans. The objective of the study was to evaluate Adverse drug reactions associated with Paclitaxel and to compare the two different formulations of Paclitaxel i.e. Nab paclitaxel (albumin bound paclitaxel) and non albumin bound paclitaxel. A total of 91 adverse drug reactions were observed in patients on Paclitaxel therapy and various parameters were analysed including yearly and gender wise ADR distribution by Pacliatxel and Nab paclitaxel, Indication wise use in gender, yearly and gender wise serious adverse drug reactions distribution and System organ class distribution in gender. Nab-paclitaxel (albumin bound paclitaxel) is significantly more effective than paclitaxel formulated as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel), with almost double the response rate, increased time to disease progression and increased survival in patients. The absence of CrEL from the formulation is associated with decreased neutropenia as compared with CrEL-paclitaxel. Nab technology has increased the therapeutic index of paclitaxel and well tolerable as compared with the conventional, solvent-based formulation and thus albumin bound paclitaxel have better safety profile than conventional paclitaxel. The availability of new drugs, such as Abraxane (albumin bound paclitaxel), in association with other traditional and non-traditional drugs will give the oncologist many different effective treatment options for patients.

Key-Words: Pharmacovigilance, Adverse drug reaction, Serious adverse drug reaction, Unexpected adverse drug reaction, Paclitaxel, Nab-paclitaxel, System organ class

Introduction

Pharmacovigilance also known as Drug Safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. Pharmacovigilance heavily focuses on Adverse drug reactions , Serious adverse drug reactions and Unexpected ADRs.[1] ADRs are defined as any response to a drug which is noxious and unintended, including lack of efficacy, which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. Medication errors such as overdose, and misuse and abuse of a drug, are also of interest because they may result in an ADR[2].

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Serious ADR, a serious adverse event or reaction is any untoward medical occurrence that at any dose that results in death, is life-threatening, requires inpatient hospitalisation or results in prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or a medically important event or reaction [3].Unexpected ADR is an ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package Insert or Summary of Product Characteristics) should be considered unexpected[2].

There are multiple reasons for increasing necessity for pharmacovigilance and some of them includes: Insufficient evidence of safety from clinical trials due to strict inclusion/exclusion criteria, subjects usually have single disease, specific groups of children, elderly and pregnant are excluded, small sample size, short duration of trial limit the detection of long term adverse effects, inability to detect ADRs under real conditions as drug-drug and drug-food interactions are not taken in to consideration [4], Trend to convert prescriptional

drugs to over-the-counter (OTC) drugs has excluded the involvement of physicians and pharmacist therefore making the assessment and reporting adverse drug reaction very difficult[4].

Paclitaxel is a mitotic inhibitor used in cancer chemotherapy. It was discovered in a National Cancer Institute program at the Research Triangle Institute in 1967 and was isolated from the bark of the Pacific Yew tree, Taxus brevifolia and named it 'taxol'. When it was developed commercially by Bristol-Myers Squibb (BMS) the generic name was changed to 'paclitaxel' and the BMS compound is sold under the trademark 'TAXOL'. In this formulation, paclitaxel is dissolved in Cremophor EL and ethanol, as a delivery agent. A newer formulation, in which paclitaxel is bound to albumin, is sold under the trademark Abraxane. Paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Chromosomes are thus unable to achieve a metaphase spindle configuration. This blocks progression of mitosis, and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division [5].

Paclitaxel is approved for ovarian, breast and lung, bladder, prostate, melanoma, esophageal, and other types of solid tumor cancers as well as Kaposi's sarcoma. It is recommended in NICE guidance of June 2001 that it should be used for nonsmall cell lung cancer in patients unsuitable for curative treatment, and in first-line and second-line treatment of ovarian cancer. In September 2001, NICE recommended paclitaxel should be available for the treatment of advanced breast cancer after the failure of anthracyclic chemotherapy, but that its first-line use should be limited to clinical trials. In September 2006, NICE recommended paclitaxel should not be used in the adjuvant treatment of early node-positive breast cancer [5]. The FDA recently approved a solvent-free formulation of paclitaxel for the treatment of metastatic breast cancer that utilises 130-nanometer albumin-bound (nab) technology (Abraxane or Pacliall; nab-paclitaxel) to circumvent the requirement for solvents. Clinical studies have shown that nab-paclitaxel is significantly more effective than paclitaxel formulated as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel), with almost double the response rate, increased time to disease progression and increased survival in second-line patients. The absence of CrEL from the formulation is associated with decreased neutropenia and rapid improvement of peripheral neuropathy with nab-paclitaxel, compared with CrEL-paclitaxel. For these reasons, nab-paclitaxel can be administered using higher doses of paclitaxel than that achievable with CrEL-paclitaxel, with shorter infusion duration and without the requirement for corticosteroid and antihistamine premedication to reduce the risk of solvent-mediated hypersensitivity reactions. Taken together, these studies have demonstrated that nab technology has increased the therapeutic index of paclitaxel compared with the conventional, solvent-based formulation [6].

Nab paclitaxel treatment was approved by the U.S. Food and Drug Administration (FDA) in January 2005 and the European Medicines Agency in January 2008 for breast cancer cases where cancer did not respond to other chemotherapy or has relapsed.

In June 2010, positive results were published from a phase III trial in first-line non-small-cell lung cancer (NSCLC) when compared with solvent-based paclitaxel, and in October 2012 the FDA widened the approved use of Abraxane to include treatment for NSCLC.

The objective of the study was to evaluate the Safety profile of Paclitaxel in PubMed from period 2011 to 2013 and to compare the Safety profile of two different formulations of Paclitaxel i.e. Nab paclitaxel (albumin bound paclitaxel) and non albumin bound paclitaxel.

Material and Methods

The data from the case reports of patients receiving paclitaxel were extracted from PubMed search engine from period 2011 to 2013 [9-25]. Adverse Drug Reactions, Indications and System organ class were coded using MedDRA[7,8]. The line listing of case reports was prepared in Microsoft excel including various parameters like Patient age, Patient age group, Gender, Product name, Indication, ADR, SOC, SADR etc. Using pivot tables various tables were generated containing various parameters which aid in analysis of various parameters like: Yearly distribution of ADRs by Pacliatxel and Nab paclitaxel (Table 1), Indication wise use in gender (Table 2), Serious adverse drug reactions distribution in gender by paclitaxel and nab paclitaxel (Table 3), Yearly distribution of SADRs (Table 4), ADR distribution in gender (Table 5), Gender wise SOC distribution (Table 6).

Results and Conclusion

This study indicates that concludes that for future prospects pharmacovigilance or drug safety plays an important role in establishing safety profile of drugs. A total of 91 ADRs were found among which 74 were SADR. During the study analysis various parameters were analysed like:

Yearly distribution of ADRs by Pacliatxel and Nab paclitaxel: Encephalopathy, neutropenia were prominent ADR in 2011, Cystoid macular oedema and metastases to lungs were observed in 2012 by

Paclitaxel and Peripheral sensory neuropathy was the most prominent in 2013 by both Paclitaxel whereas lesser ADRs were observed by nab paclitaxel (Figure 1 & 2).

Indication wise use in gender: In females: Both formulations were widely used to treat Breast cancer (metastatic, recurrent, stage ii, iii) and also used to treat ovarian cancer and gastric cancer in females (Figure 3) while In Males: Nab paclitaxel was used to treat extramammary paget's disease whereas paclitaxel was majorly used to treat lung cancer, gastric cancer and oesophageal cancer metastatic (Figure 4).

