3.3.1 Number of research papers published per teacher in the Journals notified on UGC website during the last five years

Title of paper	Name of the author/s	Department of the teacher	Name of journal	Year of publication	ISSN number	Link to the recognition in UGC enlistment of the		
						Link to website of the Journal	Link to article / paper / abstract of the article	Is it listed in UGC Care list/Scopus/Web of Science/other, mention
TO STUDY THE EFFICACY OF GOLIMUMAB PLUS METHOTREXATE IN PATIENTS WITH ACTIVE RHEUMOTOID ARTHRITIS	Jyothisahu	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	2394-4269	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	YES
TO STUDY THE QOL DEPRESSION AND SYMPTOMS IN BOTH CKD AND ESKD	Sumaya Fatima	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	2394-4269	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.Z	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.	YES
TRIPLE COMBINATION THEAPY WITH AMLODINE, VALSARTAN AND	Juveria Naaz	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	2394-4269	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.Z	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.	YES

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HYDROCHLOROTHIAZIDE vs DUAL COMBINATION THERAPY WITHAMLODIPINE AND HYDRCHLOROTHIAZIDE FOR STAGE 2 HYPERTENSIVE PATIENTS	Jabeen Farhana	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	**2394-4269**	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	YES
A SYATEMIC REVIEW ON MEDICATION ADHERENCE WITH OHS AND INSULIN IN DM PATIENTS	Jakir Hussain Sha	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	**2394-4269**	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	YES
QUALITY OF LIFE OF EPILEPSY SURGERY PATIENTS AS COMPARED WITH OUT PATIENTS WITH HYPERTENSION, DIABETES, HEART DISEASE/ DEPRESSIVE	Hamad bin Mohamr	Pharmacy	International Journal of Medicine and Nanotechnology	**2020-21**	**2394-4269**	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	YES

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A RANDAMIZED PILOT STUDY AND EFFECTS OF OMEGA 3 FATTY ACIDS ON HYPERTENSIVE PATIENTS WITH ARTERIAL STIFFNESS	Aejaz Ahmed	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
DEPRESSION AND ADVERSE DRUG REACTION AMONG HOSPITALIZED OLDER ADULTS	Aejaz Ahmed	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
A CLINICAL STUDY OF ACUTE KIDNEY INJURY ON USING ANTI TUBERCULAR DRUGS	Das	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF GLIBENCLAMIDE IN TABLET DOSAGE FORM	Jabeen Farhana	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES

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RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF RABEPRAZOLE IN TABLET DOSAGE FORM	Jabeen Farhana	Pharmacy	Indo American Journal of Pharmacy	2019-20	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF GLIBENCLAMIDE	Jakir Hussain s	Pharmacy	Indo American Journal of Pharmacy	2019-20	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
A STUDY ON EFFECT OF OMEGA 3 FATTY ACIDS ON ARTERIAL STIFFNESS IN PATIENTS SUFFERING WITH HYPERTENSION	Jyothi	Pharmacy	Indo American Journal of Pharmacy	2019-20	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
FORMULATION AND EVALUATION OF GLIMEPIRIDE LIPOSOMAL DRUG DELIVERY SYSTEM	Dr. Khaja Pasha	Pharmacy	International Journal of Research in Pharmacy and Biosciences	2019-20	2394-5893	https://journalseeker.researchbib.com/view/issn/2394-5893	https://journalseeker.researchbib.com/view/issn/2394-5893	YES
FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE SUSTAINED	Dr. Khaja Pasha	Pharmacy	International Journal of Research in Pharmacy and Biosciences	2019-20	2394-5893	https://journalseeker.researchbib.com/view/issn/2394-5893	https://journalseeker.researchbib.com/view/issn/2394-5893	YES

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FORMULATION AND EVALUATION OF CONTROLLED RELEASE OSMOTIC TABLET OF GLIPIZIDE	Dr. Khaja Pasha	Pharmacy	Indo American Journal of Pharmacy	2018-19	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
Phytochemical Analysis And Hepatoprotective Activity Of Elytraria Acaulis	DR.M.V.RAMAN	Pharmacy	Journal of Pharmaceutical Research International	2018-19	2456-9119	https://journaljpri.com/index.php/JPRI	https://journaljpri.com/index.php/JPRI	YES
Preparation and Evaluation of Solid dispersions of Febuxostat	DR.M.V.RAMAN	Pharmacy	International Journal of Medicine and Nanotechnology	2018-19	2394-4269	https://www.citefactor.org/journal/index/22108/international-journal-of-pharmacy-and-	https://www.citefactor.org/journal/index/22108/international-journal-of-pharmacy-and-	YES
Formulation and In-vitro Evaluation of Olmesartan Medoxomil Solid Dispersions,	DR.M.V.RAMAN	Pharmacy	International Journal of Medicine and Nanotechnology	2018-19	2394-4269	https://www.citefactor.org/journal/index/22108/international-journal-of-pharmacy-and-natural-medicines#.ZBVo2HZBzIU	https://www.citefactor.org/journal/index/22108/international-journal-of-pharmacy-and-natural-medicines#.ZBVo2HZBzIU	YES

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Wound Healing Activity Of Graclaria Edulis Hydro Alcoholic Extract Using Excision And Dead Cell Wound Model In Wistar Rats	DR.M.V.RAMAN	Pharmacy	international journal of pharmacy	2017-18	0253-7613	https://www.ijp-online.com/search.asp	https://www.ijp-online.com/search.asp	YES
Hepatoprotective Activity Of The Hydro Alcoholic Extract Of The Gracilaria Edulis	DR.M.V.RAMAN	Pharmacy	Research Journal of Pharmacy&Technology	2017-18	0974-360X	https://www.rjptonline.org/	https://www.rjptonline.org/	YES

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Original Article

TO STUDY THE EFFICACY OF GOLIMUMAB PLUS METHOTREXATE IN PATIENTS WITH ACTIVE RHEUMOTOID ARTHRITIS

Jyothisahu*, Mariyam Banu[1], Humera siddiqui[1], Hina Sultana[1], Rabia rahamani[1], Arshiya Banu[1]

1. Azad college of pharmacy
Corresponding Author
Name: Jyothisahu
College name: Azad College of pharmacy
Mail I'd: jyotisahupharma@gmail.com

Abstract:
Rheumatoid arthritis (RA) is an inflammatory disease which, though systemic, typically involves the small joints of the hands and feet, often symmetrically. It affects approximately 1% of the population and is more common in women. The goal of the study is treat the subjects suffering from rheumatoid arthritis with GOLIMUMAB plus methotrexate DRUGS. TO evaluate the efficacy of the IP in subjects.To evaluate the safety and efficacy of the drug in subjects. To evaluate the pharmacoeconomic analysis in the clinical efficacy evaluable (CEE) and successfully treat patients. Patients were randomized (1:1) to receive subcutaneous placebo, golimumab 50 mg or golimumab 100 mg every 4 weeks. Randomization was stratified by investigational site and baseline MTX use (yes/no). Patients and investigators were masked to study treatment assignment; golimumab and placebo were supplied in identical single-use vials. Concomitant MTX use was permitted, but not required, if continued at a stable dose.The trial demonstrated clinically relevant improvement in disease activity and physical function after switching to golimumab, regardless of which TNF inhibitor had been taken previously. Of particular note, patients who switched from either etanercept or infliximab appeared to exhibit better subsequent responses to golimumab than those that were observed among patients who previously had received adalimumab which, of the three prior TNF inhibitors, is most structurally similar to golimumab. However, further study is required to confirm the current findings.

Keywords: Golimumab, Pharmacoeconomic, Subcutaneous

1. INTRODUCTION

Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present.[1] Often, symptoms come on gradually over weeks to months.[2]

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the

body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage.[1] The diagnosis is made mostly on the basis of a person's signs and symptoms.[2] X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms.[1] Other diseases that may present similarly include systemic lupus erythematosus,psoriatic arthritis, and fibromyalgia among others.[2]

The goal of treatment is to reduce pain, decrease inflammation, and improve a person's overall functioning. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. A group of medications called disease-modifying antirheumatic drugs (DMARDs) may be used to try to slow the progression of disease. They include the medications hydroxychloroquine and methotrexate.[1] Biological DMARDs may be used when disease does not respond to other treatments.[3] However, they may have a greater rate of adverse effects.[4] Surgery to repair, replace, or fusionjoints may help in certain situations.[1] Most alternative medicine treatments are not supported by evidence.[5][6]

AIM AND OBJECTIVE:

Aim: 1. The goal of the study is treat the subjects suffering from rheumatoid arthritis with GOLIMUMAB plus methotrexate DRUGS.
2. TO evaluate the efficacy of the IP in subjects.

Objective:

- To evaluate the safety and efficacy of the drug in subjects.
- To evaluate the pharmacoeconomic analysis in the clinical efficacy evaluable (CEE) and successfully treat patients.

MATERIALS AND METHODS:

STUDY TYPE : ORAL.

STUDY SITE : Study will be conducted at PRIME HOSPITALS

SAMPLE SIZE : 137 Subjects

STUDY DURATION : study will be of 6 months.From Dec 2016 to May 2017.

WOMAC : Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

To assess pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subscales:

- **Pain (5 items):** during walking, using stairs, in bed, sitting or lying, and standing
- **Stiffness (2 items):** after first waking and later in the day
- **Physical Function (17 items):** stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties.

INCLUSION CRITIERIA:

- Subjects willing to provide informed consent
- Subjects of either sex of age group between ≥ 18 years and ≤ 65 years.
- Subjects must have at least > 4 score on the VAS scale for the inclusion in the study at the time of screening.
- Female subjects of child-bearing potential: subject is not pregnant

EXCLUSION CRITERIA:

- History of gastro esophageal reflux disease (GERD) diagnosed by a physician.
- Evidence of any medical condition that may interfere with the conduct of the study
- Subjects who require continuous use of histamine receptor (H2) blockers, or prokinetics.

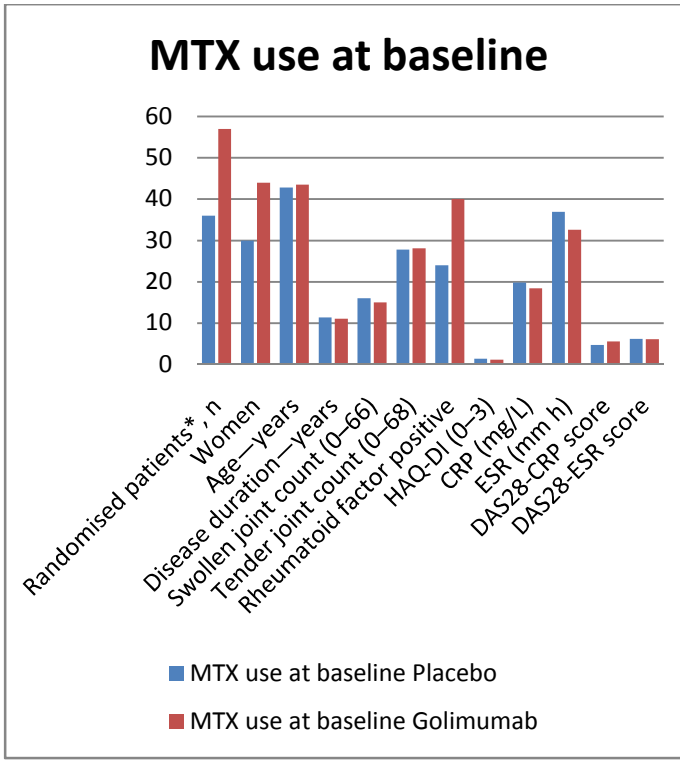
- History of hypersensitivity to non-steroidal ant-inflammatory drugs.
- History of abuse of analgesics.
- Evidence of peritoneal inflammation.
- In the GO-AFTER trial,137 patients were randomly assigned to receive placebo (n=49), golimumab 50 mg (n=44) or golimumab 100 mg (n=44) every 4 weeks.[20] Baseline characteristics for the MTX-treated subgroup of randomised patients (table 1) were generally consistent with those of the overall study population,[20] although fewer MTX-treated patients tested positive for rheumatoid factor at baseline than did patients with no MTX use at baseline.

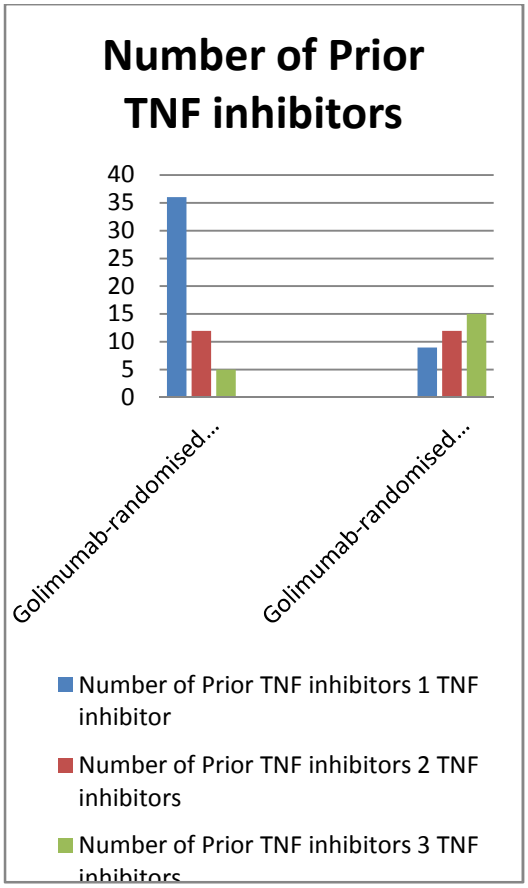
MTX use at baseline		**No MTX use at baseline**		
	Placebo	**Golimumab**	**Placebo**	**Golimumab**
Randomised patients*, n	**36**	**57**	**14**	**30**
Women	30 (83.2%)	44 (78.0%)	12 (89.6%)	22(74.3%)
Age—years	42.8±12.84	43.5±12.03	52.8±12.50	50.14±11.07
Disease duration—years	11.4±8.84	11.1±8.24	11.3±09.96	11.08±9.17
Swollen joint count (0–66)	16.08±10.90	15.0±11.02	17.6±11.37	16.8±11.12
Tender joint count (0–68)	27.8±17.09	28.1±17.20	29.3±15.50	30.4±16.85
Rheumatoid factor positive	24 (67.0%)	40 (69.5%)	12 (85.4%)	23 (77.6%)
HAQ-DI (0–3)	1.4±0.56	1.2±0.61	1.4±0.69	1.5±0.66
CRP (mg/L)	19.8±30.70	18.4±30.52	21.2±30.59	23.6±32.94
ESR (mm h)	36.9±23.94	32.6±27.10	36.3±26.26	38.4±27.97
DAS28-CRP score	4.7±1.02	5.6±1.14	5.6±1.16	5.0±1.05
DAS28-ESR score	6.2±1.10	6.1±1.14	6.0±1.27	6.4±1.14

Table – 1 Summary of baseline characteristics* in randomised patients and previous TNF inhibitor use† among patients receiving MTX at baseline

	Number of Prior TNF inhibitors		
	1 TNF inhibitor	**2 TNF inhibitors**	**3 TNF inhibitors**
Golimumab-randomised MTX-treated patients†, n	**36**	**12**	**5**
	Prior TNF inhibitor		
	Adalimumab only	**Etanercept only**	**Infliximab only**
Golimumab-randomised patients who received only one prior TNF inhibitor†, n	**9**	**12**	**15**
Reason for discontinuation of prior TNF inhibitor			
Lack of efficacy	6 (66.7%)	6 (48.9%)	5 (38.6%)
Intolerance	1 (15.2%)	1 (4.3%)	2 (14.0%)
'Other' reason ‡	2 (18.2%)	5 (46.8%)	8(47.4%)
Distribution by duration of prior treatment, n			
<4 weeks	2	5	2
≥4 to <12 weeks	8	12	4
≥12 to <24 weeks	7	3	4
≥24 to <36 weeks	5	5	3
≥36 to <48 weeks	1	2	8
≥48 weeks	10	20	36
% patients receiving therapy for ≥24 weeks	48.50%	57.40%	82.50%

Table – 2Summary of baseline characteristics* in randomised patients and previous TNF inhibitor use† among patients receiving MTX at baseline


MTX use at baseline
60
50
40
30
20
10
0
Randomised patients*, n
Women
Age—years
Disease duration—years
Swollen joint count (0–66)
Tender joint count (0–68)
Rheumatoid factor positive
HAQ-DI (0–3)
CRP (mg/L)
ESR (mm h)
DAS28-CRP score
DAS28-ESR score
MTX use at baseline Placebo
MTX use at baseline Golimumab


Number of Prior TNF inhibitors
40
35
30
25
20
15
10
5
0
Golimumab-randomised...
Golimumab-randomised...
Number of Prior TNF inhibitors 1 TNF inhibitor
Number of Prior TNF inhibitors 2 TNF inhibitors
Number of Prior TNF inhibitors 3 TNF inhibitors

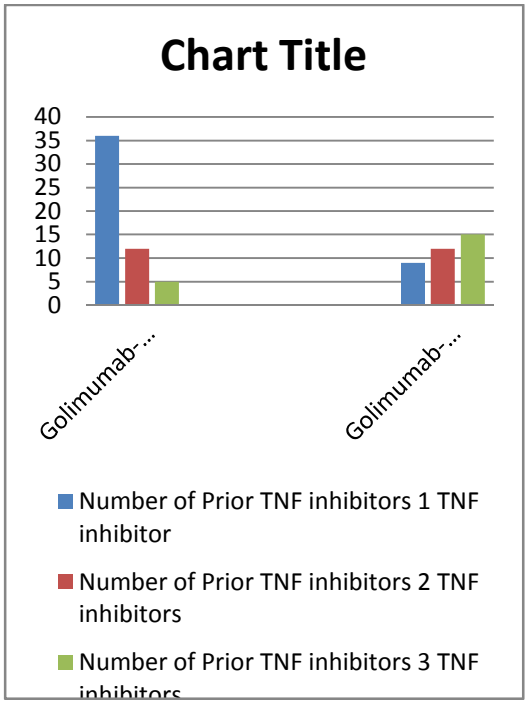
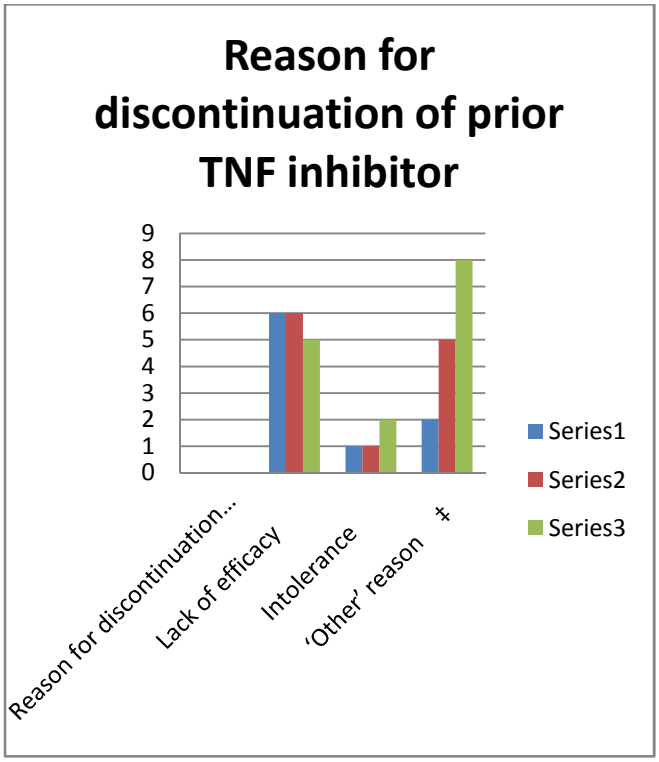


Chart Title
40
35
30
25
20
15
10
5
0
Golimumab-...
Golimumab-...
Number of Prior TNF inhibitors 1 TNF inhibitor
Number of Prior TNF inhibitors 2 TNF inhibitors
Number of Prior TNF inhibitors 3 TNF inhibitors

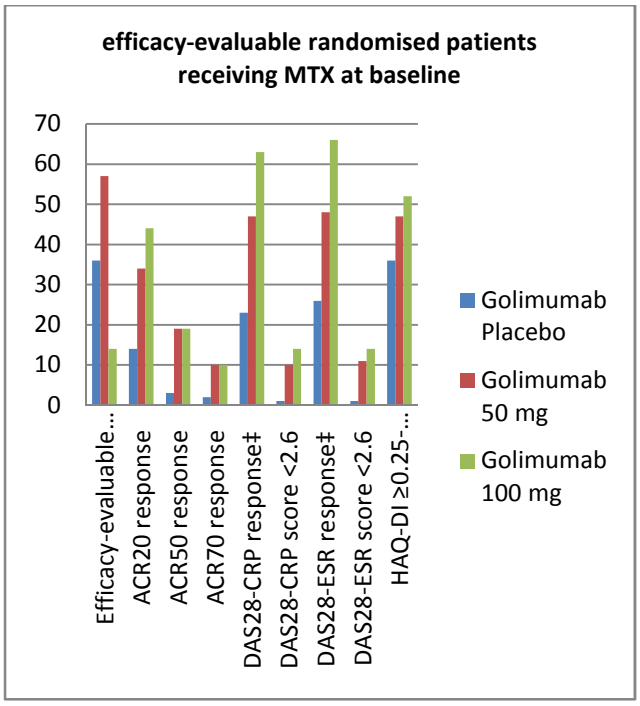

Reason for discontinuation of prior TNF inhibitor
9
8
7
6
5
4
3
2
1
0
Reason for discontinuation...
Lack of efficacy
Intolerance
'Other' reason
Series1
Series2
Series3

With the exception of shorter disease duration (8.1vs 11.6 years, respectively; p=0.023) and more women patients (90.9% vs 70.2%), respectively; p=0.023) among adalimumab-only versus infliximab-only-treated patients, no consistent baseline differences were observed across prior TNF inhibitors (data not shown).

Without the 7 patients treated at the excluded site, 130randomised patients were available for efficacy analyses, 89 of whom were also receiving MTX at baseline. Fifty nine of them were randomised to golimumab and were also receiving MTX (table 2); much smaller proportions of patients were receiving sulfasalazine (4.9%) and/or hydrochloroquine (7.4%) in addition to MTX. Among the efficacy-evaluable golimumab-randomised patients who were also receiving MTX, 36 had previously received only one TNF inhibitor (adalimumab, n=9; etanercept, n=12; and infliximab, n=15). For each prior TNF inhibitor, the proportion of patients who discontinued that agent because of lack of efficacy was 2.5-fold to 11-fold greater than those who discontinued because of intolerance (table 1). Overall, most patients received prior anti-TNF therapy for ≥24 weeks

	Golimumab			
	Placebo	**50 mg**	**100 mg**	**Combined**
Efficacy-evaluable randomised patients receiving study agent+MTX, n	36	57	14	71
ACR20 response	14 (15.6%)	34 (35.6%)	44 (46.0%)	80 (41.8%)
ACR50 response	3 (3.8%)	19 (19.8%)	19 (22.0%)	41 (19.9%)
ACR70 response	2 (2.7%)	10 (11.9%)	10 (11.0%)	21 (10.4%)
DAS28-CRP response‡	23 (23.3%)	47 (48.5%)	63 (65.0%)	112 (56.7%)
DAS28-CRP score <**2.6**	1 (1.9%)	10(11.9%)	14 (14.0%)	26 (12.9%)
DAS28-ESR response‡	26 (26.2%)	48 (48.5%)	66 (67.0%)	114 (57.7%)
DAS28-ESR score <**2.6**	1 (1.0%)	11 (10.9%)	14(16.0%)	26 (13.4%)
HAQ-DI ≥0.25-unit improvement	36 (34.0%)	47 (47.5%)	52(54.0%)	101 (50.7%

Table 3 Summary of clinical efficacy at week 24* among efficacy-evaluable randomised patients receiving MTX at baseline



Clinical improvement

All golimumab-randomised patients who were receiving MTX at baseline

Among patients with active RA who were previously treated with a TNF inhibitor, 41.8% of

golimumab+MTX-treated patients and 15.6% of placebo+MTX-treated patients achieved an ACR20 response at week 24. The ACR50 and ACR70 response rates were also higher among patients who received golimumab+MTX (19.9% and 10.4%, respectively) than among those who received placebo+MTX (3.8% and 2.7%, respectively). Similar patterns of improvement were observed when disease activity was assessed using the DAS28-CRP or the DAS28-ESR and also when using achievement of a ≥0.25-unit reduction in the HAQ-DI score to assess improvement in physical function (table 2).