Serious adverse drug reactions distribution in gender by paclitaxel and nab paclitaxel: In females dyspnoea was the major SADR found other SADR were metastases to bone, CNS, Lymph node, liver , peripheral sensory neuropathy and neutropenia whereas cystoids and macular oedema, peripheral sensory neuropathy and neutropenia were found with nab pacliatxel. Few cases of SADRs were found with Nab-pacliatxel in comparison to conventional Paclitaxel (Figure 5). In males cystoids macular oedema, metastases to lung and neutropenia were major SADRs whereas no SADRs was found with nab-paclitaxel in males (Figure 6).

Yearly distribution of SADRs: Encephalopathy, neutropenia were major in 2011, posterior reversible encephalopathy and metastases to bone were major SADR while in 2013 dyspnoea, neutropenia, peripheral sensory neuropathy and metastases to lung were found (Figure 7).

ADR distribution in gender: In Females major ADRs by paclitaxel were dysponea, maculopathy and metastases to bone, CNS and liver while by nab-pacliatxel peripheral sensory neuropathy was major ADR (Figure 8) while in Males cystoids macular oedema, neuropathy peripheral, neutropenia and metastases to lung were major only paraesthesia was found with nab paclitaxel (Figure 9).

Gender wise SOC distribution: In females the major SOC found was Nervous system disorder (28 %) [Figure 10] while in Males nervous system disorder (28%) , respiratory, thoracic and mediastinal disorders (28%) [Figure 11].

Previous studies also supported that Nab-paclitaxel (albumin bound paclitaxel) is significantly more effective than paclitaxel formulated as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel), with almost double the response rate, increased time to disease progression and increased survival in patients [6]. The absence of CrEL from the formulation is associated with decreased neutropenia as compared with CrEL-paclitaxel. Nab technology has increased the therapeutic index of paclitaxel and well tolerable as compared with the conventional, solvent-based formulation and thus albumin bound paclitaxel have better safety profile than conventional paclitaxel. Tolerability and compliance will probably become the most important factors in the future, according to the emerging value of quality of life in cancer care. The availability of new drugs, such as Abraxane (albumin bound paclitaxel), in association with other traditional and non-traditional drugs will give the oncologist many different effective treatment options for patients.

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Table 1: Yearly distribution of ADRs by Paclitaxel and Nab paclitaxel

YEARLY DISTRIBUTION OF ADVERSE DRUG REACTION BY PACLIATXEL									
	Paclitaxel			Paclitaxel Total	Paclitaxel NAB			Paclitaxel NAB Total	Grand Total
Adverse Drug Reactions	2011	2012	2013		2011	2012	2013		
Acute myocardial infarction		1		1					1
Adenocarcinoma	1			1					1
Anaemia		2		2					2
Bone marrow disorder	1			1					1
Bronchial fistula	1	1		2					2
Cushing's syndrome	1			1					1
Cutaneous lupus erythematosus							1	1	1
Cystoid macular oedema		4		4			1	1	5
Decreased appetite	1			1					1
Diarrhoea		1		1					1
Dizziness		1		1					1
Dysphagia			1	1					1
Dyspnoea	2	1	2	5					5
Encephalopathy	3			3					3
Erythema	1	1		2					2
Inappropriate antidiuretic hormone secretion	1			1					1
Interstitial lung disease	1			1					1
Intestinal fistula infection	1			1					1
Intestinal perforation		1		1					1
Leukopenia	1			1					1
Macular oedema							1	1	1
Maculopathy		2	1	3					3
Metastases to bone	1	2		3					3
Metastases to central nervous system		3	1	4					4
Metastases to eye	1			1					1
Metastases to liver	2		1	3					3
Metastases to lung	2		2	4		1		1	5
Metastases to lymph nodes	1		1	2					2
Metastases to meninges	1			1					1
Myelodysplastic syndrome			1	1					1

Nasal septum perforation	2			2					2
Neuroendocrine carcinoma		1		1					1
Neuropathy peripheral	1	1	2	4					4
Neurotoxicity		1		1					1
Neutropenia	3	1	2	6			1	1	7
Oligohydramnios	1			1					1
Onycholysis	2			2					2
Oropharyngeal pain	1			1					1
Palmar-plantar erythrodysaesthesia syndrome	1			1					1
Paraesthesia					1			1	1
Peripheral sensory neuropathy			3	3			4	4	7
Peritoneal disorder		1		1					1
Peritoneal mesothelioma malignant		1		1					1
Posterior reversible encephalopathy syndrome		2		2					2
Pyogenic granuloma		1		1					1
Recall phenomenon			1	1					1
Systemic lupus erythematosus			1	1					1
Thrombocytopenia			1	1					1
Grand Total	**34**	**29**	**20**	**83**	**1**	**1**	**9**	**11**	**94**

Table 2: Indication wise use in gender

INDICATION WISE USE IN GENDER							
	Female		Female Total	Male		Male Total	Grand Total
INDICATION	Paclitaxel	Paclitaxel NAB		Paclitaxel	Paclitaxel NAB		
Brain cancer metastatic				1		1	1
Breast cancer female	12	1	13				13
Breast cancer metastatic	6	3	9				9
Breast cancer recurrent	1	1	2				2
Breast cancer stage II	3	1	4				4
Breast cancer stage III	3	3	6				6
Cervix cancer metastatic	1		1				1
Cervix carcinoma	1		1				1
Cervix carcinoma	1		1				1

recurrent							
Duodenal stenosis	1		1				1
Endometrial cancer metastatic	1		1				1
Extramammary Paget's disease					1	1	1
Fallopian tube cancer stage III	1		1				1
Gastric cancer				1		1	1
Gastric cancer stage 0	1		1				1
Gastric cancer stage III	2		2	2		2	4
Gastric cancer stage IV	2		2	2		2	4
Gastrooesophageal cancer				1		1	1
Inflammatory myofibroblastic tumour				1		1	1
Large cell lung cancer recurrent	1		1				1
Lung adenocarcinoma				1		1	1
Lung adenocarcinoma stage III				1		1	1
Lung adenocarcinoma stage IV				2		2	2
Lung cancer metastatic	1		1	3		3	4
Metastatic pulmonary embolism	1		1				1
Non-small cell lung cancer				1		1	1
Non-small cell lung cancer metastatic				1		1	1
Non-small cell lung cancer stage I				1		1	1
Non-small cell lung cancer stage IIIA				1		1	1
Oesophageal cancer metastatic				2		2	2
Ovarian cancer	4		4				4
Ovarian cancer metastatic	3		3				3
Ovarian cancer recurrent	2		2				2
Ovarian cancer stage II	1		1				1
Ovarian cancer stage IV	1		1				1
Pancreatic carcinoma	1	1	2				2
Papuloerythroderma of Ofuji				1		1	1
Penis carcinoma				1		1	1
Renal cancer				1		1	1
Salivary gland cancer				1		1	1

Small cell lung cancer metastatic				1		1	1
Thyroid cancer	1		1				1
Transitional cell carcinoma metastatic				1		1	1
Uterine cancer	1		1				1
Vaginal cancer stage II	1		1				1
Grand Total	**54**	**10**	**64**	**27**	**1**	**28**	**92**

Table 3: Serious adverse drug reaction distribution in gender by Paclitaxel and Nab Paclitaxel

	Female		Female Total	Male	Male Total	Grand Total
SERIOUS ADVERSE DRUG REACTION	**Paclitaxel**	**Paclitaxel NAB**		**Paclitaxel**		
Acute myocardial infarction	1		1			1
Adenocarcinoma	1		1			1
Bronchial fistula				2	2	2
Cushing's syndrome	1		1			1
Cutaneous lupus erythematosus		1	1			1
Cystoid macular oedema	1	1	2	3	3	5
Diarrhoea				1	1	1
Dizziness	1		1			1
Dysphagia				1	1	1
Dyspnoea	4		4	1	1	5
Encephalopathy	2		2	1	1	3
Erythema				1	1	1
Inappropriate antidiuretic hormone secretion	1		1			1
Interstitial lung disease				1	1	1
Intestinal fistula infection	1		1			1
Intestinal perforation	1		1			1
Leukopenia				1	1	1
Macular oedema		1	1			1
Metastases to bone	3		3			3
Metastases to central nervous system	3		3	1	1	4
Metastases to eye	1		1			1
Metastases to liver	3		3			3
Metastases to lung	1	1	2	3	3	5

Metastases to lymph nodes	2		2			2
Metastases to meninges	1		1			1
Myelodysplastic syndrome	1		1			1
Nasal septum perforation	1		1			1
Neuroendocrine carcinoma	1		1			1
Neuropathy peripheral	1		1	1	1	2
Neurotoxicity	1		1			1
Neutropenia	3	1	4	3	3	7
Oligohydramnios	1		1			1
Onycholysis				1	1	1
Oropharyngeal pain				1	1	1
Peripheral sensory neuropathy	2	2	4			4
Peritoneal disorder	1		1			1
Peritoneal mesothelioma malignant	1		1			1
Posterior reversible encephalopathy syndrome				2	2	2
Systemic lupus erythematosus	1		1			1
Thrombocytopenia	1		1			1
Grand Total	**43**	**7**	**50**	**24**	**24**	**74**

Table 4: Yearly distribution of SADRs

YEARLY DISTRIBUTION OF SERIOUS ADVERSE DRUG REACTION								
	Paclitaxel			Paclitaxel Total	Paclitaxel NAB		Paclitaxel NAB Total	Grand Total
SERIOUS ADVERSE DRUG REACTION	2011	2012	2013		2012	2013		
Acute myocardial infarction		1		1				1
Adenocarcinoma	1			1				1
Bronchial fistula	1	1		2				2
Cushing's syndrome	1			1				1
Cutaneous lupus erythematosus						1	1	1
Cystoid macular oedema		4		4		1	1	5
Diarrhoea		1		1				1
Dizziness		1		1				1

Dysphagia			1	1				1
Dyspnoea	2	1	2	5				5
Encephalopathy	3			3				3
Erythema		1		1				1
Inappropriate antidiuretic hormone secretion	1			1				1
Interstitial lung disease	1			1				1
Intestinal fistula infection	1			1				1
Intestinal perforation		1		1				1
Leukopenia	1			1				1
Macular oedema						1	1	1
Metastases to bone	1	2		3				3
Metastases to central nervous system		3	1	4				4
Metastases to eye	1			1				1
Metastases to liver	2		1	3				3
Metastases to lung	2		2	4	1		1	5
Metastases to lymph nodes	1		1	2				2
Metastases to meninges	1			1				1
Myelodysplastic syndrome			1	1				1
Nasal septum perforation	1			1				1
Neuroendocrine carcinoma		1		1				1
Neuropathy peripheral	1		1	2				2
Neurotoxicity		1		1				1
Neutropenia	3	1	2	6		1	1	7
Oligohydramnios	1			1				1
Onycholysis	1			1				1
Oropharyngeal pain	1			1				1
Peripheral sensory neuropathy			2	2		2	2	4
Peritoneal disorder		1		1				1
Peritoneal mesothelioma malignant		1		1				1
Posterior reversible encephalopathy syndrome		2		2				2
Systemic lupus erythematosus			1	1				1
Thrombocytopenia			1	1				1
Grand Total	**28**	**23**	**16**	**67**	**1**	**6**	**7**	**74**

Table 5: ADR distribution in Gender by Paclitaxel and Nab-pacliatxel

	Female		Female Total	Male		Male Total	Grand Total
ADVSERSE DRUG REACTIONS	**Paclitaxel**	**Paclitaxel NAB**		**Paclitaxel**	**Paclitaxel NAB**		
Acute myocardial infarction	1		1				1
Adenocarcinoma	1		1				1
Anaemia	1		1	1		1	2
Bone marrow disorder				1		1	1
Bronchial fistula				2		2	2
Cushing's syndrome	1		1				1
Cutaneous lupus erythematosus		1	1				1
Cystoid macular oedema	1	1	2	3		3	5
Decreased appetite	1		1				1
Diarrhoea				1		1	1
Dizziness	1		1				1
Dysphagia				1		1	1
Dyspnoea	4		4	1		1	5
Encephalopathy	2		2	1		1	3
Erythema	1		1	1		1	2
Inappropriate antidiuretic hormone secretion	1		1				1
Interstitial lung disease				1		1	1
Intestinal fistula infection	1		1				1
Intestinal perforation	1		1				1
Leukopenia				1		1	1
Macular oedema		1	1				1
Maculopathy	3		3				3
Metastases to bone	3		3				3
Metastases to central nervous system	3		3	1		1	4
Metastases to eye	1		1				1
Metastases to liver	3		3				3
Metastases to lung	1	1	2	3		3	5
Metastases to lymph nodes	2		2				2
Metastases to meninges	1		1				1
Myelodysplastic syndrome	1		1				1
Nasal septum perforation	2		2				2
Neuroendocrine carcinoma	1		1				1
Neuropathy peripheral	1		1	3		3	4
Neurotoxicity	1		1				1
Neutropenia	3	1	4	3		3	7

Oligohydramnios	1		1				1
Onycholysis	1		1	1		1	2
Oropharyngeal pain				1		1	1
Palmar-plantar erythrodysaesthesia syndrome	1		1				1
Paraesthesia					1	1	1
Peripheral sensory neuropathy	3	4	7				7
Peritoneal disorder	1		1				1
Peritoneal mesothelioma malignant	1		1				1
Posterior reversible encephalopathy syndrome				2		2	2
Pyogenic granuloma	1		1				1
Recall phenomenon	1		1				1
Systemic lupus erythematosus	1		1				1
Thrombocytopenia	1		1				1
Grand Total	**55**	**9**	**64**	**28**	**1**	**29**	**93**

Table 6: Gender wise SOC distribution

GENDER WISE SOC DISTRIBUTION			
SOC	**Female**	**Male**	**Grand Total**
Blood and lymphatic system disorders	9	6	15
Bone disorder	1		1
Cardiac disorders	2		2
Endocrine disorders	2		2
Eye disorder	1		1
Eye disorders	6	3	9
Gastrointestinal disorders	4	2	6
Hepatobiliary disorders	3		3
Metabolism and nutrition disorders	2		2
Musculoskeletal and connective tissue disorders	2		2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1		1
Nervous system disorders	15	8	23
Pregnancy, puerperium and perinatal conditions	1		1
recurrence	1		1
Respiratory, thoracic and mediastinal disorders	8	8	16
Skin and subcutaneous tissue disorders	7	2	9
Grand Total	**65**	**29**	**94**