All golimumab-randomised patients who were receiving MTX at baseline and who had discontinued only one prior TNF inhibitor

Among efficacy-evaluable, golimumab-randomised patients receiving MTX at baseline, 36 had previously received only one prior TNF inhibitor (adalimumab, n= 9; etanercept, n=12; infliximab, n=15). The proportion of patients who achieved an ACR20 response at week 24 was 30.3% among those who previously had been treated only with adalimumab, 46.8% among those who previously had been treated only with etanercept and 50.9% among those who previously had been treated only with infliximab. A similar pattern of clinical response was observed when ACR50 response criteria were appliedAlso at week 24, the proportions of patients achieving DAS28-CRP response (good/moderate) and DAS28-CRP <2.6 were 39.4% and 15.2%, respectively, among those who previously had been treated only with adalimumab, 61.7% and 14.9%, respectively, among those who previously had been treated only with etanercept and 66.7% and 17.5%, respectively, among those who previously had been treated only with infliximab. Similar patterns were observed for DAS28-ESR response (good/moderate) and DAS28-ESR<2.6 (figure 1). Improvement in physical function, as assessed by achievement of a ≥0.25-unit reduction in the HAQ-DI score from baseline to week 24, was fairly consistent across the three TNF inhibitors used previously and was achieved by 48.5%, 53.2% and 56.1% of patients who had received only adalimumab, etanercept or infliximab, respectively

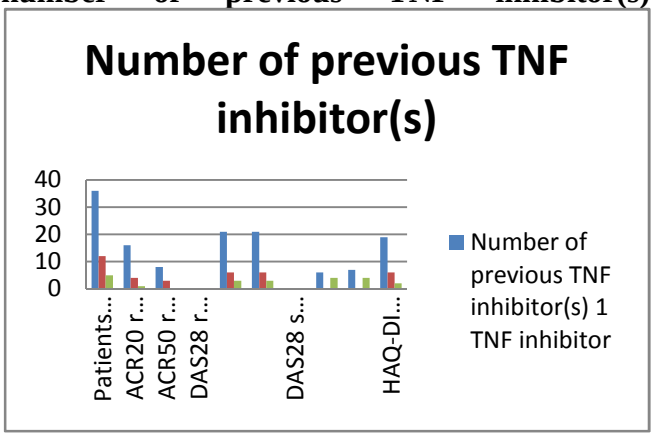
Among patients who discontinued prior TNF inhibitor treatment because of lack of efficacy, ACR20 response rates at week 24 were 36.4% for those who previously had been treated only with adalimumab, 56.5% for those who previously had been treated only with etanercept and 45.5% for those who previously had been treated only with infliximab. Among patients who discontinued previous TNF inhibitor treatment because of intolerance, ACR20 response rates at week 24 were 20.0%, 50.0% and 62.5% for adalimumab, etanercept and infliximab, respectively, but sample sizes were small. Similarly, among those who discontinued previous TNF inhibitor treatment for 'other' reasons, respective ACR20 response rates at week 24 were 16.7%, 36.4% and 51.9% for adalimumab,etanercept and infliximab, respectively (figure 1).

In table 3, clinical responses at week 24 are compared by the number of TNF inhibitors that patients had received prior to study entry. By most measures, improvement in clinical signs and symptoms and in physical function appeared to be more robust among patients who previously had received fewer TNF inhibitors. However, the numbers of patients who had received two (n=12) and three (n=5 prior TNF inhibitors were limited.

Number of previous TNF inhibitor(s)			
	1 TNF inhibitor	**2 TNF inhibitors**	**3 TNF inhibitors**
Patients who discontinued one or more previous TNF-inhibitor for any reason, n	**36**	**12**	**5**
ACR20 response	16 (44.5%)	4 (36.2%)	1(23.5%)
ACR50 response	8 (21.9%)	3 (23.4%)	0 (5.9%)
DAS28 response **(good/moderate)**			
DAS28-CRP	21 (58.4%)	6 (51.1%)	3(58.8%)
DAS28-ESR	21 (59.9%)	6 (51.1%)	3(58.8%)
DAS28 score **<2.6**			

DAS28-CRP	6 (16.1%)	0 (6.4%)	4 (5.9%)
DAS28-ESR	7 (16.8%)	0 (6.4%)	4 (5.9%)
HAQ-DI ≥0.25-unit improvement	19 (53.3%)	6 (46.8%)	2 (41.2%)

Table **4Clinical response at week 24* among golimumab+ MTX-treated patients †by number of previous TNF inhibitor(s)**



Adverse events

Safety findings for all patients enrolled in the GO-AFTER study have been reported through week 24[20] and also through up to 3 years of golimumab therapy.[30] AEs were reported by 62.3% of all MTX-treated patients. Among these, 72.5% of patients who had been intolerant of prior therapy and 56.2% of those who had an inadequate response to treatment with the prior TNF inhibitor(s) reported AEs. The overall proportions of patients developing AEs were similar among those treated with either golimumab or placebo, when grouped by number of prior TNF inhibitors received, specific prior TNF inhibitor received or reason for discontinuation of that previous agent. The incidences of serious AEs and serious infections appeared to be comparable across the subgroups of patients evaluated, with the exception of a higher incidence of serious AEs among patients who had received three (18.8%) prior TNF inhibitors, compared with those who previously had received one (2.5%) or two (3.8%) TNF inhibitors. However, interpretation of these findings is limited by the small numbers of patients who experienced serious AEs or serious infections.

Although data derived from several small case series, open-label studies and registries have suggested that patients with RA switched from one to another TNF inhibitor because of lack of efficacy or intolerance may respond to the second or even third agent,[4–9] such response patterns have not previously been examined in a randomised, controlled study. Using data from the GO-AFTER trial,[20] we evaluated the efficacy and safety of golimumab when switching from another TNF inhibitor among more than 200 patients with active RA who previously received adalimumab, etanercept and/or infliximab and reported MTX use at baseline. Our post-hoc data analyses indicate that among patients taking MTX at baseline, the response rates at week 24 are somewhat higher than those reported previously for all patients at the primary endpoint of week 14.[20] This is consistent with the generally accepted principle that concomitant use of MTX with a TNF inhibitor results in better clinical and functional outcomes.[31–33] Moreover, patients who switch from adalimumab, etanercept or infliximab to golimumab demonstrate clinically relevant responses at week 24, regardless of whether the prior TNF inhibitor was a monoclonal antibody or a soluble receptor fusion protein.

Of note and consistent with results of a comparative meta-analysis,[23]although it is difficult to compare outcomes across clinical trials due to differences in trial design, week 24 ACR response rates among patients who had discontinued prior anti-TNF therapy and received golimumab+MTX in GO-AFTER are comparable to those observed at the same week 24 time point for other biological agents with different mechanisms of action in combination with MTX. For example, week 24 ACR50 response rates for study agent versus placebo, both with concomitant disease-modifying antirheumatic drugs, were 27% and 5% for rituximab[16]; 29% (8 mg/kg), 17% (4 mg/kg) and 4% for tocilizumab[34]; and 20% and 4% for abatacept.[18]

The most straightforward approach to assess effects of switching agents is to analyse data derived from patients previously treated with only one prior TNF inhibitor. Despite our previously

reported observations of clinically relevant responses to golimumab in the overall trial population,[20] patients previously exposed to more than two TNF inhibitors appear to be less likely to demonstrate marked improvement in clinical and functional outcomes. ACR50 response rates were similar among patients who had been treated with one or two prior TNF inhibitors, but were much lower when golimumab was initiated as the fourth TNF inhibitor. Although these findings suggest that such patients might respond better to a biological agent with a different mechanism of action, it should be considered that the rates of response to each of rituximab and abatacept also decrease with previous exposure to increasing numbers of TNF inhibitors.[3536] Future studies employing biomarkers may help to predict which patients are more likely to respond to the different agents, following initial exposure to a TNF inhibitor.

Because patients were not stratified by prior TNF inhibitor use when randomised to treatment arms, the size of some of the subgroups that were evaluated was small, and our subgroup analyses were performed post-hoc, no formal statistical testing was performed. Despite these limitations, the data reveal numerical trends. For example, ACR20 response rates at week 24 for patients treated with golimumab 50 or 100 mg and MTX were numerically higher among those who switched from etanercept (46.8%) or infliximab (50.9%) compared with those who had previously received adalimumab (30.3%), the agent most similar in structure to golimumab.[37]Conversely, the proportion of patients who were previously treated with adalimumab for more than 24 weeks was much lower than that of patients who had previously received treatment with etanercept or infliximab for more than 24 weeks, which could have been due to a larger number of patients with refractory disease among those receiving adalimumab treatment. It is possible that patients previously treated with agents structurally more dissimilar to golimumab developed antibodies to the prior TNF inhibitor that precluded continued response to the previous agent[38]; these antibodies might have been less likely to cross-react with the human golimumab molecule, allowing a better subsequent response to golimumab. The presence of antibodies to prior TNF inhibitor(s) was not assessed in GO-AFTER. However, future studies of switching among TNF inhibitors should include such assessments to better characterise the mechanisms underlying differential responses to subsequent treatment.

Conclusion:

The trial demonstrated clinically relevant improvement in disease activity and physical function after switching to golimumab, regardless of which TNF inhibitor had been taken previously. Of particular note, patients who switched from either etanercept or infliximab appeared to exhibit better subsequent responses to golimumab than those that were observed among patients who previously had received adalimumab which, of the three prior TNF inhibitors, is most structurally similar to golimumab. However, further study is required to confirm the current findings.

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Original Article

TO STUDY THE QOL DEPRESSION AND SYMPTOMS IN BOTH CKD AND ESKD

Dr. Shahana Banu[1], Sameena*[2], Salma Nishath[2], Sadia Siddiqua[2], Afiya Sultana[2], Atiya Begum[2], Sumaya Fatima[2]

1. Gulbarga Unversity
2. Azad college of pharmacy

Abstract:
End-stage kidney disease is also called end-stage renal disease (ESRD). The kidneys of people with ESRD function below 10 percent of their normal ability, which may mean they are barely functioning or not functioning at all. The study was conducted to know the physical and psychological well-being in patients with advanced chronic kidney disease (CKD) and To compare symptoms, depression, and quality of life in patients with ESRD and those with CKD. To assess the impact of demographic and clinical variables on group differences in symptoms, depression, and QOL, we used linear regression, logistic regression, or the Wilcoxon-Mann-Whitney rank sum test, as appropriate. Variables included in these analyses were those that demonstrated statistically significant differences between the study groups in univariate analyses. We report differences in the eight subscales of the SF-36 as well as the PCS and MCS scores. We assessed correlations in each patient group among overall symptom burden, overall symptom severity, depression, and physical and mental well-being as measured by the PCS and MCS using Spearman's correlation coefficient, and evaluated the internal consistency reliability of the DSI using Cronbach's coefficient alpha. In conclusion, we found that patients with ESRD on maintenance dialysis and those with advanced CKD experience a similar overall burden of physical and emotional symptoms and depression and comparably low QOL. Given the substantial and well-recognized decrements in the physical and psychosocial well-being of patients with ESRD receiving chronic renal replacement therapy, our findings suggest that significant attention should be paid to these health-related domains in the large and growing number of patients who suffer from advanced CKD.

1. INTRODUCTION

Chronic kidney disease (CKD), also known as chronic renal disease, is progressive loss in kidney function over a period of months or years. The symptoms of worsening kidney function are not specific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a bloodline relative with CKD. This disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia, pericarditis or renal osteodystrophy (the latter included in the novel term CKD-MBD).[1][2] CKD is a long-term form of kidney disease; thus, it is differentiated from acute kidney disease (acute kidney injury) in that the reduction in kidney function must be present for over 3 months. CKD is an internationally recognized public health problem affecting 5–10% of the world population.[3][4]

Chronic kidney disease is identified by a blood test for creatinine, which is a breakdown product of muscle metabolism. Higher levels of creatinine indicate a lower glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products. Creatinine levels may be normal in the early stages of CKD, and the

condition is discovered if urinalysis (testing of a urine sample) shows the kidney is allowing the loss of protein or red blood cells into the urine. To fully investigate the underlying cause of kidney damage, various forms of medical imaging, blood tests, and sometimes a kidney biopsy (removing a small sample of kidney tissue) are employed to find out if a reversible cause for the kidney malfunction is present.[1]

Previous professional guidelines classified the severity of CKD in five stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is often called end-stage kidney disease, end-stage renal disease, or end-stage kidney failure, and is largely synonymous with the now outdated terms chronic renal failure or chronic kidney failure; and usually means the patient requires renal replacement therapy, which may involve a form of dialysis, but ideally constitutes a kidney transplant. Recent international guidelines reclassified CKD based on cause, glomerular filtration rate category (G1,G2,G3a,G3b,G4 and G5), and albuminuria category (A1,A2,A3).[5]

Screening of at-risk people is important because treatments exist that delay the progression of CKD.[6] If an underlying cause of CKD, such as vasculitis, or obstructive nephropathy (blockage to the drainage system of the kidneys) is found, it may be treated directly to slow the damage. In more advanced stages, treatments may be required for anemia and kidney bone disease

The aim of the study is to know the physical and psychological well-being in patients with advanced chronic kidney disease (CKD).

MATERIALS AND METHODS:

Study Setting and Design

As part of a larger, prospective cohort study of sleep, memory, and QOL in patients with advanced CKD and subjects undergoing chronic peritoneal dialysis or thrice-weekly in-center hemodialysis, we conducted a subanalysis of patients' symptoms, depression, and QOL. This study was approved by the Institutional Review Board, and all participants provided informed consent.

Between April 2016 and March 2017, patients with ESRD on maintenance dialysis and individuals with a history of stage 4 or 5 CKD receiving care at local dialysis units. Exclusion criteria included age <18 yr or >90 yr, not residing at home, active malignancy, active infection (pneumonia), active coronary artery disease (*e.g.*, unstable angina, myocardial infarction) within the last 6 mo, advanced cirrhosis, advanced dementia, active alcohol abuse, active treatment for sleep apnea, refractory psychiatric disease, or an unsafe home environment. Patients without exclusions were approached at the time of their routine CKD clinic visit, dialysis clinic visit, or initial visit to the kidney transplantation clinic and signed informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki.

We assessed patients' demographic characteristics and abstracted serologic variables from the medical record including the most recent hemoglobin and serum calcium, phosphorous, albumin, and creatinine. For patients with a history of stage 4 or 5 CKD, we used the most recent serum creatinine and 4-variable Modification of Diet in Renal Disease study equation to calculate their estimated GFR (eGFR). Some patients initially identified in the screening phase as having a history of stage 4 CKD demonstrated an eGFR that was consistent with advanced stage 3 CKD. These individuals were included in our study (21). We also assessed patients' functional status using the Karnofsky Performance Status Scale and Lawton Instrumental Activities of Daily Living Scale (22,23). Lower scores on the Karnofsky scale and higher scores on the Lawton scale indicate greater functionality. As the parent study involved the assessment of sleep quality in patients' homes, all enrolled patients self-administered the study surveys at the time of this home visit.

Assessment of Symptoms, Depression, and Quality of Life

We used the 30-item Dialysis Symptom Index (DSI) to assess the presence and severity of physical and emotional symptoms. To complete the DSI, patients were asked to report which of 30 individual symptoms had been present over the past 7 d. We considered missing responses, which were present in fewer than 4% of any of the individual symptoms to indicate that the symptom was not present. For symptoms that were present, the patient was asked to describe the severity of the symptom on a 5-point Likert scale ranging from "not at all bothersome" to "very bothersome." For missing responses on symptom severity, which were also present in fewer than 4% of responses, we confirmed that the symptom was reported as not present and assigned a severity score of zero. An overall symptom burden score ranging from 0 to 30 was generated by summing the number of symptoms reported as being present. In addition, an overall symptom-severity score ranging from 0 to 150 was generated by summing the severity of symptoms, assigning a score of zero for symptoms that were not present. Past studies confirmed the test-retest reliability and content and construct validity of the DSI in patients on hemodialysis (12,24).

We used the PHQ-9 to assess the presence and severity of depression. This 9-item tool assesses the frequency with which patients experience depressive thoughts or feelings over the prior 2 wk. The severity of depressive disorder is considered moderate for scores ranging from 10 to 14, moderately severe for scores of 15 to 19, and severe for scores of 20 to 27. The PHQ-9 has been used to assess depression in patients with ESRD and those with CKD (25–27). In patients on hemodialysis, scores >9 are 92% sensitive and specific for a diagnosis of depressive disorder (25).

We used the Medical Outcomes Study Short Form-36 (SF-36) to assess QOL. The SF-36 contains eight subscales (physical function, role limitations-physical, bodily pain, vitality, general health perceptions, role limitations-emotional, social function, and mental health) and two component summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Higher scores indicate better QOL. The SF-36 has been used extensively in patients with kidney disease and has sound psychometric characteristics in this patient population (28–30).

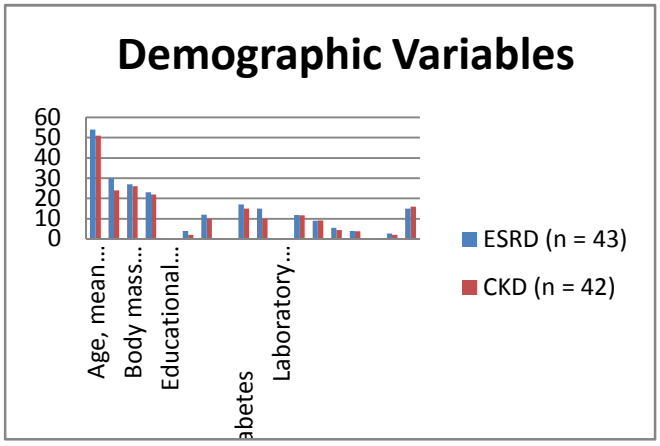
Statistical Analyses

For our analyses, we considered hemodialysis and peritoneal dialysis patients collectively as one group (herein referred to as the ESRD group). These patients were compared with those with advanced CKD (CKD group). Differences between the groups in demographic characteristics, clinical variables, the prevalence and severity of individual symptoms, overall symptom burden and overall symptom severity, depression, and QOL were assessed using *t* test or Mann-Whitney tests for continuous variables, and the χ^2 statistic or Fisher's exac*t* test for categorical variables. To assess the impact of demographic and clinical variables on group differences in symptoms, depression, and QOL, we used linear regression, logistic regression, or the Wilcoxon-Mann-Whitney rank sum test, as appropriate. Variables included in these analyses were those that demonstrated statistically significant differences between the study groups in univariate analyses. We report differences in the eight subscales of the SF-36 as well as the PCS and MCS scores. We assessed correlations in each patient group among overall symptom burden, overall symptom severity, depression, and physical and mental well-b

A total of 100 patients were screened for study participation, and 93 met eligibility criteria. Of these, eight did not complete the study surveys, resulting in a patient population of 85. 43 patients (51%) had ESRD; 33 (78%) on hemodialysis and 10 (22%) on peritoneal dialysis. This cohort included all ESRD patients from the larger cohort study as of November 2017. 42 patients (49%) had CKD. Patients with ESRD, have a higher serum phosphorous concentration, and have higher scores on the Karnofsky index and lower scores on the Activities of Daily Living Scale, indicating poorer functional status.

TABLES: 01. **Patient Characteristics**

Demographic Variables	**ESRD (*n* = 43)**	**CKD (*n* = 42)**	***P* value**
Age, mean (SD), y	54 ± 15	51 ± 15	0.2
Men % (n)	30 (51)	24 (57)	0.3
Body mass index, mean (SD), kg/m^2	27 ± 5	26 ± 15	0.4
Married (%)	23 (53)	22(52)	0.7
Educational status			
Less than 9 th grade % (n)	4 (10)	2 (4)	0.1
High school graduate % (n)	12 (28)	10 (24)	0.6
Comorbid conditions			
Diabetes	17 (39)	15(36)	0.6
Cardiovascular disease	15 (36)	10 (24)	0.07
Laboratory variables			
Hemoglobin, mean (SD) g/dl	11.9 (1.6)	11.7 (1.5)	0.5
Serum calcium, mean (SD) mg/dl	9.0 (1.0)	9.1 (0.6)	0.5
Serum phosphorous, mean (SD) mg/dl	5.5 (1.6)	4.5 (1.2)	<0.001
Serum albumin, mean (SD) g/dl	3.9 (0.5)	3.8 (0.6)	0.1
Functional status			
Karnofsky score, mean (SD)	2.75 ± 1.3	2.1 ± 1.1	0.001
ADL, median (IQR)a	15 (13, 16)	16 (14.5, 16)	0.008



Symptoms, Depression, and Quality of Life

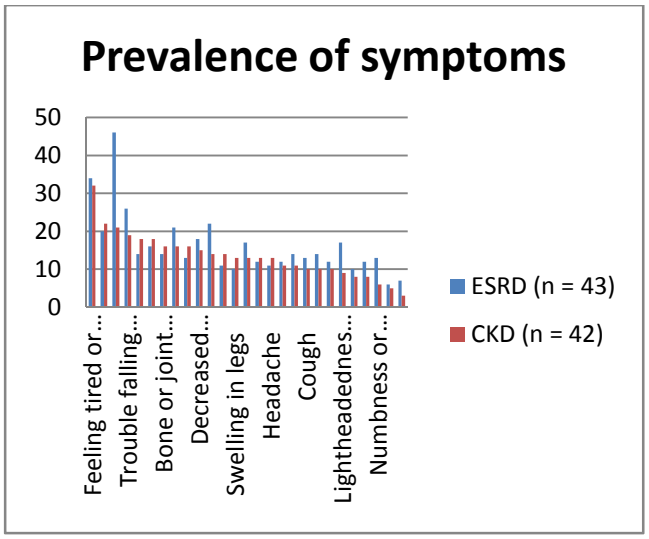
There was no difference in the mean overall number of symptoms in patients with ESRD compared with those with CKD (11.2 ± 6.4 *versus* 10.2 ± 5.6, *P* = 0.3). Patients with ESRD were more likely to report difficulty falling asleep (60% *versus* 44%, *P* = 0.04), dry mouth (50% *versus* 34%, *P* = 0.05), and lightheadedness/dizziness (39% *versus* 23%, *P* = 0.02). However, none of these differences met the level of statistical significance after Bonferroni correction (Table 2). The median overall symptom-severity score was not different in patients with ESRD compared with CKD (20.5 *versus* 15, *P* = 0.2). The median severity of itching was greater in patients with ESRD compared with CKD (2.0 *versus* 1.0, *P* = 0.001). Patients with ESRD also reported higher median severity scores for decreased interest in sex (3.0 *versus* 2.0, *P* = 0.009) and difficulty becoming sexually aroused (3.0 *versus* 2.0, *P* = 0.004), although these differences did not reach the level of statistical significance after Bonferroni correction. There was a trend toward more severe swelling in the legs among CKD patients compared with patients with ESRD (2.5 *versus* 1.0, *P* = 0.08), although this difference was also not statistically significant

TABLE :02. Prevalence of symptoms

Symptom	**ESRD (*n* = 43)**	**CKD (*n* = 42)**	P valueb
Feeling tired or lack of energy	34 (79)	32 (78)	1
Dry skin	20 (47)	22(53)	0.5
Itching	46 (51)	21(51)	0.4
Trouble falling asleep	26 (60)	19 (44)	0.04
Feeling sad	14 (33)	18 (43)	0.2
Feeling irritable	16(37)	18(43)	0.5
Bone or joint pain	14 (33)	16(39)	0.4
Muscle cramps	21 (50)	16 (38)	0.1
Feeling anxious	13 (31)	16(38)	0.3
Decreased interest in sex	18 (43)	15 (36)	0.4
Dry mouth	22 (50)	14 (34)	0.05
Constipation	11 (26)	14 (33)	0.3
Swelling in legs	10 (24)	13(32)	0.3
Restless legs	17 (39)	13(32)	0.4
Feeling nervous	12 (29)	13(31)	0.9
Headache	11 (26)	13 (30)	0.6
Diarrhea	12 (28)	11(25)	0.7
Decreased appetite	14 (32)	11(25)	0.3

Cough	13 (31)	10 (24)	0.3
Muscle soreness	14 (33)	10 (24)	0.2
Nausea	12 (27)	10 (24)	0.7
Lightheadedness or dizziness	17(39)	9(23)	0.02
Shortness of breath	10 (23)	8 (22)	0.9
Difficulty concentrating	12 (28)	8 (22)	0.4
Numbness or tingling in feet	13 (30)	6 (21)	0.2
Vomiting	6(13)	5 (11)	0.8
Chest pain	3 (8)	3(8)	1

Lightheadedness or dizziness	1	1	0.5
Feeling anxious	2	2	0.5
Nausea	2	1	0.2
Headache	1	1	0.3
Restless legs or difficulty keeping legs still	2	1	0.1
Feeling irritable	1	2	0.01
Constipation	2	1	0.7
Difficulty concentrating	2	1	0.3
Vomiting	3	1.5	0.2
Feeling nervous	2	1	0.5
Chest pain	2	2	0.6



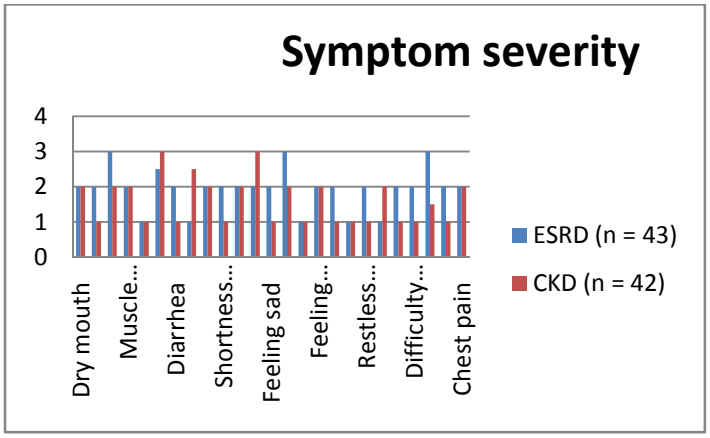


TABLE:03. Symptom severity

Symptom	**ESRD (*n* = 43)**	**CKD (*n* = 42)**	P valueb
Dry mouth	2	2	0.2
Itching	2	1	0.001
Trouble falling asleep	3	2	0.4
Muscle cramps	2	2	0.1
Cough	1	1	0.6
Bone or joint pain	2.5	3	0.7
Diarrhea	2	1	0.04
Swelling in legs	1	2.5	0.08
Muscle soreness	2	2	0.1
Shortness of breath	2	1	0.3
Decreased appetite	2	2	0.7
Numbness or tingling in feet	2	3	0.3
Feeling sad	2	1	0.6
Decreased interest in sex	3	2	0.009

The median PHQ-9 score in patients with ESRD was similar to that of patients with CKD (5.0 *versus* 4.0, *P* = 0.95). The proportion of patients with PHQ-9 scores >9 was similar in patients with ESRD and CKD (15.5% *versus* 15%, respectively, *P* = 0.9). There were no differences in the proportion of patients with moderate, moderately severe, and severe depressive disorder.

Eleven patients, four in the ESRD group and seven in the CKD group, did not complete the SF-12 and were not included in the QOL analyses. Patients with ESRD had lower physical function scores than those with CKD, with no differences noted in any of the other SF-12 subscale. However, overall physical well-being as measured by the PCS was comparable (36.6 ± 10.3 in ESRD *versus* 39.3 ± 10.5 in CKD, *P* = 0.1), as was overall mental well-being as measured by MCS (44.6 ± 7.8 in ESRD *versus* 44 ± 7.3 in

CKD, $P = 0.6$). There were no associations of stage of CKD or type of dialysis with symptoms, depression, or QOL scores.in regression analysis, we examined the attenuating or intensifying effects of race, phosphorous concentration, cardiovascular disease, Karnofsky score, and Activities of Daily Living Scale score on differences in symptoms, depression, and QOL between the study groups. Phosphorous concentration attenuated the nonstatistically significant difference in the severity of "decreased interest in sex," while functional status as measured by the Activities of Daily Living Scale attenuated the nonstatistically significant difference in the severity of the symptom "difficulty becoming sexually aroused." Adjusting for functional status as measured by the Karnofsky scale rendered the difference in the severity of itching between the groups nonstatistically significant. Adjustment for these demographic and clinical variables did not unmask differences in overall symptom burden, overall symptom severity, PHQ-9 scores, or QOL scores and did not attenuate the modest difference in the physical function subscale of the SF-12 (data not shown).

Correlations of Symptoms, Depression, and Quality of Life

Total symptom burden and total symptom severity were correlated with depression in both patient groups, with PCS scores in patients with ESRD and with MCS scores in patients with CKD. Depression was strongly correlated with MCS scores in both groups (Table 4). The Cronbach's coefficient alpha for the DSI in patients with ESRD was 0.86, and was 0.82 in patients with CKD.

TABLE 04: Correlations of symptoms, depression, and quality of life.

	PHQ-9		PCS		MCS	
	ESRD	CKD	ESRD	CKD	ESRD	CKD
Total symptom burden	0.49b	0.54	−0.47b	−0.21	−0.26c	−0.38c
Total symptom severity	0.58b	0.53b	−0.44b	−0.31c	−0.23	−0.41c
PHQ-9	-	-	−0.21	−0.19	−0.51b	−0.51b

[a]Data denote correlation coefficient (r).
[b]$P < 0.001$.
[c]$P < 0.05$.

eing as measured by the PCS and MCS using Spearman's correlation coefficient, and evaluated the internal consistency reliability of the DSI using Cronbach's coefficient alpha. We applied the Bonferroni correction for the analyses of differences in the prevalence and severity of individual symptoms on the DSI given the multiple comparisons. For these analyses, a two-sided p-value of <0.002 was considered to represent statistical significance. For all other analyses, a two-sided p-value <0.05 was applied. All analyses were performed using STATA version 8 (College Station, TX).

DISCUSSION:

Past studies demonstrated that patients receiving maintenance dialysis experience a multitude of physical and emotional symptoms, a particularly high prevalence of depression, and significant impairments in QOL. The findings of the present study suggest that patients with advanced CKD who are not dependent on chronic renal replacement therapy experience a comparable overall burden of symptoms and depression and low QOL. These novel findings have a series of important clinical implications for patients and providers.

Despite research demonstrating the impaired physical and psychosocial well-being of patients with ESRD, the clinical, treatment, and/or patient-related factors that cause symptoms, depression, and impaired QOL in this patient population remain incompletely understood. While the physical rigors of dialysis therapy and emotional, social, and vocational impact of this chronic treatment would seem to be likely mediators, the findings of this study suggest that this may not be so. A significant loss without an absence of

kidney function may be sufficient for patients to develop symptoms, depression, and impaired QOL. Determining whether this relates to metabolic derangements, retained uremic toxins, comorbid medical conditions, anxiety about the presence of CKD and potential future need for renal replacement therapy, or other factors, is important to facilitate the implementation of appropriate treatment.

Our findings have important implications for patients with CKD. Patients with advanced CKD may be unfamiliar with how chronic renal replacement therapy will impact their physical and psychosocial well-being. The need for chronic dialysis results in a significant change in lifestyle for many patients. Based on our findings, it seems plausible that many individuals with CKD may not experience a substantial change in physical and/or psychosocial well-being at the time of this transition. If confirmed in longitudinal studies, patients and providers will be able to use this knowledge to make more informed decisions on whether and when to initiate chronic renal replacement therapy.

Approximately 500,000 patients in the United States receive chronic renal replacement therapy, most of whom are treated with hemodialysis (33). Prior studies demonstrate that bothersome symptoms and depression are commonly undertreated in this population (13,34,35). It is currently unknown whether similar undertreatment of symptoms exists in patients with CKD. Recent analyses suggest that as many as 20 million Americans have moderate to advanced CKD (20). Analogous to patients with ESRD, the care of those with advanced CKD is focused in large part on the treatment of anemia, bone disease, electrolyte disturbances, and hypertension. Nonetheless, awareness among renal providers of the high burden of symptoms and depression in the large group of patients with CKD is essential for the implementation of appropriate symptom-alleviating and antidepressive therapies. Studies assessing renal and primary provider awareness and treatment of symptoms and depression in this patient group are warranted, as are efforts to examine whether the implementation of treatment translates into improvements in QOL.

It should be noted that depression has been linked with impaired QOL and increased mortality in patients receiving hemodialysis, and may be associated with mortality in CKD as well (18,36). Confirming that depression is associated with adverse outcomes including death in patients with CKD is essential, as are efforts to determine whether pharmacologic and/or nonpharmacologic therapy for depression can attenuate such adverse effects in the broad spectrum of patients with renal disease.

While the SF-36 and PHQ-9 have been used previously in patients with CKD, the DSI has not been tested in this patient group. We found moderate correlation between the DSI and PHQ-9, PCS, and MCS scores. Moreover, the DSI demonstrated strong internal consistency reliability in patients with CKD. These findings suggest that with additional examination of its psychometric characteristics, this questionnaire could be used on a broad basis to assess symptoms in patients with CKD.

It is important to note that patients with ESRD were somewhat more likely to report sleep-related symptoms, muscle cramps, dry mouth, and lightheadedness. Although these differences did not meet the level of statistical significance after adjustment for multiple comparisons, there is biologic plausibility to such differences that warrants future study. Similarly, patients with ESRD reported lower scores on the physical function subscale of the SF-36. Although this did not translate into differences in PCS scores, this finding sheds preliminary light on subdomains of QOL that may vary between these two populations.

There are limitations to this study. First, our patient population was relatively small, which may decrease the generalizability of our findings. Second, we excluded patients with severe comorbidities and those not residing at home. These are exclusion criteria that may have disproportionately affected those with ESRD and rendered our dialysis cohort healthier than dialysis

patients in general. However, it should be noted that the general demographic characteristics of our ESRD cohort were similar to the US ESRD population, while our CKD cohort comprised a larger number of men compared with the overall population of patients with CKD (33). Future studies should compare these health-related domains in a much larger and broader sample of ESRD and CKD patients, including those with serious comorbid illness. Third, the assessment of symptoms in patients on hemodialysis was conducted in patients' homes, rather than during dialysis sessions. It is possible that patients on hemodialysis experience more symptoms at the time of their treatment than in the confines of their home. However, the DSI ascertains symptoms over the past week, making it likely that patients would integrate both dialysis and nondialysis experiences in their responses. Lastly, the cross-sectional nature of our study precluded an assessment of the evolution of symptoms across the spectrum of CKD stages and did not permit us to evaluate the associations of symptoms, depression, and impaired QOL with serious adverse patient outcomes.

CONCLUSION:

In conclusion, we found that patients with ESRD on maintenance dialysis and those with advanced CKD experience a similar overall burden of physical and emotional symptoms and depression and comparably low QOL. Given the substantial and well-recognized decrements in the physical and psychosocial well-being of patients with ESRD receiving chronic renal replacement therapy, our findings suggest that significant attention should be paid to these health-related domains in the large and growing number of patients who suffer from advanced CKD.

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Original Article

TRIPLE COMBINATION THEAPY WITH AMLODINE, VALSARTAN AND HYDROCHLOROTHIAZIDE vs DUAL COMBINATION THERAPY WITH AMLODIPINE AND HYDRCHLOROTHIAZIDE FOR STAGE 2 HYPERTENSIVE PATIENTS

Dr. Shahana Banu[1], Jabeen Farhana*[2], Juveria Naaz[2], Nazneen Begum[2], Sana Banu[2], Syeda Kibriya Misbah[2], Tahur Fatima[2]

1. Gulbarga Unversity, Karnataka, India
2. Azad college of pharmacy, India

Corresponding Author:
Jebeen Farhana
Fahana_jbn@yahoo.co.in

Abstract:
Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[2] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[7] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults. Different numbers apply to children. Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement. to assess the benefits of the triple combination with Aml/Val+HCTZ compared with Aml+HCTZ dual therapy in patients with stage 2 hypertension.Evaluated the efficacy and safety of triple therapy with amlodipine/valsartan+hydrochlorothiazide (Aml/Val+HCTZ) vs dual therapy with Aml+HCTZ in stage 2 hypertensive patients. Changes in msSBP and msDBP at week 8 were analyzed using analysis of covariance model with treatment and region as factors and baseline BP (week 0 or week 4 depending on analysis) as a covariate. The results were presented as least squares mean difference between the treatment groups with 95% confidence interval and *P* value. This study provides relevant information as it follows the clinical practice of prescribing a third antihypertensive agent in a step-wise manner to initial dual therapy depending on BP levels of the patient. The present analyses, however, have certain limitations: 1) this was a *post hoc* analysis of a study not designed to evaluate the efficacy of triple therapy vs dual therapy; 2) patients were not randomized to receive Aml/Val/HCTZ and Aml/HCTZ; and 3) the duration of the treatment with triple therapy was four weeks. In conclusion, triple combination therapy with Aml/Val/HCTZ provides significantly greater BP reductions and is well tolerated compared with Aml/HCTZ dual therapy in stage 2 hypertension and can provide additional benefits in patients who require more than two agents to reach their target BP.

1. INTRODUCTION

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated.[1] High blood pressure usually does not cause symptoms.[2] Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.[3][4]

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[5] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.[5][6] Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol.[2][5] The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[5]

Blood pressure is expressed by two measurements,
the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[2] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[7] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults.[5] Different numbers apply to children.[8] Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement.[1][5]

Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications.[9] Lifestyle changes include weight loss, decreased salt intake, physical exercise, and a healthy diet.[5] If lifestyle changes are not sufficient then blood pressure medications are used.[9] Up to three medications can control blood pressure in 90% of people.[5]The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy.[10] The effect of treatment of blood pressure between 140/90 mmHg and 160/100 mmHg is less clear, with some reviews finding benefit[11][12] and others finding a lack of evidence for benefit.[13] High blood pressure affects between 16 and 37% of the population globally.[5] In 2010 hypertension was believed to have been a factor in 18% (9.4 million) deaths

SIGNS AND SYMPTOMS:

Hypertension is rarely accompanied by symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. Some with high blood pressure report headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes.[15] These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.[16]

On physical examination, hypertension may be associated with the presence of changes in the optic fundus seen by ophthalmoscopy.[17] The severity of the changes typical of hypertensive retinopathy is graded from I–IV; grades I and II may be difficult to differentiate.[17] The severity of the retinopathy correlates roughly with the duration or the severity of the hypertension

Secondary hypertension[edit]
Main article: Secondary hypertension

Hypertension with certain specific additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause. For example, Cushing's syndrome frequently causes truncal obesity, glucose intolerance, moon face, a hump of fat behind the neck/shoulder, and purple abdominal stretch
marks.[18] Hyperthyroidism frequently causes weight loss with increased appetite, fast heart rate, bulging eyes, and tremor. Renal artery stenosis (RAS) may be associated with a localized abdominal bruit to the left or right of the midline (unilateral RAS), or in both locations (bilateral RAS). Coarctation of the aorta frequently causes a decreased blood pressure in the lower extremities relative to the arms, or delayed or absent femoral arterial pulses. Pheochromocytoma may cause abrupt ("paroxysmal") episodes of hypertension accompanied by headache, palpitations, pale appearance, and excessive sweating.[18]

Hypertensive crisis[edit]
Main article: Hypertensive crisis

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110) is

referred to as a hypertensive crisis. Hypertensive crisis is categorized as either hypertensive urgency or hypertensive emergency, according to the absence or presence of end organ damage, respectively.[19][20]

In hypertensive urgency, there is no evidence of end organ damage resulting from the elevated blood pressure. In these cases, oral medications are used to lower the BP gradually over 24 to 48 hours.[21]

In hypertensive emergency, there is evidence of direct damage to one or more organs.[22][23] The most affected organs include the brain, kidney, heart and lungs, producing symptoms which may include confusion, drowsiness, chest pain and breathlessness.[21] In hypertensive emergency, the blood pressure must be reduced more rapidly to stop ongoing organ damage,[21] however, there is a lack of randomised controlled trial evidence for this approach.[23]

to assess the benefits of the triple combination with Aml/Val+HCTZ compared with Aml+HCTZ dual therapy in patients with stage 2 hypertension. Evaluated the efficacy of triple therapy with amlodipine/valsartan+hydrochlorothiazide (Aml/Val+HCTZ) vs dual therapy with Aml+HCTZ Evaluated the Safety and tolerability of triple therapy with amlodipine/valsartan+hydrochlorothiazide (Aml/Val+HCTZ) vs dual therapy with Aml+HCTZ. MATERIALS AND METHODS:

This was a *post hoc* analysis of an eight-week, multicenter (75 centers in Europe and the United States), randomized, double-blind, parallel-group study. The methods are described in detail by Destro et al.17 After a three to seven-day washout period, all eligible patients (stage 2 hypertension [msSBP ≥ 160 mmHg and < 200 mmHg]) were randomized at baseline (week 0) to receive either Aml/Val 5/160 mg or Aml 5 mg for two weeks. After two weeks, the dose of Aml was force-titrated from 5 mg to 10 mg in both treatment arms. HCTZ 12.5 mg was added to both treatment groups at week 4 (open-label), if the patient had not reached the pre-specified protocol criteria of msSBP < 130 mmHg.

All patients included in this study were aged ≥18 years. Patients were excluded at screening if msSBP was <140 mmHg while receiving more than three antihypertensive medications, or if msSBP was ≥140 mmHg and <180 mmHg while receiving more than two antihypertensive treatments, or if msSBP was ≥180 mmHg while receiving more than one antihypertensive medication. Patients with hepatic or renal impairment, secondary hypertension, clinically significant cerebrovascular and cardiovascular disease, type 1 diabetes, and inadequately controlled type 2 diabetes were also excluded.

Efficacy and safety assessments

Demographics and baseline characteristics of patients requiring HCTZ and those not requiring HCTZ at week 4 were summarized. For the efficacy and safety analyses, only the subgroup of patients that required addition of HCTZ at week 4 were evaluated. The efficacy variables were change in msSBP and mean sitting diastolic blood pressure (msDBP) from baseline to week 8, week 4 to week 8, and overall BP control rate (<140/90 mmHg) at week 8. Because HCTZ was to be added if msSBP was ≥ 130 mmHg, patients included in the efficacy analyses may have an msSBP <140 mmHg at week 4. To eliminate bias in assessing the effect of add-on HCTZ therapy on BP control at week 8, patients with BP <140/90 mmHg at week 4 were excluded from the control rate analysis. Subgroup analyses were also performed according to the severity of hypertension (msSBP ≥ 180 mmHg at baseline), diabetic status, age group (≥65 years), race (Caucasians and Non-Caucasians), and body mass index (BMI) ≥ 30 kg/m^2.

At each visit, sitting BP were measured three times at two to three-min intervals using an Omron BP monitor (Omron Healthcare, Milton Keynes, UK) in accordance with the British Hypertension Society guidelines.18 BP readings were made by the same clinician whenever possible, at drug trough (ie, 24 ± 3 h post-dose). Safety assessments for this analysis consisted of a summary of AEs during week 4 to week 8 of treatment.

Statistical analysis

Data gathered in this *post hoc* analysis was summarized with respect to demographic, efficacy, and safety variables. All efficacy analyses were conducted for the intent-to-treat population (randomized patients with a baseline and at least one post-baseline efficacy assessment).

Changes in msSBP and msDBP at week 8 were analyzed using analysis of covariance model with treatment and region as factors and baseline BP (week 0 or week 4 depending on analysis) as a covariate. The results were presented as least squares mean difference between the treatment groups with 95% confidence interval and *P* value. The proportion of patients achieving BP control was analyzed using a logistic regression model, with treatment as factor and baseline BP as a covariate. Summary statistics were performed for further subgroups by age, gender, BMI, and severe SBP at baseline.

RESULTS AND DISCUSSION:

Of the patients randomized to Aml/Val (N = 322) and Aml (N = 324) treatment arms, 136 (42%) and 208 (64%), respectively, required add-on HCTZ, of whom 133 (98%) and 200 (96%) completed the study.

Demographic and baseline characteristics of patients requiring add-on HCTZ and those not requiring add-on HCTZ at week 4 are presented in Table 1. Compared to patients who did not receive add-on HCTZ, a greater percentage of patients requiring add-on HCTZ had diabetes (6.6% vs 14.8%) and severe hypertension at baseline (13.6% vs 18.0%). The baseline msBP of patients requiring add-on HCTZ (Aml/Val+HCTZ: 171.5/96.4 mmHg, Aml+HCTZ: 171.5/95.0 mmHg) was numerically higher compared with patients who did not require add-on therapy (Aml/Val: 169.3/95.1 mmHg, Aml: 169.8/94.1 mmHg). Within the patients who received add-on HCTZ, demographic and baseline characteristics were comparable between the two treatment groups.

Characteristics	**Patients not requiring HCTZ**		**Patients requiring add-on HCTZ**	
	Aml/Val (N = 186)	**Aml (N = 116)**	**Aml/Val HCTZ (N = 136)**	**Aml HCTZ (N = 208)**
Age ± SD (years)	57.5 ± 10.6	57.3 ± 10.8	58.8 ± 9.8	58.5 ± 10.2
Age category, n (%)				
<65 years	137 (73.7)	85 (73.3)	98 (72.1)	149 (71.6)
≥65 years	49 (26.3)	31 (26.7)	38 (27.9)	59 (28.4)
Gender, n (%)				
Male	94 (50.5)	51 (44.0)	71 (52.2)	108 (51.9)
Race, n (%)				
Caucasians	159 (85.5)	93 (80.2)	102 (75.0)	174 (83.7)
Blacks	6 (3.2)	2 (1.7)	15 (11.0)	10 (4.8)
Others	21 (11.3)	21 (18.1)	19 (13.9)	24 (11.6)
msSBP ± SD, mmHg	169.3 ± 8.6	169.8 ± 9.1	171.5 ± 9.2	171.5 ± 8.1
msDBP ± SD, mmHg	95.1 ± 9.5	94.1 ± 10.9	96.4 ± 10.4	95.0 ± 10.2
Hypertension severity at baseline, n (%)	22 (11.8)	19 (16.4)	25 (18.4)	37 (17.8)
≥180 mmHg				
Diabetes; n (%)	13 (7.0)	7 (6.0)	22 (16.2)	29 (13.9)
BMI, Mean ± SD	28.9 ± 4.9	29.7 ± 5.9	31.1 ± 5.9	30.7 ± 5.6

The msSBP and msDBP of patients with week 4 HCTZ add-on therapy is plotted over time in Figure 1. For each post-baseline (week 0) measurement, patients belonging to Aml/Val+HCTZ triple therapy group achieved higher BP reduction than those in Aml+HCTZ dual therapy group, with an msBP of 141.2/82.2 mmHg vs 147.7/87.0 mmHg at week 8. An additional BP-lowering benefit was observed after the week 4 HCTZ add-on in both treatment groups. However, the incremental reduction from week 4 to week 8 was significantly greater with HCTZ added to Aml/Val compared with HCTZ added to Aml (6.9/3.5 vs 3.1/1.0 mmHg, $P < 0.01$)

N	**msSBP**		**MsDBP**		
	LSM change (SEM	**Difference (95% CI)**	**LSM change (SEM**	**Difference (95% CI)**	

	)		)		
From baseline to week 8					
Aml/Val+HCTZ	133	−30.5 (1.1)	−6.1 (−8.6, −3.6)	−13.8 (0.7)	−5.5 (−7.1, −3.9)
Aml+HCTZ	206	−24.3 (0.9)	*P* < 0.0001	−8.3 (0.6)	*P* < 0.0001
From week 4 to week 8					
Aml/Val+HCTZ	133	−6.9 (0.9)	−3.8 (−6.1, −1.5)	−3.5 (0.6)	−2.6 (−3.9, −1.1)
Aml+HCTZ	206	−3.1 (0.8)	*P* = 0.0012	−1.0 (0.5)	*P* = 0.0004

The overall reduction from baseline to week 8 was also significantly greater in the Aml/Val+HCTZ triple combination compared to Aml+HCTZ therapy (30.5/13.8 vs 24.3/8.3 mmHg, *P* < 0.0001) (Table 2).

In patients not adequately controlled (BP >140/90 mmHg) at week 4 on their existing medication, HCTZ 12.5 mg add-on for an additional four weeks facilitated attaining msBP < 140/90 mmHg in a higher proportion of patients previously on Aml/Val (37.7%) than Aml monotherapy (15.4%).