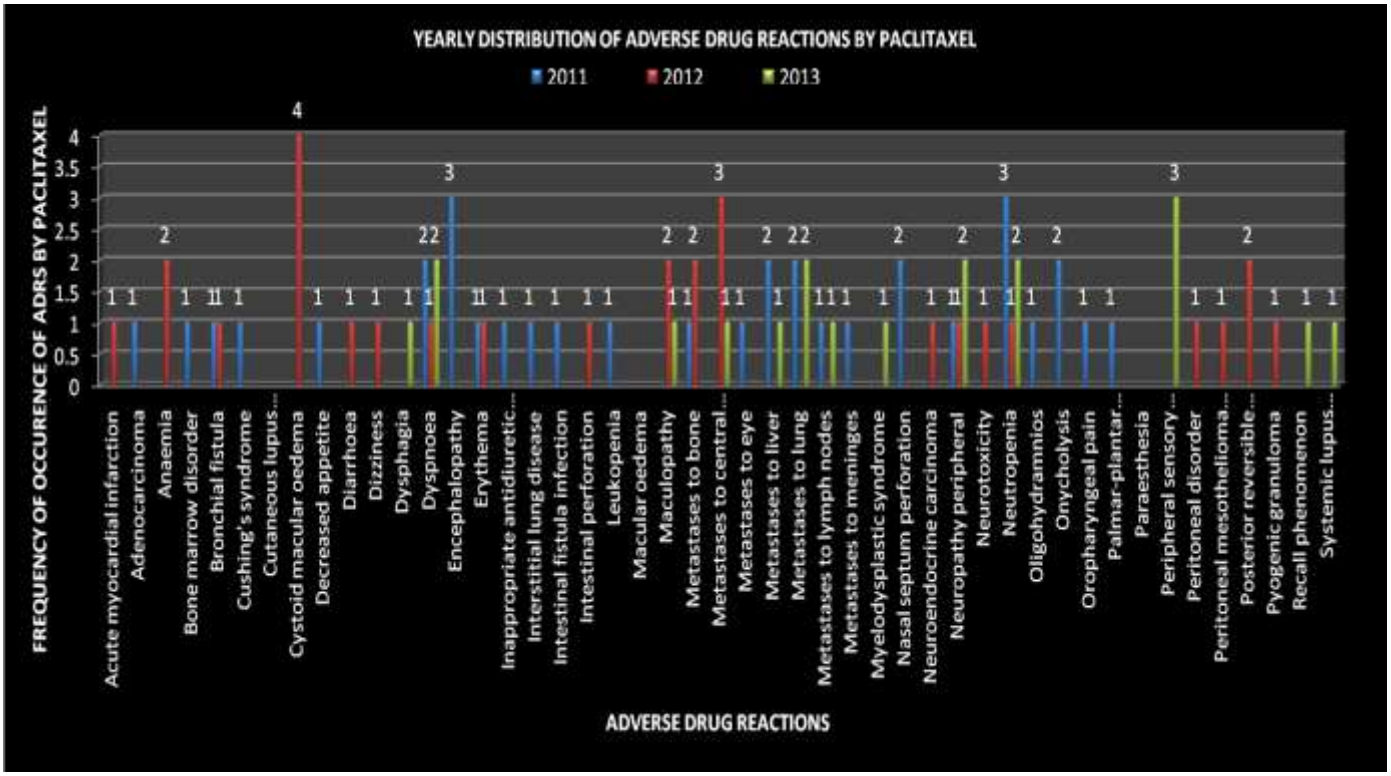

Fig 1: Yearly distribution of ADR by Paclitaxel.