Subgroups

Similarly greater reductions in msBP with Aml/Val+HCTZ triple therapy were observed in all the subgroups by severity of hypertension, diabetic status, age group, race, and BMI, compared with the reductions with Aml+HCTZ dual therapy

Event	**Aml/Val HCTZ N = 136**	**Aml HCTZ N = 208**
AEs; n (%)	46 (33.8)	69 (33.2)
Edema peripheral	19 (14.0)	37 (17.8)
Nasopharyngitis	4 (2.9)	2 (1.0)
Headache	2 (1.5)	5 (2.4)
Dizziness	2 (1.5)	1 (0.5)
Syncope	2 (1.5)	0 (0.0)
Cough	1 (0.7)	4 (1.9)
Diarrhea	1 (0.7)	3 (1.4)
Viral infection	1 (0.7)	2 (1.0)
Paresthesia	0 (0.0)	2 (1.0)
Joint swelling	1 (0.7)	2 (1.0)
Dyspepsia	0 (0.0)	3 (1.4)
Flushing	0 (0.0)	3 (1.4)
Upper respiratory tract infection	0 (0.0)	2 (1.0)
Urinary tract infection	0 (0.0)	3 (1.4)
Hypokalemia	0 (0.0)	2 (1.0)
Arthralgia	0 (0.0)	2 (1.0)
Neck pain	0 (0.0)	2 (1.0)

Safety and tolerability

Both treatment arms were well tolerated. The overall incidence of AEs was similar between the triple and dual therapies (Table 3). Peripheral edema was the most frequently reported AE, which occurred at a slightly lower frequency in the presence of Val (Aml/Val+HCTZ: n = 19, 14.0%; Aml+HCTZ: n = 37, 17.8%).

Amongst patients who received HCTZ add-on at week 4, 1.7% (n = 6) of patients discontinued the study prematurely (Aml/Val+HCTZ; 1.5% [n = 2], Aml+HCTZ: 1.9% [n = 4]) due to AEs. There were no deaths during the entire course of the study. Serious AEs were also not reported in any treatment group from week 4 to week 8.

DISCUSSION:

Current hypertension treatment guidelines state that dual combination therapy be considered as initial therapy in patients with msBP ≥ 20/10 mmHg above goal.1,2 Furthermore, recent outcome trials suggest that the percentage of patients requiring three or more antihypertensive drugs to achieve BP control can range from 23%–52% depending on the trial.5,14–16

In this study, patients with stage 2 hypertension were randomized to initiate therapy with either dual Aml/Val therapy or Aml monotherapy with the addition of HCTZ to either regimen if BP remained uncontrolled. Triple therapy with Aml/Val+HCTZ 10/160/12.5 mg provided clinically and statistically significant additional BP reductions compared with the dual therapy with Aml+HCTZ 10/12.5 mg (*P* < 0.0001). Similarly, Aml/Val+HCTZ triple therapy produced greater BP reductions compared with Aml+HCTZ dual therapy in diverse patient

populations, including patients regardless of age, diabetic status, BMI, or race. These results are consistent with those reported by Calhoun et al wherein triple therapy with Aml/Val/HCTZ at a dose of 10/320/25 mg was shown to have superior efficacy compared with Aml/Val 10/320 mg, Val/HCTZ 320/25 mg, and Aml/HCTZ 10/25 mg dual therapies in a parallel-design trial, where patients were randomized to the four treatment groups.19 The patients on triple therapy achieved a mean SBP reduction of 40–50 mmHg, which was clinically and statistically greater than that with the dual component therapies.19 In the present study, a sequential antihypertensive treatment approach dependent on BP level achieved was followed, enabling the assessment of the efficacy and safety of adding a third agent in those patients initiated on dual therapy.

Hypertension is a multifactorial disease and the results of this study confirm that combining therapies with different mechanisms of action can additively reduce BP. Both Aml and Val are vasodilators that work through different mechanisms. Aml blocks calcium channels in vascular smooth muscle and Val blocks the binding of angiotensin II to the angiotensin type 1 receptor. The antihypertensive efficacy of calcium channel blockers (CCBs), however, is reduced by the associated activation of the renin–angiotensin system (RAS) and the sympathetic nervous system.20 Coadministration of an angiotensin receptor blocker (ARB) can effectively prevent such responses.

In this study, the response to HCTZ was dependent on the initial treatment, ie, Aml/Val vs Aml. The benefit of adding HCTZ was greater in patients treated with Val. This may be explained by the fact that diuretics decrease intravascular volume, activating RAS resulting in a diminished antihypertensive response. This counter-regulatory effect is prevented in the presence of an ARB. In previous studies, Val and HCTZ in combination have demonstrated additional BP lowering effects compared with each of the component monotherapies.21,22 While diminished efficacy of CCBs has been reported with concomitant diuretic therapy, other controlled studies have reported additional antihypertensive efficacy with a CCB and diuretic combination.23,24

Adding HCTZ to Aml/Val was not only effective in lowering BP, but was also well tolerated. Treatment discontinuations and the incidence of AEs were low with triple therapy and no difference was observed compared with dual therapy. The most frequently reported AE was peripheral edema, which appeared to be attenuated in the presence of Val.

Therapies combining drugs with complimentary mechanisms of action have also been recommended because they may attenuate certain AEs like the peripheral edema associated with CCBs and the hypokalemia associated with thiazide diuretics.25,26 For example, Val has previously been reported to reduce the incidence of hypokalemia associated with HCTZ and the peripheral edema associated with Aml.21,27 Moreover, it has been suggested that combining different drugs in a single pill may lead to better compliance and hence better BP control.28,29

CONCLUSION:

This study provides relevant information as it follows the clinical practice of prescribing a third antihypertensive agent in a step-wise manner to initial dual therapy depending on BP levels of the patient. The present analyses, however, have certain limitations: 1) this was a *post hoc* analysis of a study not designed to evaluate the efficacy of triple therapy vs dual therapy; 2) patients were not randomized to receive Aml/Val/HCTZ and Aml/HCTZ; and 3) the duration of the treatment with triple therapy was four weeks. In conclusion, triple combination therapy with Aml/Val/HCTZ provides significantly greater BP reductions and is well tolerated compared with Aml/HCTZ dual therapy in stage 2 hypertension and can provide additional benefits in patients who require more than two agents to reach their target BP.

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1.TO STUDY THE EFFICACY OF GOLIMUMAB PLUS METHOTREXATE IN PATIENTS WITH ACTIVE RHEUMOTOID ARTHRITIS	Jyothisahu	Pharmacy	International Journal of Medicine and Nanotechnolo gy	**2021-22**	2394-4269	https://www.citefa ctor.org/journal/in dex/11834/interna tional-journal-of- medicine-and- nanotechnology#.Z BVY03ZBzIU	tefactor.org/jo urnal/index/11 834/internatio nal-journal-of- medicine-and- nanotechnolog y#.ZBVY03ZBzI U	YES
TO STUDY THE QOL DEPRESSION AND SYMPTOMS IN BOTH CKD AND ESKD	Sumaya Fatima	Pharmacy	International Journal of Medicine and Nanotechnolo gy	**2021-22**	2394-4269	https://www.citefa ctor.org/journal/in dex/11834/interna tional-journal-of- medicine-and- nanotechnology#.Z	https://www.ci tefactor.org/jo urnal/index/11 834/internatio nal-journal-of- medicine-and-	YES
TRIPLE COMBINATION THEAPY WITH AMLODINE, VALSARTAN AND	Juveria Naaz	Pharmacy	International Journal of Medicine and Nanotechnolo gy	**2021-22**	2394-4269	https://www.citefa ctor.org/journal/in dex/11834/interna tional-journal-of- medicine-and- nanotechnology#.Z	https://www.ci tefactor.org/jo urnal/index/11 834/internatio nal-journal-of- medicine-and-	YES

HYDROCHLOROTHIAZIDE vs DUAL COMBINATION THERAPY WITHAMLODIPINE AND HYDRCHLOROTHIAZIDE FOR STAGE 2 HYPERTENSIVE PATIENTS	Jabeen Farhana	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	**2394-4269**	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	YES
A SYATEMIC REVIEW ON MEDICATION ADHERENCE WITH OHS AND INSULIN IN DM PATIENTS	Jakir Hussain Sha	Pharmacy	International Journal of Medicine and Nanotechnology	**2021-22**	**2394-4269**	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.Z	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-	YES
5. QUALITY OF LIFE OF EPILEPSY SURGERY PATIENTS AS COMPARED WITH OUT PATIENTS WITH HYPERTENSION	Hamad bin Mohamr	Pharmacy	International Journal of Medicine and Nanotechnology	**2020-21**	**2394-4269**	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzIU	https://www.citefactor.org/journal/index/11834/international-journal-of-medicine-and-nanotechnology#.ZBVY03ZBzI	YES
A RANDAMIZED PILOT STUDY AND EFFECTS OF OMEGA 3 FATTY ACIDS ON HYPERTENSIVE PATIENTS WITH ARTERIAL STIFFNESS	Aejaz Ahmed	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES

DEPRESSION AND ADVERSE DRUG REACTION AMONG HOSPITALIZED OLDER ADULTS	Aejaz Ahmed	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
A CLINICAL STUDY OF ACUTE KIDNEY INJURY ON USING ANTI	Das	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF GLIBENCLAMIDE IN TABLET DOSAGE FORM	Jabeen Farhana	Pharmacy	Indo American Journal of Pharmacy	**2020-21**	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF RABEPRAZOLE IN TABLET DOSAGE FORM	Jabeen Farhana	Pharmacy	Indo American Journal of Pharmacy	2019-20	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF GLIBENCLAMIDE	Jakir Hussain s	Pharmacy	Indo American Journal of Pharmacy	2019-20	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES

A STUDY ON EFFECT OF OMEGA 3 FATTY ACIDS ON ARTERIAL STIFFNESS IN PATIENTS SUFFERING WITH HYPERTENSION	Jyothi	Pharmacy	Indo American Journal of Pharmacy	2019-20	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
FORMULATION AND EVALUATION OF GLIMEPIRIDE LIPOSOMAL DRUG DELIVERY SYSTEM	Dr. Khaja Pasha	Pharmacy	International Journal of Research in Pharmacy and Biosciences	2019-20	2394-5893	https://journalseeker.researchbib.com/view/issn/2394-5893	https://journalseeker.researchbib.com/view/issn/23945893	YES
FORMULATION AND EVALUATION OF AMBROXOL HYDROCHLORIDE SUSTAINED	Dr. Khaja Pasha	Pharmacy	International Journal of Research in Pharmacy and Biosciences	2019-20	2394-5893	https://journalseeker.researchbib.com/view/issn/2394-5893	https://journalseeker.researchbib.com/view/issn/23945893	YES
FORMULATION AND EVALUATION OF CONTROLLED RELEASE OSMOTIC TABLET OF GLIPIZIDE	Dr. Khaja Pasha	Pharmacy	Indo American Journal of Pharmacy	2018-19	2349-7750	https://www.iajps.com/editorial-board/	https://www.iajps.com/editorial-board/	YES
Phytochemical Analysis And Hepatoprotective Activity Of Elytraria Acaulis	DR.M.V.RAMAN	Pharmacy	Journal of Pharmaceutical Research International	2018-19	2456-9119	https://journaljpri.com/index.php/JPRI	https://journaljpri.com/index.php/JPRI	YES

Preparation and Evaluation of Solid dispersions of Febuxostat	DR.M.V.RAMAN	Pharmacy	International Journal of Medicine and Nanotechnology	2018-19	2394-4269	https://www.citefactor.org/journal/index/22108/international-journal-of-pharmacy-and-	https://www.citefactor.org/journal/index/22108/international-journal-of-	YES
Formulation and In-vitro Evaluation of Olmesartan Medoxomil Solid Dispersions,	DR.M.V.RAMAN	Pharmacy	International Journal of Medicine and Nanotechnology	2018-19	2394-4269	ctor.org/journal/index/22108/international-journal-of-pharmacy-and-natural-medicines#.ZBVo2HZBzIU	tefactor.org/journal/index/22108/international-journal-of-pharmacy-and-natural-medicines#.ZB	YES
Wound Healing Activity Of Graclaria Edulis Hydro Alcoholic Extract Using Excision And Dead Cell Wound Model In Wistar Rats	DR.M.V.RAMAN	Pharmacy	international journal of pharmacy	2017-18	0253-7613	https://www.ijp-online.com/search.asp	https://www.ijp-online.com/search.asp	YES
Hepatoprotective Activity Of The Hydro Alcoholic Extract Of The Gracilaria Edulis	DR.M.V.RAMAN	Pharmacy	Research Journal of Pharmacy&Technology	2017-18	0974-360X	https://www.rjpton	https://www.rjp	YES

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Original Article

A SYATEMIC REVIEW ON MEDICATION ADHERENCE WITH OHS AND INSULIN IN DM PATIENTS

Dr. Shahana Banu[1], Jakir Hussain Shaik*[2], Taseem Fatima[2], Nabila Zahoor[2], Syeda Rehamath[2], Malika Khatoon[2], Noman Aamer Nahdi[2]

1. 1.Gulbarga Unversity

2. Azad college of pharmacy

Corresponding Author:
Name: Jakir Hussain Shaik
Email:

Abstract:
Medication adherence usually refers to whether patients take their medications as prescribed (eg, twice daily), as well as whether they continue to take a prescribed medication. Medication nonadherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care. The study determine the extent to which patients omit doses of medications prescribed for diabetes, assess the extent of poor adherence and persistence with OHAs and insulin. Descriptive statistics (means, ranges) present data from the selected reports tabulated by methodology (retrospective database review, prospective monitoring), and class of medication (OHA, insulin). Electronic monitoring studies suffered from small size and observation limited to one OHA. An overall drawback to this review is the lack of an electronic method to monitor insulin use. Such devices are commonly used to record blood glucose measurements. The development of an electronic monitoring system for insulin dosing would be an important step toward proving better support for individuals with poor insulin adherence and improving the dialogue between patients and their healthcare providers.The implication is that instead of increasing the dose, changing the medication, or adding a second drug when glucose and HbA_{1c} levels are high, clinicians should consider counseling patients on how to improve medication adherence. A first step to improving adherence is being able to assess it. Developing methods that properly assess medication adherence as a behavior that can be modified could provide a clinically significant improvement in glycemic control for some patients.

1. INTRODUCTION

Medication adherence usually refers to whether patients take their medications as prescribed (eg, twice daily), as well as whether they continue to take a prescribed medication. Medication nonadherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care. To date, measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice. The goals of the present report are to address (1) different methods of measuring adherence, (2) the prevalence of medication nonadherence, (3) the association between nonadherence and outcomes, (4) the reasons for nonadherence, and finally, (5) interventions to improve medication adherence.In medicine, compliance (also adherence, capacitanc e) describes the degree to which a patient

correctly follows medical advice. Most commonly, it refers to medication or drug compliance, but it can also apply to other situations such as medical device use, self care, self-directed exercises, or therapy sessions. Both the patient and the health-care provider affect compliance, and a positive physician-patient relationship is the most important factor in improving compliance,[1] although the high cost of prescription medication also plays a major role.[2]

Compliance is commonly confused with concordance, which is the process by which a patient and clinician make decisions together about treatment.[3]

Worldwide, non-compliance is a major obstacle to the effective delivery of health care. Estimates from the World Health Organization (2003) indicate that only about 50% of patients with chronic diseases living in developed countries follow treatment recommendations.[1] In particular, low rates of adherence to therapies for asthma, diabetes, and hypertension are thought to contribute substantially to the human and economic burden of those conditions.[1] Compliance rates may be overestimated in the medical literature, as compliance is often high in the setting of a formal clinical trial but drops off in a "real-world" setting.[4]

Major barriers to compliance are thought to include the complexity of modern medication regimens, poor "health literacy" and lack of comprehension of treatment benefits, the occurrence of undiscussed side effects, the cost of prescription medicine, and poor communication or lack of trust between the patient and his or her health-care provider.[5][6][7]Efforts to improve compliance have been aimed at simplifying medication packaging, providing effective medication reminders, improving patient education, and limiting the number of medications prescribed simultaneously. Current studies show a great variation in terms of characteristics and effects of interventions to improve medicine adherence.[8]It is still unclear how adherence can consistently be improved in order to promote clinically important effects.

To determine the extent to which patients omit doses of medications prescribed for diabetes.

To assess the extent of poor adherence and persistence with OHAs and insulin

To link adherence rates with glycemic control.

MATERIALS AND METHODS:

A systematic literature search was conducted to identify articles containing information on the rate of adherence or persistence with OHAs or insulin. Abstracts captured by the systematic literature search of MEDLINE (1966 to April 2003), Current Contents (1993 to April 2003), Health & Psychosocial Instruments (1985–2003), and Cochrane Collaborative databases were first screened against the protocol inclusion criteria. The Level 1 screen identified papers related to the main topic of interest. Abstracts passing the Level 1 screen were then retrieved for screening against the inclusion criteria (Level 2 screen). Full articles meeting the inclusion criteria were reviewed in detail (Level 3 screen).

Inclusion criteria

Papers were included in this review if *1*) a dosing regimen was evaluated and medication adherence or persistence rates were reported and *2*) study design and methods for calculation of adherence were described. The papers must have included details of the methods used to determine adherence with a hypoglycemic agent (e.g., self-report, physician/nurse estimate, tablet count, prescription refill, electronic monitoring) and some numeric results. Categorical results were considered a lower level of information than data. The most desirable reports included both adherence rates and HbA_{1c} levels. Reports of interventions that did not include adherence rates were excluded. Reports of adherence with diet or exercise that did not also include medication adherence rates were also excluded. Reports may be retrospective surveys, prospective clinical trials, or prospective studies of adherence interventions. Methods may be database analyses of populations or electronic monitoring of individual patients.

Search strategy

Key words for the database search were “patient adherence” and “patient compliance” cross-linked with “diabetes mellitus,” “hypoglycemic agents,” and “insulin.” The term “adherence” was linked automatically to the term “compliance” in MEDLINE as the preferred term. Within the terms, sub-items were selected as: Administration & Dosage, Adverse Effects, Therapeutic Use, Prevention & Control, Drug Therapy, Psychology, Statistics & Numerical Data, and Economics, as available for each term. The databases identified 186,188 publications.

Level 1 searches combining terms identified 242 publications that appeared to relate to the topic of interest.

Level 2 was a review of abstracts from the reports identified in Level 1, using the inclusion criteria. This stage identified 38 reports as potentially having relevant data.

Level 3 was a review of the papers identified in Level 2. These citations were supplemented with selected references from articles. This stage identified 19 papers and one abstract (with additional information from the authors) that met the inclusion criteria.

The systematic search resulted in 20 publications with adequate data on measurement of adherence with an OHA or insulin.

Adherence assessment

Definitions.

For this review, medication adherence was operationalized as “taking medication as prescribed and/or agreed between the patients and the health care provider.” No studies provided information about the level of the patient’s agreement with the regimen. The “adherence rate” was the proportion of doses taken as prescribed. Some reports used categorical endpoints (e.g., 90%), below which patients were considered “noncompliant” with the regimen. Adherence with “dose intervals” was defined as the proportion of doses taken within the appropriate window (e.g., 24 + 12 h for once-daily regimens, 12 + 6 h for twice-daily regimens).

Treatment “persistence” was defined as either the proportion of patients who remained on treatment for a specified period (e.g., 12 months) or the mean number of days to treatment discontinuation.

Retrospective database assessment.

Prescription benefit organizations (PBOs) that manage prescriptions and health maintenance organizations (HMOs) that manage the overall healthcare of patients have databases containing information about use of prescription medications. Records of new prescriptions and refills can be tabulated using unique patient identifiers. Some databases also are linked to diagnostic codes as well as laboratory and medical visit data that describe health service utilization for a cohort. Searches can be made to ascertain the types of medications, prescribed dose and regimen, and number of times the patient obtained a refill. These population-based surveys provide an overview of drug utilization during a period of time.

Prospective monitoring.

Electronic monitoring technology collects events based on taking medication from a monitored container, stores events, and lists medication dosing for an individual. Medication Event Monitor Systems (MEMS; APREX, Division of AARDEX, Union City, CA) were used in some prospective studies. MEMS are standard medication container bottle caps with a microprocessor that records every bottle opening. Patients are given bottles with a MEMS cap and instructions to take all doses of the oral medication from that bottle. Data are downloaded for display as a calendar of events (8). Electronic monitoring provides information about medication usage at the level of the individual patient. Some researchers do not inform patients that they are being monitored to avoid an effect of observation (Hawthorne effect). Cramer (9,10) developed a method, the Medication Usage Skills for Effectiveness Program (MUSE-P), that uses electronic monitoring data displayed on a computer screen as a teaching tool to enhance medication adherence.

Analyses.

Descriptive statistics (means, ranges) present data from the selected reports tabulated by methodology (retrospective database review, prospective monitoring), and class of medication (OHA, insulin).

RESULTS AND DISCUSSION:

The systematic review was based on 20 reports that included quantitative information on adherence or persistence with diabetes medications (11–30). The few studies that included laboratory data all showed HbA_{1c} levels >7%.

OHA: retrospective analyses

Adherence rates among 11 retrospective studies (19 cohorts) (11,14–16,18–22,24,25) using large databases ranged from 36 to 93% (excluding the study with categorical adherence rates) (17) (Table 1). The mean age of patients in all these studies was >50 years, indicating that these were older patients with type 2 diabetes. The open observational (noncomparative) studies (11,20,22,24,25) had similar results, ranging from 79 to 85% adherence with OHAs during 6–36 months of observation. Several studies compared cohorts with different regimens. Depressed patients had lower adherence rates than nondepressed patients (85 vs. 93%) (14). Once-daily regimens had higher adherence than twice-daily regimens (61 vs. 52%) (16). Monotherapy regimens had higher adherence than polytherapy regimens (49 vs. 36%) (14) or a higher proportion of patients achieving high adherence rates (35 vs. 27% at 90% or higher adherence rates) (17). Patients converting from monotherapy or polytherapy to a single combination tablet improved their adherence rates by 23 and 16%, respectively (19). The only report with adherence rates <50% was a survey of California Medicaid (MediCal) patients newly treated with OHAs (15). Other studies included patients with chronic treatment.

Seven reports (nine cohorts) of OHA treatment persistence ranged from 16 to 80% in patients remaining on treatment for 6–24 months. Four studies reported 83–300 days to discontinuation (Table 1). The methodology differed among studies, so that cross-overs to an alternative OHA or insulin might not have been counted as discontinuation. Two reports with large proportions (58 and 70%) of patients remaining on treatment for 12–24 months included all OHAs in the analyses (11,12). However, a study of Medicaid recipients in South Carolina showed low treatment persistence (39% at 6 months) (23). Three reports (four cohorts) with smaller proportions (16–49%) of patients remaining on treatment for 6–12 months focused on specific drug treatments (13,16) and monotherapy/polytherapy (15). Persistence expressed as days to discontinuation was similar in the two reports using similar methodology (83–105 days) (11,13) but was longer (300 days) in the report with descriptive data (17).

Reference	Population	Medications	Follow-up (months)	HbA1c	Age (years)	*n*	Adherence rate	Persistance (percent)	Persistance (days)
Boccuzzi et al. (11)	PBO, new start	OHA monotherapy	12	—	60 ± 14	79,498	79%	58%*	83 ± 71
Brown et al. (12)	HMO, new start	OHA + Insulin	(10 years)	—	—	693 all	—	70%†	—

Catalan et al. (13)	Canada	Acarbose	12	—	51 ± 9	216 young		16%*	83
				—	72 ± 5	677 elderly		20%*	105
Chlechanowski et al. (14)	HMO, all	OHA + Insulin	12	7.4 ± 1.4	64 ± 11	119 not depressed	93%	—	—
				8.0 ± 1.5		121 depressed	85%	—	—
Dailey et al. (15)	Medicaid, new start	Monotherapy	18	—	—	37,431	49%	36%*	—
		Polytherapy					36%	22%*	—
Dezii and Kawabata (16)	PBO	Glipizide, o.d.	12	—	55 ± 13	992	61%	44%*	—
		Glipizide, b.i.d.					52%	36%*	—
Donnan et al. (17)	Scotland	Monotherapy	12	—	68	2,849	(35% > 90%)	—	300
	and								
		Polytherapy					(27% > 90%)	—	—
Evans et al. (18)	Scotland	Sulfonylurea	6	—	67	2,275	87%	—	—
		Metformin			64	1,350	83%	—	—
Mellkian et al. (19)	PBO	Monotherapy	6	—	63 ± 15	105	54%	—	—
		Monotocombination					77%	—	—
		Polytherapy	6	—		59	71%	—	—
	PBO	Polytocombination					87%	—	—
Morningstar et al. (20)	Canada	OHA	36	—	—	3,358	86%	—	—
Rajagopalan et al. (21)	PBO	OHA + Insulin	24	—	53	195,400 all	81%	—	—
						28,001 new start	81%	—	—
Schecl man et al. (22)	Clinic	OHA + Insulin	15	8.1 ± 2	50 ± 11	810	80 ± 21%	—	—

				.0					
Sclar et al. (23)	Medicaid	OHA	12	—	59 ± 10	975		39%‡	—
Spoelstra et al. (24)	Netherland and	OHA	12	—	63	411	85 ± 15%	—	—
Venturini et al. (25)	HMO	Sulfonylurea	24	—	59 ± 11	786	83 ± 22%	—	—

OHA: prospective studies

Three groups performed small prospective studies with electronic dose monitoring, with two centers each publishing two reports describing different aspects of the studies. Adherence rates were more consistent than was found in the retrospective database analyses (Table 1). Mean adherence with OHAs was in a narrow range of 61–85% during up to 6 months' observation (Table 2). All of the prospective studies used MEMS electronic monitoring to determine when doses were taken. Electronic monitoring also demonstrated that adherence rates decreased with larger numbers of OHA doses to be taken daily. One report showed mean adherence of 79.1 ± 19% for once-daily regimens, 65.6 ± 30% for twice-daily regimens, and 38.1 ± 36% for three-times daily dosing regimens ($P < 0.05$) (28). The accuracy of taking doses at appropriate time intervals also decreased (77.7 ± 21% for once-daily regimens, 40.7 ± 28% for twice-daily regimens, 5.3 ± 5% for three-times daily regimens; $P < 0.01$).

The adherence rate for patients taking sulfonylurea was 74.5% using electronic monitoring, compared with 92.4% for self-reported adherence (26). Matsuyama et al. (27) used electronic monitoring reports to guide clinical decision making. Adherence reports for a subset of patients were provided to their doctors to assist in making treatment decisions. The information revealed a need for additional patient education because of inconsistent dosing (47% of reports). The control group had several instances of dose increases because the clinician was not aware that erratic dosing was the problem rather than low dose.

Rosen et al. (29,30) used electronic monitoring with the MUSE-P medication enhancement program (29) to demonstrate that poor adherence can be improved when patients and clinicians are aware of the frequency of missed doses. They monitored a series of patients (mean adherence 78%) (29) to find a group of poor OHA compliers (mean 61%) in order to start with a cohort needing improvement. The control group remained unchanged, whereas the group receiving the intervention improved to 79% adherence ($P < 0.05$) with their OHA regimen (Table 2) (30).

Reference	***n***	**Population**	**Age (years)**	**Medications**	**Follow-up**	**HbA1c**	**Adherence rate**	Dose interval*
Mason et al. (26)	21	Clinic	—	Sulfonylurea	3 months	>8 %	74.50 %	
Matsuyama et al. (27)	15	Intervention	84 ± 8	OHA	3 months	12.7 ± 1.9	85.10 %	
	17	Control				12.1 ± 2.6	82.80 %	
Paes et al. (28)	91	Community	69	OHA	6 months	—	67.2 ± 30%	
						(40 o.d.)	79.1 ± 19%	77.7 ± 21%
						(36 b.i.d.)	65.6 ± 30%	40.7 ± 28%
						(15 t.i.d.)	38.1 ± 36%	5.3 ± 5%
Rosen et al. (29)	77	Clinic	65	Metformin	4 weeks	7.9 ± 1.1	77.7 ± 18%	
Rosen et al. (30)	16	Intervention	63 ± 11	Metformin	6 months		79.3 ± 13%	
	17	Control					60.7 ± 13%	

Insulin

Adherence rates among the three studies that assessed insulin use were not comparable because of different methods of analysis (Table 3). The retrospective database method (21) showed a mean 63 ± 24% adherence for large cohorts of long-term and new-start adult type 2 diabetic insulin users. Adherence rates were lower for insulin use than for OHA use (73–86%) in both populations (21). A 10-year follow-up of a large cohort of patients newly started on insulin found that 80% of patients persisted with insulin treatment for 24 months (12). Fewer patients in the insulin-only group (20%) than patients taking an OHA (31%) discontinued treatment (obtained no refill) during the second year of follow-up (11). A study of children and adolescents presented evidence that poorer compliers had higher mean HbA_{1c} levels (R^2 = 0.39) (7). They calculated an index of days with insulin obtained from the pharmacy, based on the prescribed dose. HbA_{1c} levels ranged from 9.44 ± 1.7 for the lowest amount of insulin obtained to 8.98 ± 1.5, 7.85 ± 1.4, and 7.25 ± 1.0 for the higher categories of adherence, respectively ($P < 0.001$). Additional information about clinical status demonstrated that 36% of patients with poorest adherence were admitted to the hospital for diabetic ketoacidosis ($P = 0.001$ compared with patients with higher adherence rates) and other complications related to diabetes ($P = 0.02$ compared with patients with higher adherence rates). Adolescents (10–20 years of age) were significantly more likely to be in the lowest adherence category and have the highest HbA_{1c} levels compared with younger and older patients (both $P < 0.001$).

Reference	*n*	Population	Age (years)	Follow-up	HbA_{1c}	Adherence rate
Brown et al. (12)	102	HMO new start	—	10 years	—	Persistence 79.6% at 24 months
Morris et al. (7)	89	Scotland	16 ± 7	12 months	9.4 ± 1.7	33–86% days supply*
					9.0 ± 1.5	87–116% days supply*
Rajagopalan et al. (21)	27,274 all	PBO	53	24 months	—	62 ± 24%
	1,323 new start					64 ± 24%

This systematic review confirms that many patients with diabetes took less than the prescribed amount of medication, including both OHA and insulin. Given the central importance of patient self-management and medication adherence for health outcomes of diabetes care (31), surprisingly few studies were found that adequately quantified adherence to diabetes medication. The overall rate of adherence with OHA was 36–93% in retrospective and prospective studies. Previous surveys have found that people took ~75% of medications as prescribed, across a variety of medical disorders (32,33). Decreasing adherence related to polytherapy and multiple daily dosing schedules also matched reports from other medical disorders (32,33).

This survey adds to the general finding that adherence rates are not related to the simplicity of regimen, the severity of the disorder, or the possible consequences of missed doses. The persistence with OHAs of 6–24 months, as seen in this survey, suggests that brief treatment persistence is a major issue that could lead to deleterious health outcomes. These data parallel other chronic medical disorders in which persistence often is <1 year (34,35). Even with good OHA adherence, the natural progression of

type 2 diabetes eventually leads many patients to require insulin treatment. The study that evaluated type 2 diabetic patients receiving insulin showed 63% of doses taken as prescribed (21). In one cohort, only 80% of patients persisted with insulin for 2 years despite the need for long-term glycemic control (12). The detailed analysis of a group of children and adolescents showed that poor adherence with the prescribed insulin regimens resulted in poor glycemic control, as well as more hospitalizations for diabetic ketoacidosis and other complications related to diabetes (7). Self-reported insulin use (not included in this analysis) showed that patients frequently omit injections. In 31% of women who reported intentionally omitting doses (8% frequently), weight gain was the reason (36). One-fourth of adolescents reported having omitted some injections during the 10 days before a clinic visit (37). Therefore, clinicians cannot assume that patients with either type 1 or type 2 diabetes are fully compliant with insulin regimens, even if the consequences might be hazardous.

The second goal of this study was to estimate the strength of the association between adherence and glycemic control. Too few studies included HbA_{1c} levels to allow a precise conclusion, although interventions that improve self-management have been associated with better clinical outcomes (38). Further research is needed to quantify the specific improvement in glycemic control that might be obtained from improved medication adherence. Such studies should demonstrate the health benefits that may be derived from more convenient therapeutic regimens that are being developed for diabetes.

A bright spot among these reports of poor adherence and persistence was the finding that electronic monitoring tools exist to help enhance medication adherence for individual patients. One study demonstrated that doctors and pharmacists were able to adjust treatment plans more appropriately when they had electronic monitoring data than when they used the usual mode of employing only laboratory data (27). The difference was in understanding that elevated glucose or HbA_{1c} levels were related to missed doses and not underprescribing. This information avoided changing prescriptions, increasing drug dose, and switching or adding medication. Rosen et al. (30) screened a clinic population to select patients with low adherence rates for randomization to a control group or the MUSE-P intervention. MUSE-P consists of a dialogue between the patient and health care provider about daily medication dosing structured around their personal record of electronic monitoring data (39). This simple technique resulted in a significant improvement in adherence rates compared with the control subjects, who received the same amount of personal attention but not focused on adherence. This program has been effective in enhancing adherence in other medical disorders (39–41). However, electronic monitoring is not a readily available tool. Several simple measures usually are helpful in clinical practice, such as once-daily dosing and combining multiple medications into the same regimen (e.g., several drugs premeal rather than some before and some with meals). Patients should be given information about what to do if a dose is missed or if adverse effects are bothersome, in addition to the purpose of the medication (9,10).

Similar electronic monitoring systems for insulin administration are needed to record patterns of insulin use by individual patients. This information could help healthcare providers determine which patients need additional support to achieve consistent glycemic control. Further studies with electronic monitoring of diabetes medications may identify and define the characteristics of poorly compliant patients to improve treatment outcomes. Improved understanding of the way patients use medication could also affect healthcare utilization. Improved glycemic control could reduce overall healthcare costs (42). This has important implications because of the potential to improve the currently poor adherence with all aspects of diabetes self-management. Inadequate adherence to medication and lifestyle recommendations by patients with diabetes may play an important role in adding to the economic burden of the disease.

The major drawback of this survey is the methodology used for adherence analyses in the reports reviewed. A shortcoming in the literature

is the lack of studies evaluating interventions to improve adherence in which adherence was measured using appropriate methods. The retrospective analyses used various definitions of adherence and persistence and different durations of follow-up. Some included all patients, whereas others censored cohorts based on arbitrary conditions. Analyses did not always account for patients who changed to another hypoglycemic agent or were no longer eligible for observation because of a change in health insurance. Attempts are underway to define optimum analytic methods for retrospective database studies (43). Electronic monitoring studies suffered from small size and observation limited to one OHA. An overall drawback to this review is the lack of an electronic method to monitor insulin use. Such devices are commonly used to record blood glucose measurements. The development of an electronic monitoring system for insulin dosing would be an important step toward proving better support for individuals with poor insulin adherence and improving the dialogue between patients and their healthcare providers.

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CONCLUSION:

The finding that patients prescribed an OHA or insulin take less than the prescribed number of doses over long periods of follow-up indicates an urgent need for prescribers to understand that failure to reduce HbA_{1c} levels might be related to inadequate self-management. The implication is that instead of increasing the dose, changing the medication, or adding a second drug when glucose and HbA_{1c} levels are high, clinicians should consider counseling patients on how to improve medication adherence. A first step to improving adherence is being able to assess it. Developing methods that properly assess medication adherence as a behavior that can be modified could provide a clinically significant improvement in glycemic control for some patients. Although methods are not yet available for routine use, such information could enhance patient-clinician relationships by providing information to guide individualized self-management to support patients.

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Original Article

QUALITY OF LIFE OF EPILEPSY SURGERY PATIENTS AS COMPARED WITH OUT PATIENTS WITH HYPERTENSION, DIABETES, HEART DISEASE/ DEPRESSIVE SYMPTOMS

Dr.Shahana Banu[1], Das*[2], Hamad bin Mohammed[2], Mohammed Mazhar uddin[2],Mohammed Ahmed[2], Mohd. Majid[2], Mohammed Muzammil[2]

1. Gulbarga Unversity
2. Azad college of pharmacy

Abstract:

Epilepsy is a group of neurological disorders characterized by epileptic seizures.[1][2] Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking. To compare the HRQOL of epilepsy surgery patients with hypertension, diabetes, heart disease, depression patients. The questionnaire collected demographic data, information on seizure type and frequency, and employed precoded and open questions. This health related quality of life model contained measures of Hypertension, DM, Heat desease and depression, impact of epilepsy, overall quality of life, and health status.These scales have been found to be reliable and valid in patients with both refractory epilepsym 29 and epilepsy in remission. For purposes of analysis patients were placed in four categories; seizure free postoperatively (SF), less than 10 seizures per year postoperatively (S<10), more than 10 seizures per year postoperatively (S>10), unsuitable for surgery and managed medically , This study compared the differences in QALE for those who had diabetes, hypertension, heart disease, or stroke to those have epilepsy surgery. The proposed method can be particularly useful when examining burdens for common chronic diseases over time and at the local level for program planning and evaluation. this small retrospective study has shown that health related quality of life is related to postoperative seizure status. However, prospective studies are required to elucidate the role of other factors such as preoperative status and changes in psychosocial status with postoperative duration. Satisfactory studies should be prospective and longitudinal, comparing patients' preoperative and postoperative seizures and psychological status. To produce meaningful statistical data multicentre collaboration will be essential. Resultant data might assist in the construction of specified quantitative targets for *Healthy People 2020* objectives and setting priorities for prevention in a given population as well as in sociodemographic subgroups.

1. INTRODUCTION

Epilepsy that occurs as a result of other issues may be preventable.[3] Seizures are controllable with medication in about 70% of cases.[9] Inexpensive options are often available.[3] In those whose seizures do not respond to medication, then surgery, neurostimulation, or dietary changes may be considered.[10][11] Not all cases of epilepsy are lifelong, and many people improve to the point that treatment is no longer needed.[3]. Epilepsy is characterized by a long-term risk of recurrent seizures.[23] These seizures may present in several ways depending on the part of the brain involved and the person's age.[23][24]The most common type (60%) of seizures are convulsive.[24] Of these, one-third begin as generalized seizures from the start, affecting both hemispheres of the brain.[24] Two-thirds begin as focal seizures (which affect one hemisphere of the brain) which may then progress to generalized seizures.[24] The remaining 40% of seizures are non-convulsive. An example of this type is the absence seizure, which presents as a decreased level of consciousness and usually lasts about 10 seconds.[5][25]

Focal seizures are often preceded by certain experiences, known as auras.[26] They include sensory (visual, hearing, or smell), psychic, autonomic, and motor phenomena.[5] Jerking activity may start in a specific muscle group and spread to surrounding muscle groups in which case it is known as a Jacksonian march.[27] Automatisms may occur, which are non-consciously-generated activities and mostly simple repetitive movements like smacking of the lips or more complex activities such as attempts to pick up something.[27]

To compare the HRQOL of epilepsy surgery patients with hypertension, diabetes, heart disease, depression patients

MATERIALS AND METHODS:

The questionnaire collected demographic data, information on seizure type and frequency, and employed precoded and open questions. This health related quality of life model (table 1) contained measures of Hypertension, DM, Heat desease and depression, impact of epilepsy, overall quality of life, and health status.These scales have been found to be reliable and valid in patients with both refractory epilepsym29 and epilepsy in remission. Forpurposesofanalysispatientswereplaced in four categories; seizure free postoperatively (SF), less than 10 seizures per year postoperatively (S<10), more than 10 seizures per year postoperatively (S>10), unsuitable for surgery and managed medically (NSurg). We chose these seizure frequencies as similar definitions have been used previously in studies reporting the results of epilepsy surgery. To be classified as seizure free, patients had to have been seizure free for at least the year immediately before the censor date. Before the study we had planned to subdivide patients with postoperative seizures into those with auras only and those with attacks similar to the preoperative type, on the basis that auras may have less impact on quality of life.18 However, the numbers of patients reporting postoperative auras only was too small for suitable statistical analysis,and,therefore,auras were treated as seizures and classified accordingly.This may have artificially reduced the psychological scale scores for patients having frequent seizures postoperatively.

STATISTICS:

As the numbers in the groups are small, median scores and quartile ranges are quoted unless otherwise stated. The data were analysedusingArcusProcomputersoftware.Tests of significance used were the Mann-Whitney U test with exact probabilities corrected for ties, Kendall's ô b correlation coeYcient corrected for ties and continuity corrected, and the Kruskal-Wallis one way analysis of variance (ANOVA) with multiple comparisons if significant diVerences were detected.32 For categorical variables odds ratios (ORs) with exact 95% confidence intervals (95% CIs) relative to the NSurg group were calculated,33 unless otherwise stated. Information was missing on some of the scales; this is indicated by * in the text.

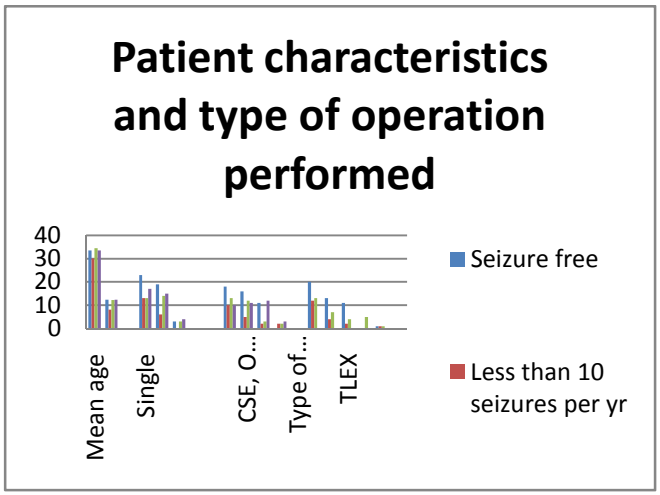
RESULTS AND DISCUSSION:

fifty four of 100 patients undergoing surgery and 36 of 70 (51%) patients unsuitable for surgery returned questionnaires that were suitable for analysis. Nine questionnaires were unsuitable for analysis; seven because of incomplete data and two which were completed by carers and, therefore, contained subjective information only. Overall, 45 (47.9%) patients were seizure free postoperatively. Twenty of 45 (44.4%) patients having anterior temporal lobectomies, 13 of 24 (54.2%) having amygdalohippocampectomies, 11 of 17 (64.7%) having temporal lesionectomies, and one of eight (12.5%) having extratemporal surgery were seizure free

Table 1: Patient characteristics and type of operation performed.

	Seizure free	Less than 10 seizures per yr	More than 10 seizures per year	No surgery
Mean age	33.5	30.1	34.5	33.6
Age of onset	12.4	8.17	12.2	12.4
Maternal status				
Single	23	13	13	17
Married	19	6	14	15
Divorced	3	0	3	4

Higher qualification No formal qualification CSE, O level, or equivalent A level, HND, or degree Other unspecified	18 16 11 0	10 5 2 2	13 12 3 2	10 11 12 3
Type of operation ATL AHX TLEX ETLEX Other	20 13 11 0 1	12 4 2 0 1	13 7 4 5 1	



QUALITY OF LIFE OUTCOME

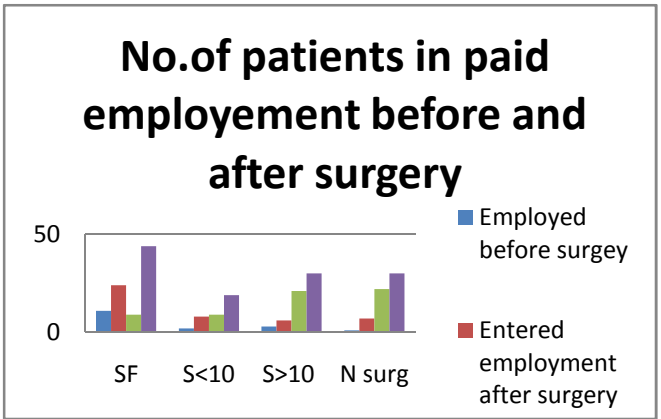
Patients in the seizure free group had significantly better scores than those having greater than 10 seizures per year or those who were deemed unsuitable for surgery. There were no diVerences between the S>10 and NSurg groups. On all measures the scores of patients with less than 10 seizures per year were between the SF and NSurg or S>10 groups (figs 1 and 2). On the anxiety scale scores diVered significantly between all groups (table 3 and fig 1). On the depression scale scores for both the SF and S<10 groups were better than the S>10 or NSurg groups (table 3 and fig 1). Mastery scores were significantly better in SF than in any of the other groups (table 3 and fig 1).The SF patients were least stigmatised with only 35.6% of patients reporting positive stigma scores, compared with 57.9%, 67.9% and 77.8%intheS<10,S>10*,andNSurgpatients respectively (fig 2). Self esteem was significantly higher in the SF than S>10 or NSurg with the S<10 achieving intermediate scores (table3andfig1).Epilepsyhadleastimpacton the SF group and feelings of wellbeing (aVect balance) were greatest in SF and S<10 groups (table 3 and figs 1 and 2). Similarly self reported general health and overall quality of life were best in the SF group and worst in the S>10 and NSurg groups.

EMPLOYMENT AND DRIVING

Eleven of 44 seizure free patients reported being in paid employment before surgery compared with only six of 79 in the other three groups combined (OR 5.82, 95% CI 21.0 – 1.75) (table 4). The proportions of patients unemployed before surgery who entered employment after surgery or investigation for surgery were 24/33 (73%) SF and 8/17 (47%) S<10 compared with 6/27 (22%) S>10 and 7/29 (24%) NSurg. There was no diVerence in preoperative educational attainment—that is, proportion of patients obtaining no qualifications,CSE or "O"level equivalents or "A"levels or degrees between the outcome groups (÷2 6 df = 8.33, P = 0.22). Similarly, there was no diVerence in qualifications obtained between employed or unemployed patients in the group as a whole (÷2 2 df = 0.32,P = 0.85).Twenty of 45 (46%) seizure free patients obtained driving licences after surgery.

Table 2: No.of patients in paid employement before and after surgery

	SF	S<10	S>10	N surg
Employed before surgey	11	2	3	1
Entered employment after surgery	24	8	6	7
Unemployed after surgery	9	9	21	22
Total	44	19	30	30



OUTCOME AND POSTOPERATIVE DURATION

There was a weak but significant correlation indicating falling impact of epilepsy scores with increasing postoperative duration (ô b=−0.23, Z=1.996, P=0.046). On the remainder of the quality of life scales there was no relation between outcome and postoperative duration (table 5). However, there was a tendency for postoperative duration to be longer in seizure free patients who were in gainful employment (median duration = three years) compared with those unemployed (medianduration=2.5 years; Mann-Whitney U = 83.5, P = 0.07). Similarly, the median postoperative duration was one year longer in those driving (median = three years) compared with those not driving (median = two years; Mann-Whitney U = 333.5, p =0.011).

Diabetes Mellitus

In 2010, 18-year-old diabetic persons were expected to live 53.8 years while nondiabetic persons of the same age were expected to live 62.8 years. This 9.0-year difference was the individual-level loss in life expectancy due to diabetes mellitus. The corresponding QALE for 18-year-old diabetic and nondiabetic persons were 43.4 and 54.5 years, respectively. Therefore, the diabetes-related QALE loss for an 18-year-old diabetic person was 11.1 years. Of the 11.1 years of QALE loss, about two thirds (66.2% or 7.3 years) was due to mortality. QALE loss to diabetes declined gradually with age, going from 11.1 years at age 18 years to 3.0 years at age 85 years. The consistent decline suggests that diabetes significantly affects patients' health during both early adulthood and later adulthood. The diabetes-related QALE loss differed somewhat between men and women .Diabetic women lost 3.9 (95% confidence interval 3.3–4.5) more years of QALE to diabetes than diabetic men did (12.9 vs. 9.0 years in QALE loss; $P < 0.0001$). The trend of QALE loss shows that diabetes-related QALE was relatively unchanged between 2010-2016. This is because 1) life expectancy for both diseased and nondiseased had increased (from 50.7 to 53.8 vs. from 59.7 to 62.8 years, respectively) and 2) HRQOL scores for both diseased and nondiseased also had decreased .

Table 3: Life expectancy (LE), quality-adjusted life expectancy (QALE), and individual and population loss in LE and QALE due to diabetes, hypertension, heart disease at 18 y of age

	n*	HRQOL†	Life expectancy	SE	QALE	SE	% QALE lost to mortality
Total population	403,841	0.876	61.1	0.03	52.6	0.02	
By disease status							
Diabetes							
Yes	47,284	0.781	53.8	0.25	43.4	0.23	
No	356,238	0.885	62.8	0.2	54.5	0.16	
LE/QALE loss			9	0.09	11.1	0.15	66.2
Population LE/QALE loss			1.7	0.17	1.9	0.15	72.2
Hypertension							
Yes	154,627	0.829	59.3	0.23	48.4	0.19	
No	248,526	0.896	62.4	0.2	54.8	0.17	
LE/QALE loss			3.1	0.29	6.3	0.24	40.7
Population LE/QALE loss			1.3	0.17	2.2	0.15	48.1
Heart diseases							
Yes	35,004	0.718	55.3	0.26	43.4	0.3	
No	365,426	0.885	62.1	0.2	53.8	0.17	
LE/QALE loss			6.8	0.29	10.3	0.32	54.1

Population LE/QALE loss			1	0.18	1.2	0.15	72.1

Table 4: Individual quality-adjusted life expectancy (QALE) loss and population QALE loss due to diabetes, hypertension, heart disease, at different ages.