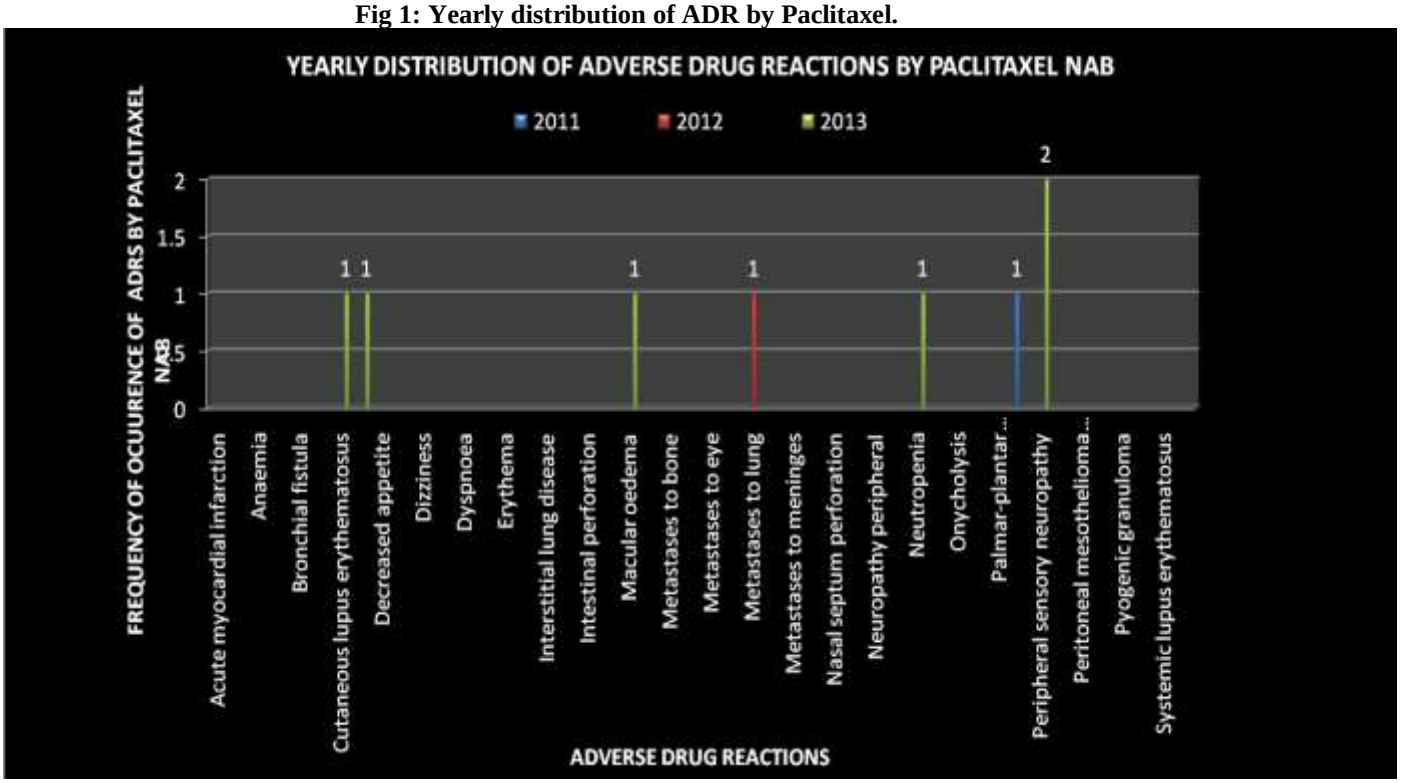

Fig. 2: Yearly distribution of ADR by Nab-Paclitaxel

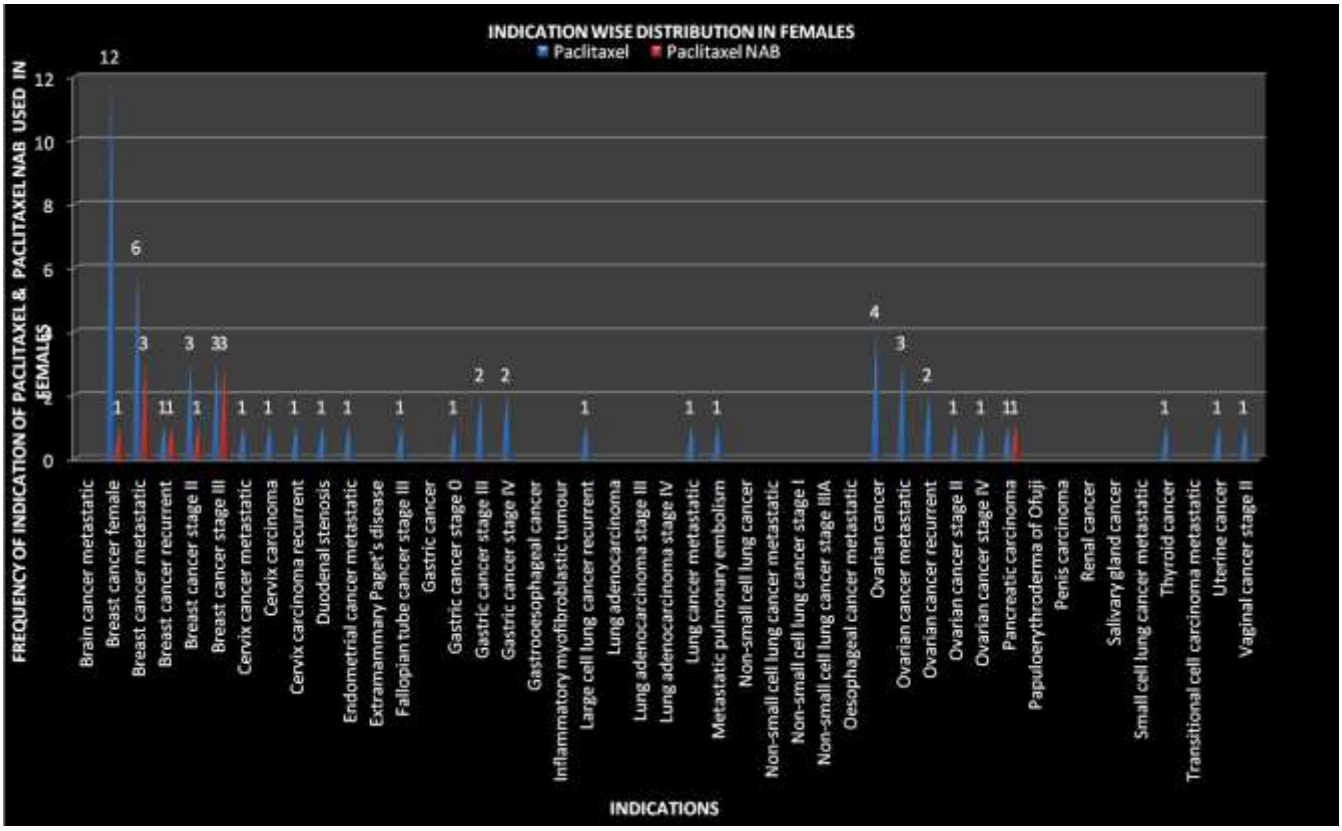

Fig. 3: Indication wise use in Female

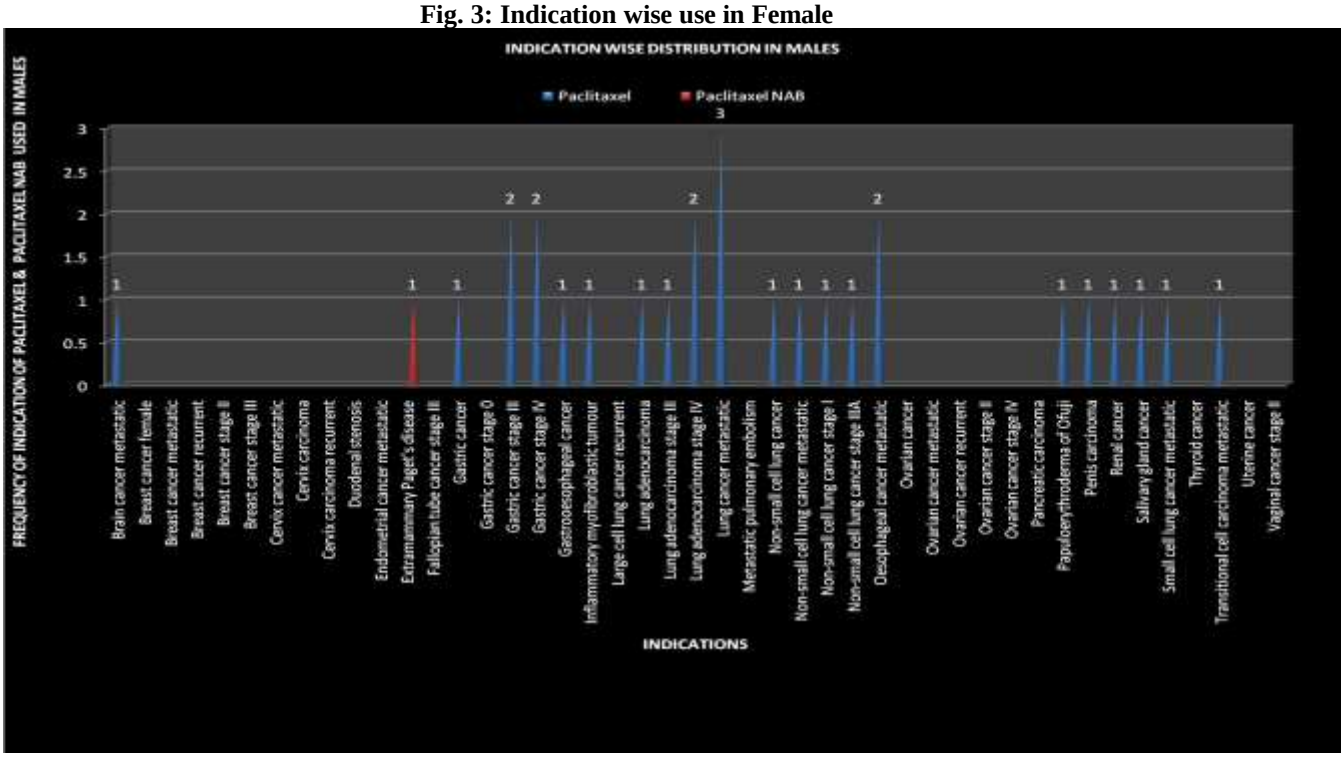

Fig. 4: Indication wise use in Males

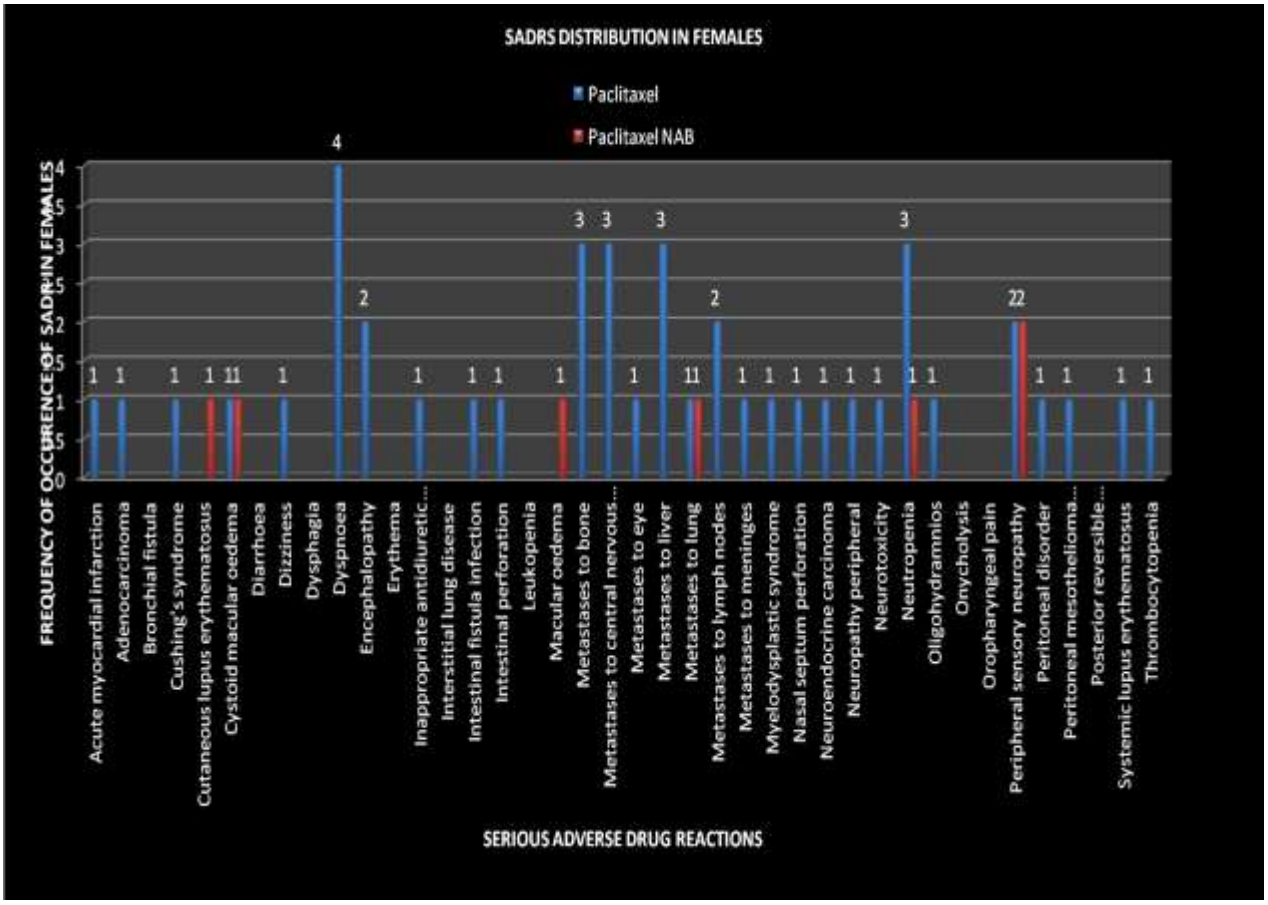

Fig. 5: SADR distribution in Females

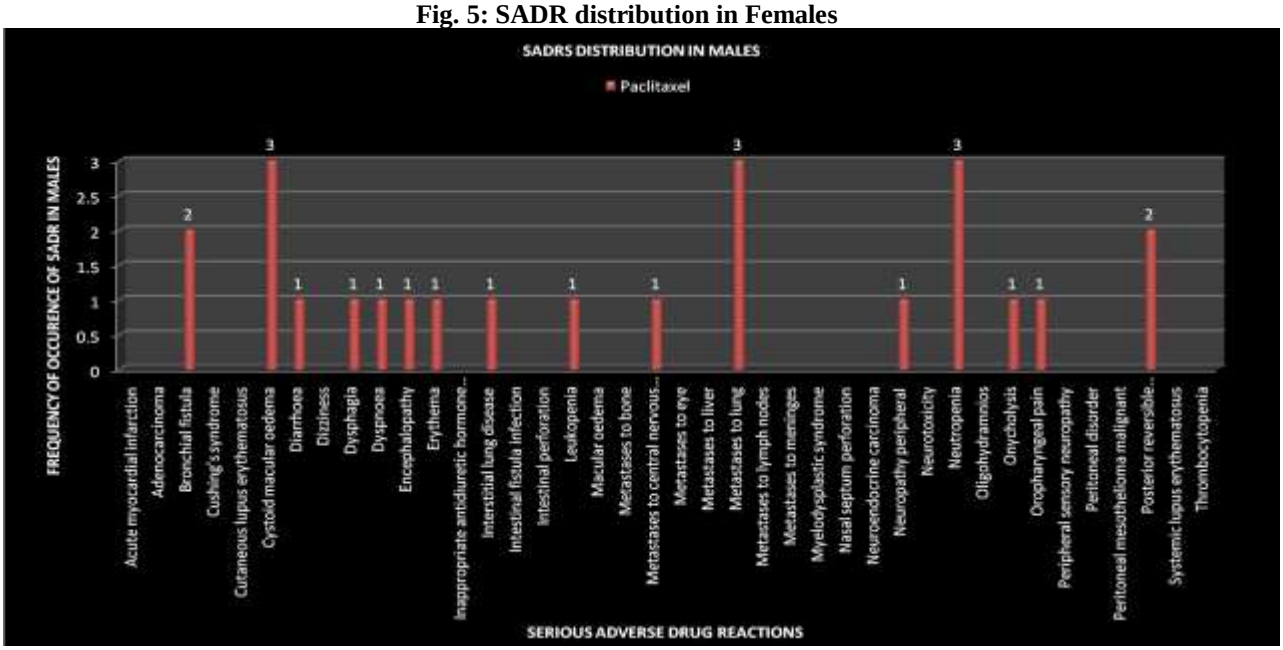

Fig. 6: SADR distribution in Males