	DM		HTN		Heart disease	
	Value	SE	Value	SE	Value	SE
At age (y)	QALE loss					
18	11.1	0.15	6.3	0.24	10.3	0.32
25	10.8	0.14	6	0.24	10.2	0.29
35	10	0.11	5.2	0.23	9.3	0.25
45	8.9	0.09	4.3	0.22	7.9	0.22
55	7.3	0.07	3.3	0.22	5.9	0.21
65	5.5	0.06	2.3	0.2	4.3	0.19
75	4	0.05	1.3	0.15	2.7	0.12
85	3	0.04	0.9	0.03	2.1	0.04
At age (y)	Population QALE loss					
18	1.9	0.15	2.2	0.15	1.2	0.15
25	1.9	0.15	2.2	0.15	1.2	0.15
35	1.9	0.14	2.1	0.14	1.3	0.15
45	1.9	0.14	2	0.14	1.3	0.14
55	1.7	0.14	1.8	0.14	1.3	0.14
65	1.4	0.13	1.3	0.13	1.1	0.13
75	1	0.09	0.7	0.1	0.9	0.1
85	0.7	0.02	0.5	0.03	0.7	0.02

Table 5: Gender differences in individual quality-adjusted life expectancy (QALE) loss and population QALE loss due to diabetes, hypertension, asthma, heart disease, and stroke at 18 y of age

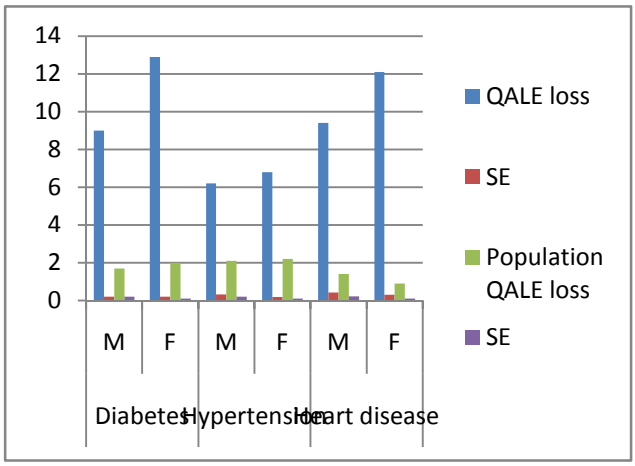
Diseases	Sex	QALE loss	SE	Population QALE loss	SE
Diabetes	M	9	0.2	1.7	0.21
	F	12.9	0.2	2	0.11
Hypertension	M	6.2	0.33	2.1	0.21
	F	6.8	0.19	2.2	0.11
Heart disease	M	9.4	0.42	1.4	0.22
	F	12.1	0.31	0.9	0.11

At the population level, diabetes caused in adult population to lose 1.9 years of QALE starting at age 18 years in 2016. The population QALE loss also declined with age, but at a smaller rate and only for those aged 55 years and older, indicating that diabetes prevalence was significantly higher among older populations (3.2% for those younger than 55 years and 5.8% for those 55 years or older). The burden of diabetes for the population had increased significantly, from 1.0 year of population QALE loss in 2010 to 1.9 years of population QALE loss in 2016, an 84% increase.This is different from the trend of individual-level QALE loss. Such an increase in the burden of diabetes to the population paralleled the increases in the prevalence of diabetes for US adults, from 4.5% to 8.9%, a 95% increase. Like the individual-level burdens, more than two-thirds (72.2% or 1.3 years) of the population QALE loss was due to mortality.

Because the state prevalence of diabetes varies greatly, the difference in state-level population QALE loss due to diabetes also varied greatly

State population quality-adjusted life expectancy (QALE) loss due to diabetes, hypertension, asthma, heart disease, and stroke for 18-y-old US adults, 2009.

Hypertension



Although QALE loss for persons diagnosed with hypertension was the lowest among the five diseases, the population QALE loss due to hypertension was the highest due to its substantially higher prevalence of hypertension .Like diabetes, the individual-level hypertension-related QALE loss declined gradually with older ages. The population hypertension-related QALE loss also declined at a smaller rate and only after age 45 years. The hypertension prevalence was 6.5% for those younger than 45 years versus 22.7% for those 45 years or older. Also, like diabetes, the individual-level hypertension-related QALE loss did not change much during the study period, but the population QALE loss had increased significantly since 2010, from 1.7 in 2010 to 2016, a 29% increase. Such an increase in population QALE loss paralleled the increasing prevalence of hypertension from 21.6% to 29.2%, a 35% increase. Unlike the other diseases, less than half of the QALE loss and population QALE loss could be attributed to mortality alone, probably because the hazard ratio of dying for people with hypertension was only 1.06, which was substantially smaller than those for the other four diseases (all ≥1.3). Also, the gender differences in the burden of hypertension, both at the individual and the population levels, were very small.

Heart Disease

Data on the burden of heart disease (coronary heart disease and myocardial infarction) for the whole nation were available only for 5 years, 2010-2013. Therefore, there is not enough data to draw any conclusion regarding the trend of heart disease. The population QALE loss, however, had declined 1.6% annually since 2005 and in 2009, heart diseases contributed 1.2 years of population QALE loss. For those reporting heart disease, QALE was 43.4 years, 10.3 years less than for those without heart disease.

More than three-quarters (75.8%) of heart disease patients were aged 55 years and older. Therefore, the population-level QALE losses due to heart diseases were nearly unchanged between the ages 18 and 55 years. Nearly all the population QALE loss due to heart disease occurred after age 55 years (age-specific data are available on request) because 75% of the heart disease occurred after age 55 years, and the prevalence of heart disease for those aged 55 years and older was 14.5%, much higher than the 2.1% prevalence rate of those aged 54 years or younger.

Unlike the other four diseases, heart disease had contributed more population QALE losses for men (1.4 years) than for women (0.9 years) because of much higher prevalence of heart disease among men (7.3% compared with 4.9% among women).

In this study we administered a health related quality of life model to patients undergoing surgery for epilepsy and compared the results with those for patients found to be unsuitable for surgery. It is a retrospective, cross sectional study and some of the analysis groups have small numbers;therefore,the results should be interpreted with some caution. However, similar methodology has been used in other published studies of postoperative quality of life.19 Thegroupsweresimilarinseizurecharacteristics; all patients had complex partial or secondarily generalised tonic-clonic seizures, but, because of the small numbers, assessment of outcome was limited to total seizure frequency only. The control group (NSurg) had seizures similar in frequency and nature to those undergoing surgery. In this postal questionnaire 47.9% of our respondents were completely seizure free in the year before censor date, and a further three patients had experienced at least two years of

freedom from seizures after surgery but then relapsed. One patient in the S<10 group and four in the S>10 group had auras only, 53.2% would fall into class I of Engel's classification,7 whereas a further 20% with less than 10 seizures per year would probably fall into class II. Therefore, overall our figures are representative of other studies.7 8 19 The study disclosed that quality of life in various psychosocial domains is significantly better in seizure free patients than those who continue to have frequent seizures after surgery for epilepsy or who are unsuitable for surgery. Quality of life in patients with reduced numbers of seizures seems improved but to a lesser degree. These results are at odds with previous studies, which have suggested that improved psychosocial status after surgery is dependentonbeingcompletelyseizurefree.12 13 Rausch and Crandall, using measures including degree of dependency, work performance and family and non-family relationships,found that improvements were dependent on freedom from seizures one year after surgery. Two of the above studies used the WPSI, a psychosocial measure designed for epilepsy, which has been criticized because it refers to fixed events in the past which will not change with any outcome, and also because its format utilizes yesor noanswerswhichmaynot be sensitive to change.15 The use of generic measures, the short duration of follow up, and generally small numbers, may explain the inability to detect differences in patients with reduced frequency of seizures in the above studies. We attempted to compare outcome using a control population of medically treated patients. Only two other studies have used this format, and only one study used a validated health related quality of life measure.

ESI 55 has already been found capable of distinguishing between different outcome groups based on seizure frequency. The failure to detect a greater difference compared with medically treated controls in the latest study probably reflects combining the various outcome groups to give an overall surgery group figure. We were unable to analyse our patients with auras only because the numbers were too small. In a previous study using the ESI, 55 patients with auras only were found to perform similarly to patients with less than 10 seizures per year after surgery, with scores intermediate between seizure free patients and those having more than 10 seizures per year.18 At least four patients in our S>10 group had auras only; including them in this group may have impaired our ability to distinguish between the S<10 and S>10 groups and, therefore, underestimated the differences in quality of life outcome. All the scales we used detected differences between the groups but the patterns of improvement were not the same on all the scales. The mastery scale disclosed small but significant differences between the seizure free and all other groups. This differs from a previous study suggesting that mastery does not change after surgery even in seizure free patients.35 In that study, assessment was performed only six months postoperatively, and, therefore, the patients could be still expected to be coming to terms with freedom from seizures. The mastery scale we used considers wider issues and is likely to be more sensitive. The same mastery scale, used in a placebo controlled trial,29 detected a significant difference in favour of patients receiving a novel antiepileptic drug. Furthermore, on intuitive grounds, patients gaining relief from unpredictable adverse events—that is, seizures—would be expected to feel a greater degree of control. Similarly it is not surprising thatlevelsofstigmaarelowerintheseizurefree group than in the other three groups.Perceived stigma36 may not resolve until epilepsy is completely cured, thence removing the label of "epileptic." Psychiatric and psychological morbidity is an important problem in epilepsy,12with clinically significant anxiety and depression being common.3 37 Previous postoperative studies have reported improved depression and reduction in psychological distress but only in patients who were seizure free, those with 75% or less reduction in seizures showed no improvement.By contrast, this study identified improvements in psychological wellbeing,not able anxietyanddepression,inboththe seizure free and S<10 groups. Unemployment is a major problem in people with chronic epilepsy6 38 especially in areas where competition for jobs is fierce.39

Gainful employment is a good predictor of overall wellbeing6 and patient satisfaction postoperatively,40 and, therefore, represents an important outcome for patients. Furthermore, in defining the proportion of patients likely to become productive members of society, it should be considered as an important measure of the cost effectiveness of epilepsy surgery programmes. Some studies have reported that, although "vocational adjustment"15 and working capacity34 may improve, rates of new employment do not.19 41 One of the most interesting findings in this study was the difference inemploymentratesineachgroup.Seizurefree patients were more likely to have been employed before surgery than in the other outcome groups, suggesting that they may be less disabled by their seizures and,therefore,would be more likely to have better postsurgery outcome. However, significantly more previously unemployed people obtained employment in the seizure free group compared with the other groups after surgery, consistent with findings from a recent American study. The overall employment figure of 80% in the seizure free group is comparable with recently reported employment rates of 79% for men and 64% for women in people with well controlled epilepsy and similar to rates found in the general population.43 The finding of better preoperative employment rates in patients who become seizure free implies that other factors influence employability. Clearly baseline preoperative status should be measured in future studies to further elucidate the relation between seizures and health related quality of life. Outcomes such as driving are potentially important outcome measures, as driving and transport are often cited as major problems,44 which are likely to influence many other aspects of quality of life in people with epilepsy. There is a lag phase of at least 18 months between becoming seizure free and obtaining a driving licence in the United Kingdom. The finding of significantly longer outcome duration in seizure free patients who were driving compared with those who were not, suggests that the figure of 45% obtaining driving licences may increase with further follow up. There is a lag between improvement in seizure control and reduced levels of anxiety and depression in medically treated patients attending a specialist clinic.45 Somewhat surprisingly we failed to show a direct relation between duration of postoperative seizure freedom and any of the psychological measures other than impact of epilepsy. However, the driving and employment data from this and other studies46 suggest a lag between freedom from seizures and the tangible psychosocial benefits thereof. Furthermore, the nature of this study (retrospective cross sectional) and thefewseizurefreepatientsmakesitdiYcultto make categorical statements about the importance of duration of postoperative freedom from seizures but demands that long term psychosocial follow up should be the focus of future prospective studies.

CONCLUSION:

In conclusion, This study compared the differences in QALE for those who had diabetes, hypertension, heart disease, or stroke to those have epilepsy surgery. The proposed method can be particularly useful when examining burdens for common chronic diseases over time and at the local level for program planning and evaluation. This small retrospective study has shown that health related quality of life is related to postoperative seizure status. However, prospective studies are required to elucidate the role of other factors such as preoperative status and changes in psychosocial status with postoperative duration. Satisfactory studies should be prospective and longitudinal, comparing patients' preoperative and postoperative seizures and psychological status. To produce meaningful statistical data multicentre collaboration will be essential.Resultant data might assist in the construction of specified quantitative targets for *Healthy People 2020* objectives and setting priorities for prevention in a given population as well as in sociodemographic subgroups.

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Original Article

A RANDAMIZED PILOT STUDY AND EFFECTS OF OMEGA 3 FATTY ACIDS ON HYPERTENSIVE PATIENTS WITH ARTERIAL STIFFNESS

Aejaz Ahmed*, Abeda siraj[1], Nikhath Anjum[1], Nusrathunnisa Begum[1], Shagufta Adeeb[1], Hajera Nausheen[1]

Azad college of pharmacy, Hyderabad, India

Abstract: The force of blood against the wall of arteries is known as blood pressure. High blood pressure can lead to many heart diseases and it also increases the risk of heart attacks and strokes. To assessed the effects of esterified omega–3 fatty acids on PWV and serum markers of inflammation among patients with hypertension. To Assess of effect of high-dose (3.36 g) omega-3 fatty acids on PWV and secondarily high sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and serum adiponectin. Subjects were recruited from outpatient primary care clinics or a preexisting registry of hypertension patients. This cohort consisted of 52 individuals; the inclusion and exclusion criteria for this registry have been previously reported. Eligible patients were ≥18 years of age, of either Latino or non-Latino White ethnicity and had at least one other CVD risk factor including diabetes, dyslipidemia, obesity, chronic kidney disease, microalbuminuria, current smoking, or age >55 for men or >65 for women, but were excluded if they had pre-existing CVD. Sensitivity analyses were performed to assess changes in outcomes among the following subgroups: patients naïve to statin therapy, those with baseline systolic blood pressure ≥ 140 mm Hg, and diabetic patients, *P*-values <0.05 were considered statistically significant. SAS Version 9.4 (Cary, NC) was used for all statistical analyses. In conclusion, high-dose purified omega-3 fatty acids did not significantly improve arterial stiffness among hypertensive patients extending the negative results of previous studies. Given the absence of benefits of omega-3 fatty acids on CVD events in large randomized controlled clinical trials, this therapy cannot be uniformly recommended in primary prevention patients despite widespread use.

Keywords: Phospholipase, microalbuminuria, Omega-3 fatty acid.

Corresponding Author: Aejaz Ahmed, E Mail: azmathkhasn75@gmail.com

1. INTRODUCTION

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated.[8] High blood pressure usually does not cause symptoms.[1] Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.[2][3]

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[4] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.[4][5] Lifestyle factors that increase the risk include excess salt, excess body

weight, smoking, and alcohol.[1][4] The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[4]

Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[1] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[9] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults.[4] Different numbers apply to children.[10] Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement.[8][4]To Assess of effect of high-dose (3.36 g) omega-3 fatty acids on PWV and secondarily high sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and serum adiponectin.

2. MATERIALS AND METHODS:

We conducted a prospective, randomized placebo-controlled, double-blind pilot study. Patients received either 4 omega-3 fatty acid capsules or identically matched corn-oil placebo. Each Lovaza capsule includes 465 mg of EPA and 375 mg of docosahexaenoic acid (DHA) for a total daily dose of 3.36 g. The treatment period was 3-months with baseline and follow-up measurements performed in the morning in a fasted state. The Colorado Multiple Institutional Review Board approved the study and it was registered with clinical trials.gov. All study participants signed written informed consent.

Subjects were recruited from outpatient primary care clinics or a preexisting registry of hypertension patients. This cohort consisted of 177 individuals; the inclusion and exclusion criteria for this registry have been previously reported [11]. Eligible patients were ≥18 years of age, of either Latino or non-Latino White ethnicity and had at least one other CVD risk factor including diabetes, dyslipidemia, obesity, chronic kidney disease, microalbuminuria, current smoking, or age >55 for men or >65 for women, but were excluded if they had pre-existing CVD.

Arterial PWV measurements were performed in the recumbent position. Supine blood pressure was measured in duplicate in the non-dominant arm. Bilateral brachial-ankle PWV was derived from the pulse transit time between and the estimated path length between proximal and distal arterial sites expressed as cm/s. Inflammatory markers and adiponectin were also assessed while fasting. We chose hsCRP because it has incremental CVD risk discrimination beyond standard Framingham risk factors [12] and Lp-PLA2 given its specificity for inflammation localized to atherosclerotic plaque [13].

Statistical analysis

Means, standard deviations, and medians were calculated for all continuous variables. For univariate analyses, comparisons were made using analysis of variance, chi-squared or Wilcoxon rank sum tests. For change over time analyses, mixed-effects models were used to account for repeated measures within participants. Univariate associations between baseline risk markers and change in PWV were assessed, and multivariate models were fitted to assess for predictors of change. Sensitivity analyses were performed to assess changes in outcomes among the following subgroups: patients naïve to statin therapy, those with baseline systolic blood pressure ≥ 140 mm Hg, and diabetic patients, *P*-values <0.05 were considered statistically significant. SAS Version 9.4 (Cary, NC) was used for all statistical analyses.

3. RESULTS;

Baseline characteristics of the 62 participants are shown in Table 1 and were consistent with a safety-net population. The majority of patients were receiving medication for chronic hypertension and half had diabetes. Overall, baseline characteristics were well matched; specifically, PWV values did not differ by randomization group. Among baseline variables, older age, higher systolic blood pressure,

and adiponectin were significantly associated with increased PWV: 16 cm/s increase in mean PWV per year of increasing age ($p < .0001$), 7.3 cm/s increase in mean PWV per each mm Hg of higher systolic blood pressure ($p = 0.005$), and 14 cm/s per unit of adiponectin ($p = 0.008$).

Table 1: Placebo, Omeg-3 and Over all conc

		Placebo (*N* = 35) **N (%) or Mean (SD)**	**Omega-3 (*N* = 27)** **N (%) or Mean (SD)**	**Overall (*N* = 62)** **N (%) or Mean (SD)**
Age (years)		60.2 (10.8)	62.3 (9.7)	61.1 (10.3)
Female Gender		22 (63 %)	18 (67 %)	40 (65 %)
Educational Status	Did Not Complete High School	18 (51 %)	10 (37 %)	28 (45 %)
	Completed High School	9 (26 %)	10 (37 %)	19 (31 %)
	Completed College	8 (23 %)	7 (26 %)	15 (24 %)
Unemployed		28 (80 %)	21 (81 %)	49 (80 %)
Body Mass Index (kg/m2)		31.5 (7.1)	33.9 (8.6)	32.6 (7.8)
Systolic Blood Pressure (mm Hg)a		137 (16)	128 (14)	133 (16)
Diastolic Blood Pressure (mm Hg)		82 (9)	78 (10)	81 (10)
Antihypertensive Medication		32 (91 %)	21 (78 %)	53 (85 %)
Statin therapy		17 (49 %)	11 (41 %)	28 (45 %)
Total cholesterol (mg/dL)		179 (43)	179 (38)	179 (40)
Triglycerides (mg/dL)		188 (103)	173 (65)	182 (89)
HDL-C (mg/dL)		48.4 (14.9)	44.9 (12.4)	46.9 (13.9)
LDL-C (mg/dL)		97 (38)	99 (29)	98 (34)
Diabetes diagnosis		19 (54 %)	12 (48 %)	31 (52 %)
Hemoglobin A1c (%)		6.7 (1.8)	6.3 (1.3)	6.6 (1.6)
Glucose (mg/dL)		127 (61)	111 (25)	120 (49)
Smoking status	Current	12 (34 %)	6 (22 %)	18 (29 %)
	Former	23 (66 %)	21 (78 %)	44 (71 %)
hsCRP (mg/L)		3.42 (3.35)	5.63 (5.05)	4.38 (4.29)
Adiponectin (ug/mL)		10.6 (8.3)	12.2 (7.8)	11.4 (8.1)
LpPLA2 mass (ng/mL)		244 (46)	252 (62)	247 (53)
Mean PWV (cm/s)		1690 (335)	1602 (324)	1652 (330)

Changes in risk factors, inflammatory markers, and PWV are shown in Table 2. Comparative percentage change in Lp-PLA2 mass, PWV, and hsCRP were all directionally more favorable in the omega-3 arm but did not achieve statistical significance (Fig. 1). Absolute change in mean PWV was −97 cm/s in the omega-3 arm compared to −33 cm/s in the placebo group ($p = 0.36$). Reductions were also seen in mean hsCRP (−0.9 mg/L vs. 0.9 mg/L in placebo group) and Lp-PLA2 mass (−18.1 ng/mL vs. −6.1 ng/mL). Numeric mean reductions in risk markers were relatively larger within subgroups: Among 34 statin-naïve subjects, the difference in arterial PWV was larger (−82 vs. +50 cm/s), but remained non-significant ($p = 0.20$), though the reduction in mean hsCRP (− 0.8 vs. +1.6 mg/dl) achieved significance ($p = 0.03$). Among 31 diabetic subjects, PWV (−100 vs. −18 cm/s), hsCRP (−0.8 vs. +1.7 mg/L), and LpPLA-2 mass (−11.1 vs. −4.1 ng/ml) were non-significantly lower with active treatment (minimal *p*-value 0.19). Among 24 subjects with baseline systolic blood pressure ≥ 140 mm Hg PWV (−98 vs. −65 cm/s), hsCRP (−1.0 vs. +0.8 mg/L), and LpPLA-2 mass (−32.7 vs. −3.2 ng/ml) were non-significantly lower with active treatment (minimal *p*-value 0.09).

Table 2: Cholesterol, HDL labels

	Placebo (*N* = 35) **Mean (SD)**	**Omega-3 (*N* = 27)** **Mean (SD)**
Pulse Wave Velocity (cm/s)	−33 (306)	−97 (182)
Total cholesterol (mg/dL)	−6.6 (30.4)	−0.8 (18.1)
Triglycerides (mg/dL)	−30.0 (58.1)	−17.6 (45.6)
HDL-C (mg/dL)	0.2 (8.5)	2.9 (14.6)

LDL-C (mg/dL)	−2.8 (28.6)	0.7 (18.3)
Hemoglobin A1c (%)	−0.13 (0.94)	0.06 (0.44)
Glucose (mg/dL)	−13.1 (44.0)	0.6 (23.0)
hsCRP (mg/L)	0.9 (4.4)	−0.9 (3.1)
Adiponectin (ug/mL)	0.3 (3.4)	−0.4 (2.4)
LpPLA2 mass (ng/mL)	−6.1 (31.7)	−18.1 (41.1)

In multivariate analysis accounting for baseline age, systolic blood pressure and adiponectin, no significant change in mean PWV [parameter estimate (standard error) = -22 (24), $p = 0.36$] was observed. In analysis including only time and treatment group, the reductions in hsCRP and Lp-PLA2 mass were numerically greater with omega-3 therapy, but were not statistically significant ($p = 0.08$, and 0.21, respectively).

4. DISCUSSION:

To our knowledge, this is the first prospective randomized trial evaluating the effects of prescription doses of omega-3 fatty acids on arterial stiffness in a Latino-predominant population. Short-term treatment with omega-3 fatty acids was not associated with a significant reduction in arterial PWV. Moreover, with the exception of a reduction in serum hsCRP among statin-naïve subjects, no significant improvements in markers of vascular inflammation were observed despite a high prevalence of obesity and diabetes. Given an association between the metabolic syndrome and increased arterial stiffness [14], a positive effect of omega-3 fatty acids might have been expected.

A number of possible explanations for our findings merit consideration. One potentially important factor is the dose of omega-3 utilized. In one study, PWV was assessed among overweight patients receiving 2, 4, and 6-g of omega-3 fatty acids daily [15]. Reductions in PWV were observed only in the group receiving 6-g per day. It is possible that despite the 3.36 g dose in the current study, it was still inadequate to reduce PWV, particularly if compliance was sub-optimal. Although no medication diary or formalized drug reconciliation process was utilized in our study, this is plausible given the absence of a significant triglyceride reduction observed in the active treatment arm, which may reflect medication non-adherence in our vulnerable population. Also, half of the patients in our study were already receiving statin therapy, which could limit our ability to further discern a treatment effect. In support of this possibility, a recent trial among patients with peripheral arterial disease already receiving statin therapy, found no improvement in PWV after omega-3 fatty acid treatment [16]. Our findings are in line with this possibility since the difference in PWV over time between the groups was larger among statin-naïve subjects. Analogously, an expected greater reduction in hsCRP was seen among statin-naïve subjects. One further study limitation is that fatty acid bioavailability data were not evaluated, so we don't know if there was a relationship between plasma fatty acid level and changes in PWV.