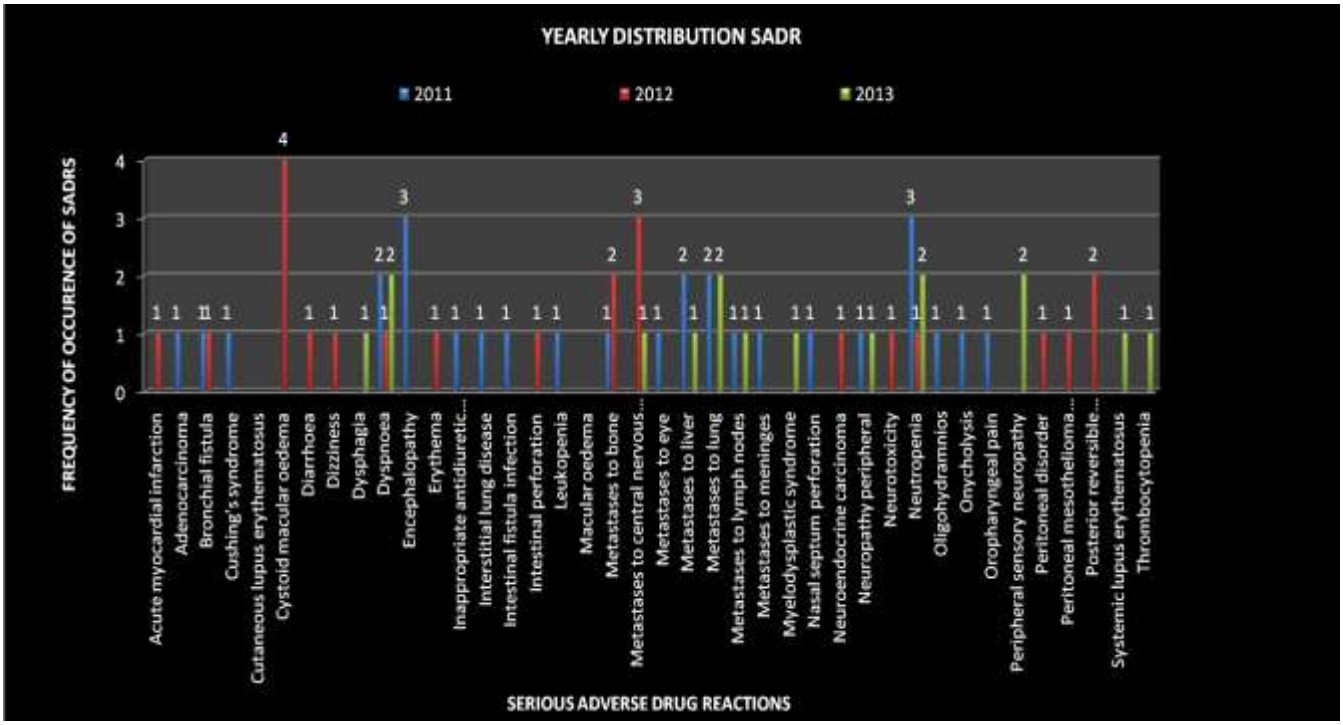

Fig. 7: Yearly distribution of SADRs

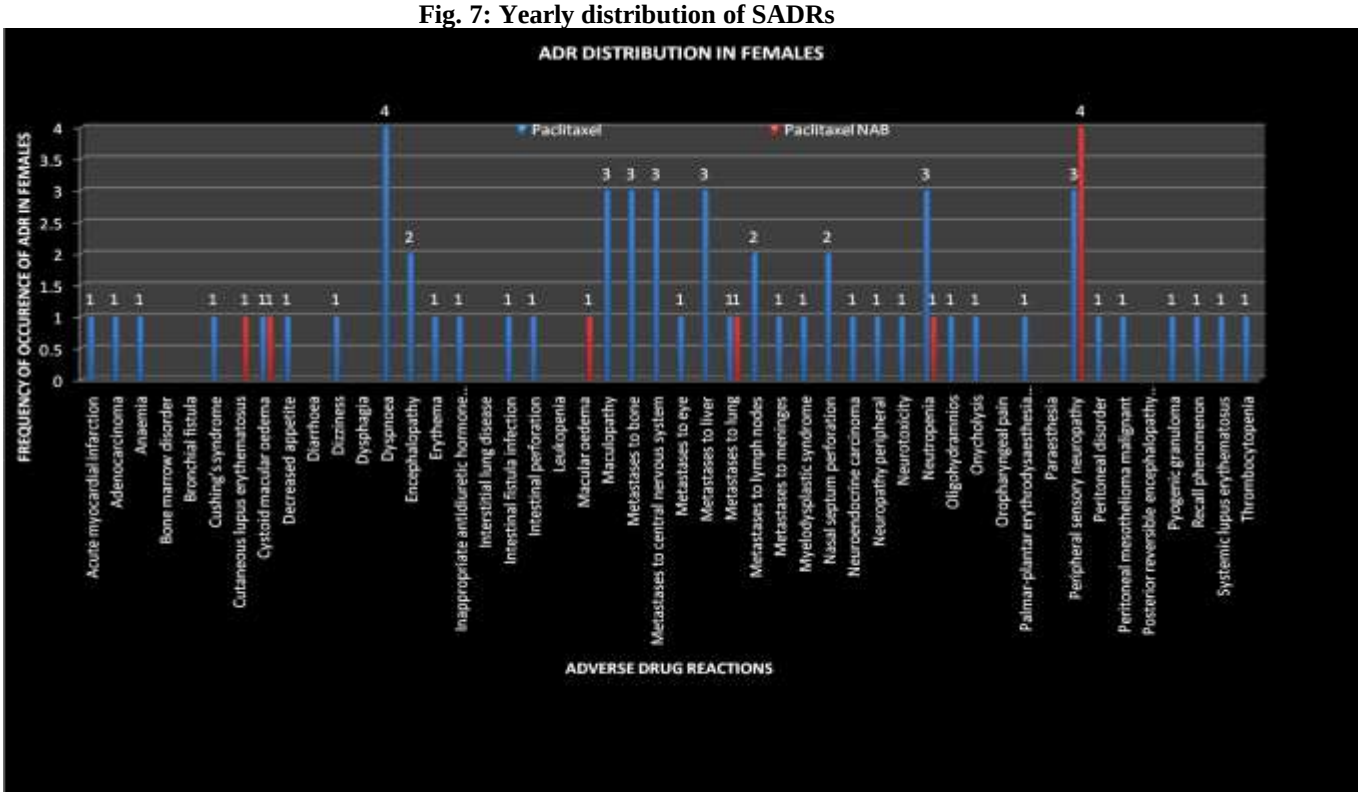

Fig. 8: ADR distribution in Females

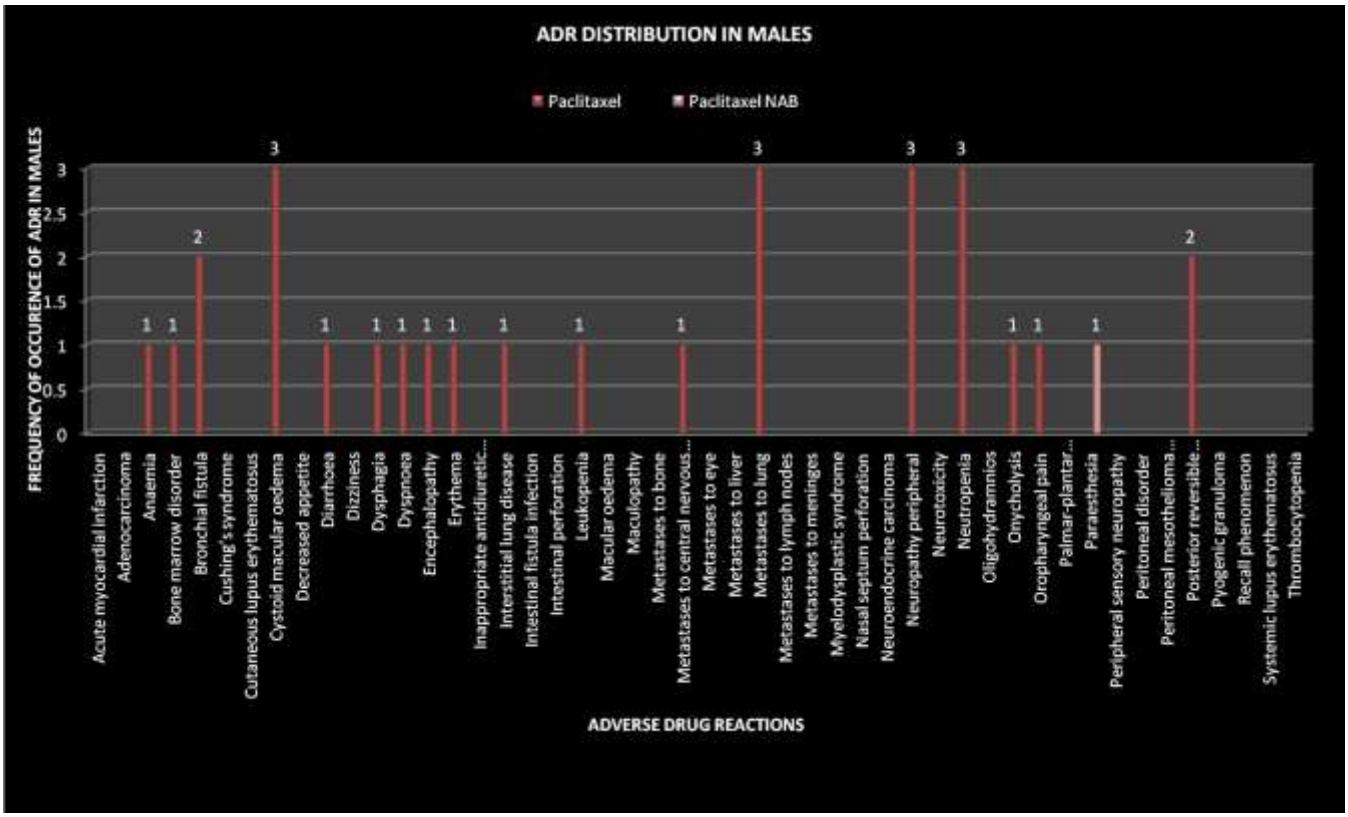

Fig. 9: ADR distribution in Males