Another potential explanation for the findings in the current study is the relatively small sample size. Root and colleagues also found no reduction in PWV with omega-3 therapy in a short-term study of 57 patients [17]. In assessing sample size, approximately 100 subjects would provide > 80 % power to detect a 10 % decrease in PWV (standard deviation [SD] 350 cm/s) assuming a baseline PWV of 1700 cm/s. With 62 randomized patients, the current study had just over 60 % power under those assumptions. Although the numeric effect size in the current trial was consistent with this reduction, and the standard deviation was within assumed range, the placebo-corrected absolute reduction in PWV was only 4 %. The clinical significance of this numeric finding may be gleaned from a meta-analysis of observational data from 17,635 subjects, where a 10 % increase in PWV was associated with a hazard ratio for CVD events of 1.07 (95 % CI: 1.02 to 1.12) [18].

In addition, the relatively short duration of therapeutic exposure, may have limited our ability to detect alterations in vascular stiffness. There was also a numeric imbalance of subjects between arms, which

likely reflects a chance finding in the randomization sequence given the small sample size. This theoretically may have made a Type II error more likely. Most importantly, however, no pharmacologic therapy to date has been shown to reduce PWV independent of blood pressure reductions, suggesting the possibility that any salutatory effects of omega-3 treatment on inflammation and plaque may be inadequate to alter vessel wall physiology.

5. CONCLUSION:

In conclusion, high-dose purified omega-3 fatty acids did not significantly improve arterial stiffness among hypertensive patients extending the negative results of previous studies. Given the absence of benefits of omega-3 fatty acids on CVD events in large randomized controlled clinical trials, this therapy cannot be uniformly recommended in primary prevention patients despite widespread use.

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Original Article

DEPRESSION AND ADVERSE DRUG REACTION AMONG HOSPITALIZED OLDER ADULTS

Dr. Shahana Banu[1], Aejaz*[2], Afreen Sultana[2], Asma Jahan[2], Fareeza Kauseen[2], Mir Fazil Hassan Ali[2], Aiman Shagufta[2]

1. Gulbarga Unversity, India.
2. Azad college of pharmacy, India

Depression is a common disorder among hospitalized older adults, and it has been associated with adverse outcomes during hospital stays, including increased risk of morbidity and mortality and reduced recovery rates from illness and disability. Feeling down from time to time is a normal part of life, but when emotions such as hopelessness and despair take hold and just won't go away, you may have depression. Depression makes it tough to function and enjoy life like you once did. Just getting through the day can be overwhelming. But no matter how hopeless you feel, you can get better. Learning about depression—and the many things you can do to help yourself—is the first step to overcoming the problem. We assessed whether depression may represent a risk factor for ADRs among hospitalized in older adults. Differences between depressed and nondepressed patients in categorical variables were tested using the Fisher exact test. Differences between continuous variables were assessed using analysis of variance comparisons for normally distributed variables; alternatively, the Kruskal-Wallis test was adopted. On the basis of our findings in hospitalized older patients, depression seems to be associated with an increased risk of developing ADRs. This association increases with severity of depression. Depression seems to be associated with a higher rate of developing ADRs. This finding may be relevant to physicians prescribing medications, who may want to monitor patients with depressive symptoms more closely. Future studies on ADRs in the older population should consider multiple complex aspects of aging, including depression.

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1. INTRODUCTION

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being.[1][2]

Feeling down from time to time is a normal part of life, but when emotions such as hopelessness and despair take hold and just won't go away, you may have depression. Depression makes it tough to function and enjoy life like you once did. Just getting through the day can be overwhelming. But no matter how hopeless you feel, you can get better. Learning about depression—and the many things you can do to help yourself—is the first step to overcoming the problem.

While some people describe depression as “living in a black hole” or having a feeling of impending

doom, others feel lifeless, empty, and apathetic. Men in particular may even feel angry and restless. No matter how you experience it, depression is different from normal sadness in that it engulfs your day-to-day life, interfering with your ability to work, study, eat, sleep, and have fun.

Some people feel like nothing will ever change. But it's important to remember that feelings of helplessness and hopelessness are symptoms of depression—not the reality of your situation. You can do things today to start feeling better.

People with a depressed mood can feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, angry,[3][4] ashamed, or restless. They may lose interest in activities that were once pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details or making decisions, experience relationship difficulties and may contemplate, attempt or commit suicide. Insomnia, excessive sleeping, fatigue, aches, pains, digestive problems, or reduced energy may also be present.[5]

Depressed mood is a feature of some psychiatric syndromes such as major depressive disorder,[2] but it may also be a normal temporary reaction to life events such as bereavement, a symptom of some bodily ailments or a side effect of some drugs and medical treatments. A DSM diagnosis distinguishes an episode (or 'state') of depression from the habitual (or 'trait') depressive symptoms someone can experience as part of their personality

Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working. To be diagnosed with depression, the symptoms must be present for at least two weeks.

We assessed whether depression may represent a risk factor for ADRs among hospitalized in older adults.

2. MATERIALS AND METHODS:

All patients admitted to 81 geriatric and internal medicine wards participating in the study were enrolled and followed until discharge. The study periods were Dec 2016 to April 2017. The study was approved by the ethical committee.

For each participant, a questionnaire was completed at hospital admission, and it was updated daily by a study physician who received specific training. Data recorded included sociodemographic characteristics, indicators of physical function and cognitive status, clinical diagnoses at admission and at discharge, and medication use before and during the hospital stay as well as medications prescribed at discharge.

For the present analysis, we used data collected in 2016-2017, because the depression survey (the short form [15 items] of the Geriatric Depression Scale [GDS]) was administered only during this period.[13] This instrument, which was administered to hospitalized study patients in stable health condition, has proved to be reliable for detecting depression among inpatients.[14] It has also been validated in the Italian population.[15] Patients with GDS scores of 5 or greater were considered to be depressed, based on previous observations among in-hospital patients.[14]

Cognitive performance was assessed using the Hodkinson Abbreviated Mental Test.[16]Based on a previous observation in an Italian population, a score of less than 7 defined cognitive impairment.[17]

Drugs were coded according to Anatomical Therapeutic and Chemical codes.[18]Discharge diagnoses were coded according to International Classification of Diseases, Ninth Revision,

Clinical Modification, codes.[19] Comorbidity was quantified using the Charlson Comorbidity Index by adding scores assigned to specific discharge diagnoses, as illustrated in the original publication.[20]

3. ADVERSE DRUG REACTIONS

An ADR was considered to be any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and abuse.[21] A study physician investigated each ADR detected during hospital stays by gathering information from patients, nurses, and attending physicians and by reviewing medical charts and records. For each suspected ADR, the study physician coded the clinical description, severity, and outcome of the ADR and collected detailed information about the drug(s) that potentially caused the ADRs. Causality between drug use and ADR was assessed using scores on the Naranjo algorithm.[22] Adverse drug reactions were classified as definite (score, 9-12), probable (score, 5-8), possible (score, 1-4), or doubtful (score, ≤0). Only definite and probable ADRs observed during hospital stays were used in this study.

4. DATA ANALYSIS

Differences between depressed and nondepressed patients in categorical variables were tested using the Fisher exact test. Differences between continuous variables were assessed using analysis of variance comparisons for normally distributed variables; alternatively, the Kruskal-Wallis test was adopted. To establish whether depression represented a risk factor for experiencing any ADR, a logistic regression model was performed in the 3134 patients participating in the 1998 survey who had valid GDS data. To explore a potential trend between depressive symptom severity and ADRs, an additional logistic regression model was conducted using categorization of the GDS score: 0 to 1 (n = 839), 2 to 4 (n = 932), 5 to 7 (n = 664), 8 to 10 (n = 464), and 11 to 15 (n = 235). Variables considered for adjustment were those associated with depression at P≤.05 in the univariate analyses.

To assess whether depression was associated with ADRs independent of comorbidity level, we performed additional stratified analyses across 3 groups, classified on the basis of the Charlson Comorbidity Index score: 0 to 1 (n = 1745), 2 to 3 (n = 973), and 4 or higher (n = 416). We also assessed the association between depression and (1) ADRs that reflect subjective symptoms (headache, abdominal pain, nausea, etc) and (2) ADRs that reflect objective signs, laboratory tests, or diagnostic procedures (skin rashes, hemorrhagic complications, electrolyte disturbances, etc). All analyses were performed using statistical software (SPSS for Windows, version 10.0; SPSS Inc, Chicago, Ill).

On the basis of our findings in hospitalized older patients, depression seems to be associated with an increased risk of developing ADRs. This association increases with severity of depression.

The prevalence of depression in our sample is higher than that observed among patients in the community, but it is similar to that found in other studies[1-4] conducted in the hospital setting. The correlation between depression and hospitalization has been documented by other researchers,[23] who reported that depressive symptoms frequently represent a reaction to severe disability and discomforts that are associated with medical illness.

The higher risk of ADRs that we observed among depressed patients may be due to a variety of factors. First, depressed patients can amplify somatic symptoms, leading to a higher reported rate of ADRs.[24] In this context, it has been suggested that emotional distress can lead to increased attention directed toward one's body, with a consequent decrease in the threshold of any

noxious somatic sensation.[25] However, this hypothesis is not supported by our results, given that in our study population, associations between depression and either subjective or objective ADRs were similar.

Second, it has been hypothesized that psychological distress can activate neurally regulated biological processes. This can result in diminished ability to combat pathologic processes, thus favoring the onset of negative outcomes such as ADRs. This phenomenon, described by Engel[26] as the "giving-up–given-up complex," could explain the increased risk of adverse outcomes observed in depressed patients. According to this hypothesis, depression adversely affects cardiac, gastrointestinal, endocrine, neurologic, and immune processes by increasing sympathetic tone and decreasing vagal tone.[27- 29]

A third possible explanation for our findings is that depressive symptoms may occur as a consequence of ADRs and the high comorbidity associated with ADRs. Because depression data for our study were collected on inpatients with stable health conditions, we are unable to evaluate whether a temporal relationship existed between the onset of ADRs and subsequent development of depression.

The present study has several strengths. First, the relationship between depression and ADRs was studied using a dedicated database. Second, the hospital was an ideal setting to evaluate this association because pharmacologic noncompliance, which can play an important role in the onset of ADRs among depressed patients, is reduced. Finally, to describe the causal relationship between ADRs and drug exposure, we used an algorithm that is associated with 85% interobserver agreement.[22]

An important limitation of this study relates to generalizability of the results. Our findings, which are based on an elderly hospitalized population, cannot be extrapolated to younger individuals living in the community.

5. RESULTS AND DISCUSSION:

PATIENT CHARACTERISTICS

A total of 313 patients were enrolled in the 2017 portion of the study, during which GDS data were collected. Mean ± SD patient age was 72.0 ± 14.1 years, and 45.6% of the study population was female. Of the total enrolled sample, 136 (43.5%) experienced depression during hospitalization (GDS score, ≥5). The mean ± SD GDS score was 4.5 ± 3.7. Other characteristics of the study population are summarized in Table 1. Compared with nondepressed patients, those with depression were older, were more likely to be female, had a higher prevalence of cognitive impairment and disability, and had a more severe Charlson Comorbidity Index. Depression was associated with a significantly higher prevalence of congestive heart failure, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, and neoplasms. Patients with depression used more drugs during hospital stays. In particular, they were more likely to use cardiovascular medications, antidiabetic drugs, corticosteroids, and neurotropic drugs.

VARIABLES	PATIENTS		P VALUE
	NONDEPRESSED N=177	DEPRESSED N=136	
AGE,MEAN SD	70.4+-15.3	74.0+-12.1	0.001
FEMALE	39.0	54.3	

LIVING ALONE	12.8	20.4	
ALD Disablity	19.1	25.1	
Congnitive impairment	20.1	23.1	0.04
Alcohol users	49.3	45.5	0.046
Smokers	14.0	11.5	0.8
Education	6.3+-4.5	506-+3.7	0.01
Charison comorbidity Index score 0-1 2-3 4	 59.1 29.5 11.4	 51.3 33.0 15.7	
Conditions Hypertension CHD CHF	 37.7 30.1 20.7 18.7	 39.7 27.2 26.3 23.6	
DM CVD COPD Neoplasm Liver disease	15.1 13.2 6.3 5.8	18.4 16.8 9.8 5.9	
Drug intake during hospital stay Drugs Diuritics ACE Inhibitors ASA and Antiplatelet drugs Antibiotics NSAIDS Nitrites Digoxin Anticoagulents Calciu	6.4+-4.0 42.0 36.6 37.2 35.3 34.5 31.5 27.2 26.0 24.3 15.6 12.1 11.1 7.3 5.4	7.7+-4.2 51.1 41.2 36.7 37.5 32.5 35.9 32.9 27.1 26.3 27.6 15.8 12.6 10.5	0.0001

m Channel Blockers Benzodiazepines Corticosteroids Oral antidiabetics Insulin Antidepressives Antipsycotics	5.1	14.3 6.0	
BMI	27.0+-16.6	26.6+-7.4	0.54
Length of stay in Hospital	12.1+-7.7	12.9+-7.4	0.006

6. ADRs AND DEPRESSION

During the hospital stays, a total of 192 probable or definite ADRs were diagnosed in 183 patients (5.8% of the sample). An ADR was recorded in 98 of the 136 patients with depression and in 62 of the 177 patients without depression (P = .001) (Table 2). In the unadjusted model, depression was associated with a 65% increased risk of developing ADRs (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.22-2.23).

After adjusting for potential confounders, this association was still present (OR, 1.58; 95% CI, 1.14-2.20). The adjusted association between depression and risk of developing ADRs was more pronounced in women (OR, 1.85; 95% CI, 1.16-2.95) than in men (OR, 1.38; 95% CI, 0.85-2.34) (Table 2), although the interaction was not significant (P = .41). Associations between depression and ADRs were similar for ADRs reflecting subjective symptoms (n = 60; OR, 1.59, 95% CI, 0.90-2.81) and those reflecting objective signs or measures (n = 123; OR, 1.56; 95% CI, 1.05-2.31).

	ADRs, NO.OF pts	OR(95%cl)	
		unadjusted	adjusted
All pts Nondepressed Depressed P value	62 98 0.001	Ref 1.65 0.001	Ref 1.58 0.006
Men Nondepressed Depre	48 37	Ref 1.36	Ref 1.

ssed P value	0.17	0.17	38 0.19
Women Non depressed Depressed pvalue	34 54 0.005	Ref 1.83 0.006	Ref 1.85 0.01

Table 3 provides the frequency of ADRs by type in depressed and nondepressed patients. Cardiovascular and arrhythmic complications (20.3% of all ADRs) were the most frequent ADRs, followed by gastrointestinal (18.8%), dermatologic and allergic (12.5%), hemorrhagic (11.5%), and electrolyte disturbances (9.9%). Except for neurologic and neuropsychiatric ADRs, which were significantly more common among depressed patients (P = .001), no significant differences were found for other types of ADRs between the 2 groups.

Figure 1 shows the drug classes that contributed most frequently to ADRs in the study sample. The most common culprit drugs were diuretics, antibiotics, and angiotensin-converting enzyme inhibitors among depressed patients, and digoxin, nitrates, and anticoagulants among nondepressed patients.

Figure 2 summarizes the ORs for ADRs across different groups, according to GDS scores. The risk of developing ADRs progressively and significantly increased as GDS score increments increased (signifying more severe depression) (P = .002 for linear trend).

Type	ADR No	
	Nondepressed	Depressed
Cardiovascular and arrythemic	18 17	21 19
Gastrointestinal	11	13
Dermatological and allergic	14 9	8 10
Hemorrhagic	2 5	12 3
Electrolyte disturbances	3 2	4 3
Neurological and neuropsychiatric	1 2	3 1
Headache	1	3
Metabolic and endocrine	0 3	2 2
Respiratory		
Hemotologic		
Musculokel		

etal Hepatic Renal and genitourinary others		

An ADR was observed in 7.3% of depressed and 4.3% of nondepressed participants scoring 0 to 1 in the Charlson Comorbidity Index (P = .007), in 7.3% of depressed and 5.0% of nondepressed participants scoring 2 to 3 (P = .12), and in 7.9% of depressed and 5.4% of nondepressed participants scoring 4 or more (P = .31). After adjusting for potential confounders, depression was associated with a similar increased risk of ADRs in all 3 comorbidity groups (Charlson Comorbidity Index score, 0-1: OR of ADRs for depression, 1.54; score, 2-3: OR, 1.60; score, ≥4: OR, 1.94). Results of these stratified analyses indicate that the risk of ADRs associated with depression is independent of the level of comorbidity because ORs were similar across groups.

7. CONCLUSION:

Depression seems to be associated with a higher rate of developing ADRs. This finding may be relevant to physicians prescribing medications, who may want to monitor patients with depressive symptoms more closely. Future studies on ADRs in the older population should consider multiple complex aspects of aging, including depression

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A CLINICAL STUDY OF ACUTE KIDNEY INJURY ON USING ANTI TUBERCULAR DRUGS

Dr.Shahana Banu[1], Das*[1], Mohammaed abdul Fazal Muzzafar-ul-haq Parvez[1], Mohammed Faraz Yausuf1, Zia-Ul-Haq[1], Mohammed Ismail Fahad[1],Yousaf Jaber[1]

Gulbarga Unversity, Karnataka, India
Azad College Of Pharmacy, India

Tuberculosis is a global disease affecting one-third of the world's population. This study aimed to calculate the incidence of AKI due to anti TB drugs and analyze the outcomes and predictors of renal recovery, to assess the onset of AKI and to assess the status of renal recovery. All TB patients received a standard anti-TB treatment of daily INH, RIF, EMB, and pyrazinamide (PZA) for the first two months, and daily INH and RIF for the next four months. For patients with an estimated creatinine clearance of < 30 ml/minute, the frequencies of EMB and PZA were changed to once every two days with the unit dose unchanged. The regimen was modified by the primary care physician if necessary, e.g. when there were adverse drug effects. Within a follow-up period of 180 days since the onset of AKI, No one died.Nine did not recover from AKI (AKI-unrecovered group), (median age, 68.5 years [IQR 59–81.5 years]) who required long-term renal replacement therapy. Very few had hypoalbuminemia. Among the 31 patients who recovered from AKI (AKI-recovered group), 44 recovered within 100 days. Serum BUN level ($p = 0.005$) and the prevalence of hematuria ($p = 0.033$) and proteinuria ($p = 0.048$) at the onset of AKI were significantly higher in the AKI-unrecovered group, whereas thrombocytopenia was less common ($p = 0.064$). The AKI recovery rate was not different among the different AKIN stages. Anti-tuberculosis drug-induced acute kidney injury is not rare in an aging population. It usually develops within two months of treatment and resolves within three months after onset. Although about some of patients with AKI will have permanent renal impairment, those who present with fever, rash, and GI disturbance at the onset of AKI have better renal recovery. Of the 51 patients who had recovery of renal function, successfully continued rifampicin or had rifampicin re-introduced.

1. INTRODUCTION

The present study was conducted to investigate the incidence of aki during anti-tb treatment in india and to determine outcomes and predictive factors for renal recovery[1]. Acute renal failure (arf) is an abrupt and usually reversible decline in the glomerular filtration rate (gfr). This results in an elevation of serum blood urea nitrogen (bun), creatinine, and other metabolic waste products that are normally excreted by the kidney[2-6]. The term acute kidney injury (aki), rather than arf, is increasingly used by the nephrology community to refer to the acute loss of kidney function. This term also highlights that injury to the kidney that does not result in "failure" is also of great clinical significance[7]. In this topic review, the acute loss of kidney function will be referred to as aki. The initial assessment of patients with aki and management of the major complications of aki are discussed here. The incidence, causes, diagnosis, and prevention of aki are presented separately[9]. Patients who are hypotensive due to surgery, sepsis, bleeding, or other causes are at risk of developing postischemic (also called ischemic) acute tubular necrosis (atn), especially if the impairment in renal perfusion is either severe or prolonged in duration. This disorder is characterized by a rising plasma creatinine concentration, a urine volume that may be reduced or

normal, and a characteristic set of changes in the urinalysis, including many granular casts and a fractional excretion of sodium above 1 percent and fractional excretion of urea above 35 percent[10-12]. Serum and urine biomarkers of tubular injury have been proposed as early biomarkers for the diagnosis of atn. The pathogenesis and etiology of postischemicatn will be reviewed here. The diagnosis of atn, potential therapies for postischemicatn, and other causes of atn are discussed separately.

The study aimed to calculate the incidence of AKI due to Anti TB drugs and analyze the outcomes and predictors of renal recovery.

2. MATERIALS AND METHODS:

This prospective study was observed omSai hospitals balapurhyderabad. The hospital's Research Ethics Committee approved the study protocol. Patients were included if they met the following criteria: (1) age ≥18 years; (2) clinical diagnosis or suspicion of TB; (3) under rifampin-containing anti-TB treatment; and (4) had onset of AKI during anti-TB treatment. Acute kidney injury (AKI) was defined according to the criteria established by the Acute Kidney Injury Network (AKIN) and was classified into three stages (Stages 1 to 3) based on serial changes in serum creatinine level. Stage 1 was defined as an increase in serum creatinine ≥26.52 μmol/L or by 1.5-fold but less than twice the baseline level. Stage 2 was defined as a two-fold increase but less than three-fold increase from baseline, while Stage 3 was defined as a three-fold increase from the baseline level.All TB patients received a standard anti-TB treatment of daily INH, RIF, EMB, and pyrazinamide (PZA) for the first two months, and daily INH and RIF for the next four months. For patients with an estimated creatinine clearance of <30 ml/minute, the frequencies of EMB and PZA were changed to once every two days with the unit dose unchanged. The regimen was modified by the primary care physician if necessary, e.g. when there were adverse drug effects.Patients were excluded if they: 1) had shock or urinary tract infection; 2) were under potentially nephrotoxic drugs other than rifampin at the onset of AKI; 3) had other conditions possibly resulting in AKI, such as hypercalcemia and nephrotic syndrome; 4) had end-stage renal disease and was under renal replacement therapy; and 5) had non-tuberculous mycobacteria infection.

3. Data collection

Demographic data, including sex, age, smoking status, excessive alcohol consumption (defined according to a single-question alcohol screening test), co-morbidities, results of sputum acid-fast bacilli (AFB) smear and mycobacterial culture, anti-TB regimen, laboratory results, onset, and management of AKI, were collected. Chronic kidney disease was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines, with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 for three months or more. Baseline laboratory tests included a hemogram, renal function (blood urea nitrogen [BUN], creatinine) tests, and levels of liver enzymes (aspartate aminotransferase and alanine aminotransferase), total bilirubin, albumin, and uric acid.The patients were classified into two groups based on hemoglobin $<$ or $\geq$100 g/L, leukocyte $>$ or $\leq 10\times10^9$/L, eosinophil count $>$ or $\leq 0.5\times10^9$/L, and platelet $<$ or $\geq 100\times10^9$/L. Hepatitis was defined as increased serum alanine aminotransferase >3 times the upper limit of normal (ULN) in symptomatic patients, or >5 times the ULN in asymptomatic patients, or serum total bilirubin >51.3 μmol/L [17, 20]. Hypoalbuminemia was defined as albumin <35 g/L, hematuria as urine red blood cell >5 per high-power field (HPF), sterile leukocyturia as urine leukocyte >5 per HPF with negative urine bacterial culture, and proteinuria as urine protein >30 mg/dL. TB laboratory tests were repeated every two weeks in the first two months and every eight weeks thereafter or when the primary care physician deemed it necessary. The time to AKI was defined as the interval between the start of anti-TB treatment and the onset of AKI.Renal recovery was defined as a return of serum creatinine to baseline and the absence of AKI features. Time to recovery was

defined as the interval between the onset of AKI and renal recovery. If renal recovery was not achieved after 180 days from the onset of AKI, the AKI was considered "unrecovered".

4. Statistical analysis

All data were expressed as either mean ± standard deviation or median [inter-quartile range]. Inter-group difference was compared using the *t*-test or Mann–Whitney *U*-test for continuous variables based on their normality, and the *chi*-square test or Fisher's exact test for categorical variables, as appropriate. Time to renal recovery for each variable was compared . All variables with a p value ≤ 0.1 in univariate analysis were entered into a multivariate Cox proportional hazards regression analysis to compute the adjusted hazard ratios (HR) and 95% confidence intervals (CI. Statistical significance was set at $p < 0.05$. Sensitivity analysis was performed in the sub-population without CKD, since it was difficult to differentiate an "acute-on-chronic" disease from progression of CKD.