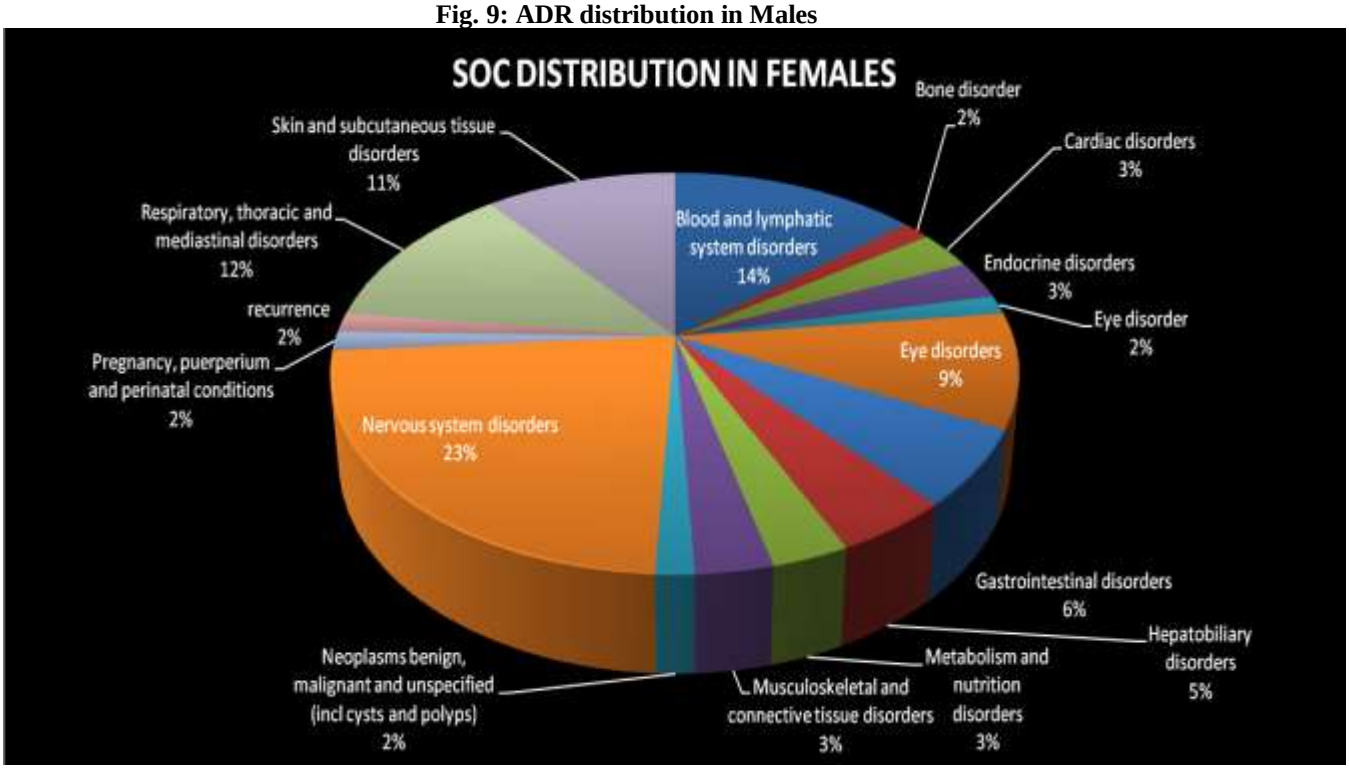

Fig. 10: SOC distribution in females

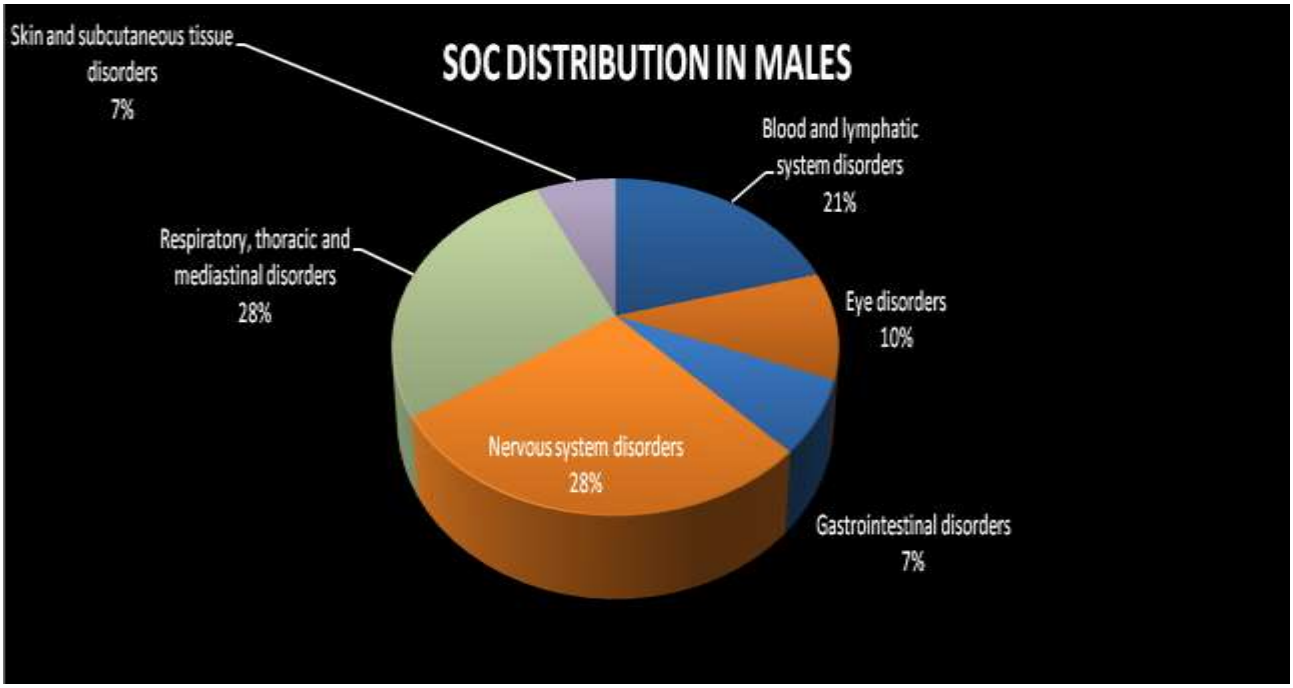

Fig. 11 SOC distribution in Males

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