5. RESULTS AND DISCUSSION:

Patient characteristics

From 2015-2016. 200 TB patients were identified, including 150 with serum creatinine data before and after the start of anti-TB treatment. Of the 80 patients with increased serum creatinine level ≥17.68 μmol/L, 30 were excluded and only 50 (7.1%) were included for further analysis. In terms of severity, 45 (84%) patients were in AKIN Stage 1, 10 in Stage 2, and 5(6%) in Stage 3. The patients' median age was 68 years (56–76 years), and there was a male predominance (71%). The diagnosis of TB was culture-confirmed in 11. Of the 60AKI patients, 16 had regular alcohol intake and 48 were smokers (Table 1). The most common underlying co-morbidities were pre-existing chronic kidney disease, diabetes mellitus, and malignancy.

6. Table 1: Demographic data based on recovery status of AKI

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Male	49	41 (72)	8 (69)
Age ≥ 65	49	43 (59)	6 (62)
Smoking	18	17 (52)	1(38)
Alcoholism	6	3 (18)	3 (8)
Malnutrition	29	25 (34)	4 (54)

7. Table 2: Data of comorbidities based on recovery status of AKI

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Old TB history	3	2 (3)	1 (4)
CKD	30	21 (30)	9 (35)
DM	25	15 (21)	10 (38)
Malignancy	25	19 (27)	6 (19)
Gout	15	10 (14)	5 (19)
Autoimmune disease	6	4 (6)	2 (8)
HIV	2	2 (3)	0 (0)
AFB-positive	29	22 (31)	7 (23)
Culture-positive	39	38 (79)	1 (81)

8. Table 3: ADR data based on recovery status of AKI

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Rash	21	18 (25)	3 (12)
Gastro-intestinal upset	17	14 (20)	3 (12)
Fever	6	5 (7)	1 (3.8)

Arthralgia	4	4 (6)	0 (0)

9. Table 4: Data of patients based on stages of AKI

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Stage 1	25	24 (89)	1 (73)
Stage 2	10	6 (8)	4 (12)
Stage 3	5	1 (6)	4(15)

10. **Table 5: Patient characteristics based on recovery status of acute kidney injury (AKI)**

Variable	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Onset of AKI after ATT (days)	44 [20–102]	40 [15–104]	4[27–91]
Management after AKI			
Hold rifampin	34 (34)	24 (31)	10 (38)
Hold pyrazinamide	35 (51)	24 (28)	11 (42)
Re-challenge rifampin	21 (21)	14 (20)	7 (27)

Abbreviations:AFB acid-fast bacilli smear, *AKI* acute kidney injury, *ATT* anti-TB treatment, *TB* tuberculosis.Note: Data are either number or median . There was no statistically significant difference between the AKI-recovered and -unrecovered groups.*Re-treatment meant that AKI recurred after re-exposure to rifampin.[#]Only 69 patients received pyrazinamide-containing anti-TB regimen at the onset of AKI.

11. Onset of AKI

Within six months after anti-TB treatment, there was a continuous probability of developing AKI (Figure 2). The median interval in all of the study subjects between the start of anti-TB treatment and the onset of AKI was 44 days]. Moreover, 61% of AKI episodes happened in the first two months of treatment. In all patients taking rifampin at the onset of AKI, some were also taking isoniazid, ethambutol, and pyrazinamide.The most common presenting symptoms at the onset of AKI were skin rash (21%) and gastro-intestinal disturbance (17%), followed by fever (6%) and arthralgia (4%) (Table 1).The most common laboratory findings were hypoalbuminemia, increased eosinophil count ($>0.5\times10^9$/L), and anemia (hemoglobin <100 g/L) (Table 2). Urinalysis showed proteinuria in 20%, sterile leukocyturia in 17%, and hematuria in 5%. Aside from elevated serum creatinine level, serum uric acid level was also elevated during AKI compared to baseline ($p < 0.001$).

12. **Table 6:Laboratory data of patients who did and did not recover from acute kidney injury (AKI)**

	No. of patients with data	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Uric Acid (μmol/L)	22	37.7 [285.5-440.2]	34.7 [267.7-434.2]	3.0 [339.0-493.7]
Creatinine (μmol/L)	29	12.8 [97.2-246.8]	11.2 [97.2-159.1]	1.6 [106.1-238.7]

	No. of patients with data	Overall (n = 50)	AKI-recovered (n = 41)	AKI-unrecovered (n = 9)
Blood urea nitrogen (mmol/L)	46	8.4 [6.0-15.4]	7.5 [5.6-13.3]	1.4 [7.9-20.7]*
Uric Acid (mmol/L)	23	29.4 [386.6-678.1]	25.2 [386.6-695.9]	4.2 [350.9-565.1]
Hemoglobin < 100 (g/L)	24	22 (26)	15 (25)	7 (33)
Eosinophil >0.5 (10^9/L)	33	21 (29)	14 (25)	7 (44)
White blood cell >10 (10^9/L)	35	15 (18)	11 (18)	4 (19)
Platelet < 100 (10^9/L)	25	9 (11)	9 (15)	0 (0)**
Hepatitis [#]	17	4 (4)	3 (4)	1 (4)
Jaundice [§]	11	3 (4)	2 (3)	1 (6)
Hypoalbuminemia	24	17 (41)	14 (36)	3 (54)
Hematuria	25	5 (5)	2 (7)	3 (38)*
Proteinuria	25	20 (20)	13 (48)	7 (88)*
Sterile leukocyturia	25	17 (17)	13 (48)	4 (50)

Note: Data are either median [inter-quartile range] or number (%) unless otherwise stated.*Significantly different ($p < 0.05$) between the AKI-recovered and –unrecovered groups.**$p = 0.064$.[#]Hepatitis was defined as increased serum alanine aminotransferase >3 times the upper limit of normal (ULN) in symptomatic, or >5 times the ULN in asymptomatic patients.

[§]Jaundice was defined as serum total bilirubin level >51.3 μmol/L.

13. Modifications of anti-TB treatment during AKI

After the onset of AKI, rifampin was discontinued in some patients. Among them, re-challenge was performed in few. Of the remaining few patients who did not undergo rifampin re-challenge, few were treated with regimens not including rifampin, while some had clinical observation only (without anti-TB medication). Overall, rifampin was successfully re-introduced or continued without interruption in 60 of the 31 AKI-recovered patients and 9 AKI-unrecovered patients Pyrazinamide was discontinued in some patients after the onset of AKI. Anti-TB drugs were interrupted in some, including few who failed to complete the trail, no one died. In the remaining few patients, the median duration of treatment interruption was 14 days (IQR, 7–28 days).

14. Outcome and prognostic factors of AKI

Within a follow-up period of 180 days since the onset of AKI, No one died.Nine did not recover from AKI (AKI-unrecovered group), (median age, 68.5 years [IQR 59–81.5 years]) who required long-term renal replacement therapy. Very few had hypoalbuminemia.Among the 31 patients who recovered from AKI (AKI-recovered group), 44 recovered within 100 days. Serum BUN level ($p = 0.005$) and the prevalence of hematuria ($p = 0.033$) and proteinuria ($p = 0.048$) at the onset of AKI were significantly higher in the AKI-unrecovered group, whereas thrombocytopenia was less common ($p = 0.064$) . The AKI recovery rate was not different among the different AKIN stages ($p = 0.061$).In the Kaplan-Meier

analysis, fever (HR 3.65 [1.43-9.37]), gastro-intestinal disturbance (HR 2.32 [1.27-4.27]), and thrombocytopenia (HR 2.20 [1.08-4.50]) at the onset of AKI were significant predictors of renal recovery, whereas skin rash (HR 1.69 [0.99-2.90]) and arthralgia (HR 2.78 [0.99-7.78]) had borderline significance. Multivariate Cox proportional hazard regression analysis including all of these five variables revealed that the VIFS of all variables were <3. The independent predictors of renal recovery were fever, gastro-intestinal disturbance, and skin rash.

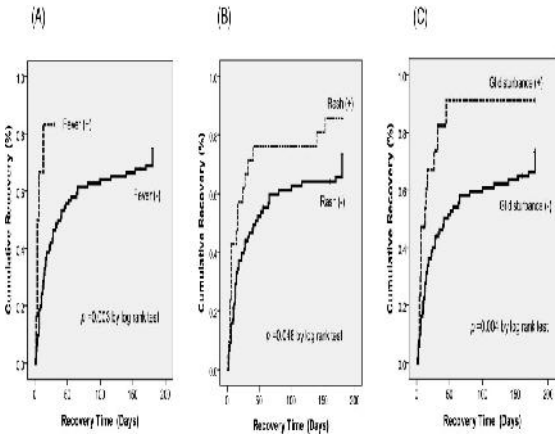

Figure 3

Kaplan-Meier curves for time to recovery from acute kidney injury among patients with or without (A) fever, (B) rash, and (C) gastro-intestinal (GI) disturbance. Sub-group difference was compared by log-rank test.

Table 7:Predictive factors of recovery from acute kidney injury (AKI), by multivariate Cox proportional hazard regression analysis

Variables	Median days for AKI recovery	Pvalue	HR	95% CI
Fever at onset of AKI: yes vs. No	4 vs. 40	0.013	3.43	1.29-9.12
Rash at onset of AKI: yes vs. No	17 vs. 45	0.044	1.79	1.02-3.14
GI disturbance at onset of AKI: yes vs. No	13 vs. 41	0.023	2.07	1.11-`3.89

Sensitivity analysis focusing on the sub-population without CKD revealed that fever at AKI onset remained a significant predictor of renal recovery ($p = 0.002$; HR 11.99 [2.43-59.19]), whereas thrombocytopenia ($p = 0.051$; HR 2.40 [1.00-5.78]) and gastro-intestinal disturbance ($p = 0.091$; HR 1.94 [0.90-4.17]) had borderline significance.The definition of rifampin-induced renal impairment varies in previous studies. The exact incidence rate is unknown. Only the review article from Romania reports that 0.05% of patients receiving rifampin (mean age, 45 years) develop acute renal failure, defined as elevated serum creatinine>44.2 μmol/L or >20% of baseline in two weeks . Using the criteria established by the AKIN , AKI during anti-TB treatment in the current study is not uncommon (7.1%), probably reflecting the old age (mean age, 65.9 years) and high prevalence of systemic co-morbidity, such as DM and CKD, that can predispose to more kidney damage .The findings that 60% of patients are older than 65 years and 80% have positive mycobacterial culture are similar to the country-wide epidemiologic data reported by the Taiwan Center of Disease Control (TCDC) (age >65 years, 52%; culture-positive rate, 80%), implying that the study

subjects here are representative of the whole TB population in Taiwan [3]. With the global trend of aging, determining the local incidence rate of AKI is necessary to improve the quality of TB care and to determine the frequency and duration of monitoring.The mechanism of rifampin-induced AKI is not well established. Several studies suggest that it is either a type II or type III hypersensitivity reaction induced by rifampin antigens in which anti-rifampin antibodies form immune complexes that are deposited in renal vessels, the glomerular endothelium, and the interstitial area. These reactions cause two different pathologic changes in the kidneys. The deposition of immune complexes in the vessels causes vascular constriction and tubular ischemia, leading to acute tubular necrosis, whereas the deposition of immune complexes in the interstitial area leads to acute interstitial nephritis. Renal biopsies performed in several studies with a total of 106 patients reveal that the most common pathologies are acute interstitial nephritis (54%) and acute tubular necrosis (38%) [4,11-13]. The immune reaction is indirect proof by the Romania study of a positive correlation between the duration of anuria and serum gamma-globulin level .In previous studies, more than 80% of patients recover from AKI within 120 days. The recovery rate in the present study (73%) is slightly lower, probably due to the older age and the presence of underlying co-morbidities. Because AKIN stage includes mild renal impairment, some patients who improve their renal function but still fulfill the stage I criteria of AKI may be classified as "unrecovered". One report reveals that age may predict delayed renal function recovery in patients with drug-induced acute interstitial nephritis. However, the present study has different findings. The recovery time of AKI-recovered patients is similar to those of previous reports, with 90% recovery within 100 days . Thus, close monitoring and avoidance of further kidney injury for three-to-four months after the onset of AKI during anti-TB treatment are necessary.The prognostic factors of AKI during anti-TB treatment are rarely investigated. Only the duration of anuria and leukocytosis have been associated with renal recovery. The current study lacks data on the duration of anuria and few patients ($n = 33$) underwent urinalysis. After including clinical symptoms, demographic data, and laboratory results into the statistical model, the multivariate Cox regression analysis reveals that the presence of fever, rash, and GI disturbance at the onset of AKI are associated with better renal recovery. Because fever and skin rash are common manifestation of acute interstitial nephritis [23], the underlying pathophysiology of AKI in patients with these two symptoms is more likely to be acute interstitial nephritis. Since acute interstitial nephritis has better prognosis than acute tubular necrosis, these patients also have better renal recovery [24,25]. For patients with GI disturbance, AKI may be partly due to dehydration and hypo-perfusion. With careful fluid management, renal impairment may be quickly overcome.More than 50% of the AKI events occurred within two months of anti-TB treatment, indicating that an acute phase reaction may be contributory. The findings also suggest that patients with CKD and hypoalbuminemia maybe more vulnerable to severe and permanent renal damage. After AKI develops, more physicians decide to discontinue pyrazinamide, rather than rifampin, implying that they do not know which of the first-line anti-TB drugs is the most common offending drug for AKI. Continuous medical education on the correct regimen modification is necessary to prevent further renal damage in TB patients with

AKI.In this study, the diagnosis of AKI is not confirmed because renal biopsy was not performed. However, the results of previous studies suggest that even without histology studies, the diagnosis of rifampin-induced AKI can be made based on the typical time course and by excluding other etiologies [11]. In the present study, the medical records were reviewed extensively to exclude other possible causes of AKI like sepsis, hypotension, or use of other nephrotoxic medication. Seven patients had a second AKI episode after rifampin re-challenge, further confirming that rifampin may be the leading cause of AKI.Re-treatment or re-exposure to rifampin causes repeat antigen exposure, which can lead to a high antibody surge and subsequent severe immune response [11,26]. This theory is supported by the finding that a high percentage of patients with rifampin-induced AKI are re-treatment cases [4,11-13]. However, the findings here are different from previous observations and show that only 11% of AKI patients are re-treatment cases. Rifampin has been successfully re-introduced in 71%. The possible explanation is drug desensitization [26]. Although the rifampicin desensitization protocol varies, success rates (80-82%) of re-introducing rifampin are high in some studies [27-30]. Further large-scale studies are needed to address whether re-exposure to rifampin is an independent risk factor of developing AKI, and to determine the method of rifampin re-introduction.The present study has some limitations. First, there is no strong evidence to confirm rifampin as the cause of AKI due to the lack of pathology results. Only seven patients had a second AKI episode after re-challenge rifampin. However, this may not be a serious problem because possible causes other than anti-TB medication have been excluded and AKI due to first-line anti-TB drugs other than rifampin is rarely reported [5,6]. Second, in this retrospective study, there is no standard protocol of laboratory follow-up for every TB patient during anti-TB treatment. Follow-up depends on the primary care physicians. Patients who did not have any symptoms or signs suggestive for AKI usually had no follow-up data on renal function. Therefore, risk factors of AKI during anti-TB treatment were not identified. Furthermore, asymptomatic patients with AKI may be missed, resulting in lower incidence and recovery rates of AKI. Third, although some characteristics of the study subjects are similar as those of the general TB population, the results here may not be applicable to all TB patients because this is a retrospective study conducted in a medical center.

15. CONCLUSION:

Anti-tuberculosis drug-induced acute kidney injury is not rare in an aging population. It usually develops within two months of treatment and resolves within three months after onset. Although about some of patients with AKI will have permanent renal impairment, those who present with fever, rash, and GI disturbance at the onset of AKI have better renal recovery. Of the 51 patients who had recovery of renal function, successfully continued rifampicin or had rifampicin re-introduced.

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Original Article

RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF GLIBENCLAMIDE IN TABLET DOSAGE FORM

Dr. Shahana Banu[1], Jabeen Farhana[2]*, Safiya Begum[2], Shaik Riyyan[2], Mohammed Ishtiyaq Ahmed[2], Mohd.Tousif Pasha[2], Mohd. Nishad Uddin[2]

1. Department of Zoology, Gulbarga University Gulbarga, Karnataka.
2. Azad College of Pharmacy, Peddamangalaram, Moinabad, Rangareddy District, Hyderabad-500079, Telangana, India.

A simple, precise, accurate,rapid and economic high performance liquid chromatographic (RP-HPLC) method has been developed for the determination of Glibenclamide in tablet dosage form. A Develosil ODS HG-5 RP C18, 5µm, 15cmx4.6mm i.d.column was used for the determination of Glibenclamide using Acetonitrile and Phosphate buffer (pH-2.75) adjusted with orthophosphoric acid, as mobile phase in the ratio of 70:30 v/v, at ambient temperature and the detector was set at 246.5nm at flow rate of 1ml/min. The Run time was found to be 8minutes. The developed method was validated for accuracy, precision, robustness and recovery studies. The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines with respect to linearity, accuracy, precision and robustness. The developed method was linear for Glibenclamide from 0-70µg/ml and the linear regression obtained was 0.998. In precision the intraand inter-day assays had relative standard deviation (% R.S.D) values within 2%. Percentage Recovery data were in the range 98.% to 102% with R.S.D. values 2%. The method is precise, accurate, linear, robust and fast. The developed RP-HPLC method for quantitative determination of Glibenclamide was proved by validation in accordance with the ICH guidelines. The developed method can be successfully applied in the routine analysis of commercial pharmaceutical tablets.

Key words: Atazanavir, RP-HPLC, Method development, Method Validation, ICH Guidelines.

Correspondence Address:
Dr.Shahana banu, Azad College of Pharmacy, India

1. INTRODUCTION

Glibenclamide is an oral ant hyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Glibenclamide belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Sulfonylureas also

increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Sulfonylureas are associated with weight gain, though less so than insulin. Due to their mechanism of action, sulfonylureas may cause hypoglycemia and need consistent food intake to reduce this risk. The risk of hypoglycemia is increased in elderly, debilitated and malnourished individuals. It has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Glibenclamide appears to be completely metabolized in the liver. Although its metabolites exert a small hypoglycemic effect, their contribution to Glibenclamide's hypoglycemic effect is thought to be clinically unimportant. Glibenclamide metabolites are excreted in urine and feces in approximately equal proportions.

Glibeclamide can be used as an adjunct to diet to lower the blood glucose in patients with NIDDM whose hyperglycemia cannot be satisfactorily controlled by diet alone.

Glibenclamide is a second-generation sulfonylurea ant diabetic agent, decreases the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β cells in the pancreatic islets. With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extra pancreatic effects may be involved in the mechanism of action of oral sulfonyl-urea anti diabetic drugs. The combination of glibenclamide and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms. In addition to its blood glucose lowering actions, Glibenclamide produces a mild diuresis by improvement of renal free water clearance.

Sulfonylureas such as Glibenclamide bind to ATP-sensitive potassium channels on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates Ca ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin. The chemical structure of Glibenclamide shown in following Fig-1.

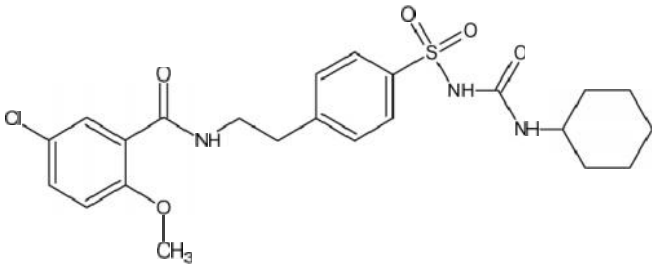

Fig-1: Structure of Glibenclamide

2. METHODOLOGY

2.1. Instrument

Table-1:List of Instruments

Sl. No	Instruments/Equipments/Apparatus
1.	**HPLC WATERS**with Empower2 Software with Isocratic with UV-Visible Detector.
2	**ELICO SL-159** UV – Vis spectrophotometer
2	Electronic Balance **(SHIMADZU ATY224)**
3.	Ultra Sonicator **(Wensar wuc-2L)**
4.	Thermal Oven
5.	Develosil ODS HG-5 **(C_{18}) RP Column, 150mm x 4.6 mm, 5µm**
6.	P^H Analyzer **(ELICO)**
7.	Vacuum filtrationkit **(BOROSIL)**

2.2. Chemicals / Reagents

Table-2:List of Chemicals

S. No.	Name	Specifications		Manufacturer/Supplier
		Purity	Grade	
1.	Doubled distilled water	99.9 %	HPLC	Sd fine-Chem ltd; Mumbai
2.	Methanol	99.9 %	HPLC	Loba Chem; Mumbai.
3.	Acetonitrile	99.9 %	HPLC	Loba Chem; Mumbai.
4.	Potassium dihydrogen orthophosphate	99.9 %	L.R.	Sd fine-Chem ltd; Mumbai
5.	Sodium hydroxide	99.9 %	L.R.	Sd fine-Chem ltd; Mumbai

2.3.HPLC Instrumentation & Conditions

The HPLC system employed was **WATERS**with Empower2 Software with Isocratic with UV-Visible Detector.

Standard Preparation for the Analysis

25 mg of Glibenclamide standard was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase.

Further dilution was done by transferring 0.5 ml of the above solution into a 10 ml volumetric flask and make up to volume with mobile phase.

Sample Preparation for the Analysis

25 mg of Glibenclamide sample was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase.

Further dilution was done by transferring 0.5 ml of the above solution into a 10 ml volumetric flask and make up to volume with mobile phase.

Mobile phase preparation

The mobile phase used in this analysis consists of a mixture of Buffer (0.01M potassium dihydrogen phosphate & pH adjusted to 2.75 with orthophosphoric acid) and Acetonitrile in a ratio of 30:70.

300ml of this buffer solution was added and properly mixed with 700ml of Acetonitrile and a homogenous solution is achieved. This mobile phase was filled and sonicated for 15 minutes before using in the experiment.

Diluent

Mobile phase can be used as diluent.

3. METHOD VALIDATION PROCEDURE

6.1. Accuracy: *Recovery study:*

To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of pure drug of GLIBENCLAMIDE were taken and added to the pre-analyzed formulation

Conc. In ppm	**AUC API**	**Conc. Found**		**%Recovery**
40	3595426	39.42		98.55
40	3623514	39.73		99.325
40	3563483	39.07		97.67
			AVG.	98.515
			SD	0.828055
			%RSD	0.840537

Conc. In ppm	AUC API	**Conc. Found**		% Recovery
50	4629039	50.81		101.62
50	4471363	49.07		98.14
50	4501884	49.41		98.82
			AVG.	99.5267
			SD	1.844487
			%RSD	1.853259

Conc. In ppm	AUC API	**Conc. Found**		% Recovery
60	5384304	59.12		98.533
60	5484934	60.23		100.383
60	5490235	60.29		100.483
			AVG.	99.79967
			SD	1.098104
			%RSD	1.100309

of concentration 50µg/ml. From that percentage recovery values were calculated. The results were shown in Table-3.

Table-3: Accuracy Readings

3.2.PRECISION

3.2.1.Repeatability

The precision of each method was ascertained separately from the peak areas & retention times obtained by actual determination of six replicates of a fixed amount of drug. Glibenclamide (API). The percent relative standard deviation were calculated for Glibenclamide are presented in the Table-4.

Table-4: Repeatability readings

HPLC Injection Replicates of Glibenclamide	Retention Time	Peak Area
Replicate – 1	4.765	1024568
Replicate – 2	4.767	1025433
Replicate – 3	4.768	1024578
Replicate – 4	4.768	1032541
Replicate – 5	4.773	1021023
Replicate – 6	4.768	1047812
Average	4.768167	1029326
Standard Deviation	0.002639	9811.684
% RSD	0.055356	0.953215

3.2.2. Intermediate Precision

3.2.2.1. Intra-assay & inter-assay:

The intra & inter day variation of the method was carried out & the high values of mean assay & low values of standard deviation & % RSD (% RSD < 2%) within a day & day to day variations for Glibenclamide revealed that the proposed method is precise.

Table-5: Results of intra-assay & inter-assay

Conc. Of Glibenclamide(API) (µg/ml)	Observed Conc. Of Glibenclamide (µg/ml) by the proposed method			
	Intra-Day		Inter-Day	
	Mean (n=6)	% RSD	Mean (n=6)	% RSD
40	39.46	0.82	60.28	0.98
50	49.26	0.42	49.53	0.23
60	60.51	0.13	49.59	0.33

3.3. LINEARITY AND RANGE

The calibration curve showed good linearity in the range of 0 – 70 µg/ml, for Glibenclamide (API) with correlation coefficient (r^2) of 0.998 (Fig-6). A typical calibration curve has the regression equation of y = 90803x + 15229 for Glibenclamide.

Fig-2:Calibration curve of Glibenclamide (API).

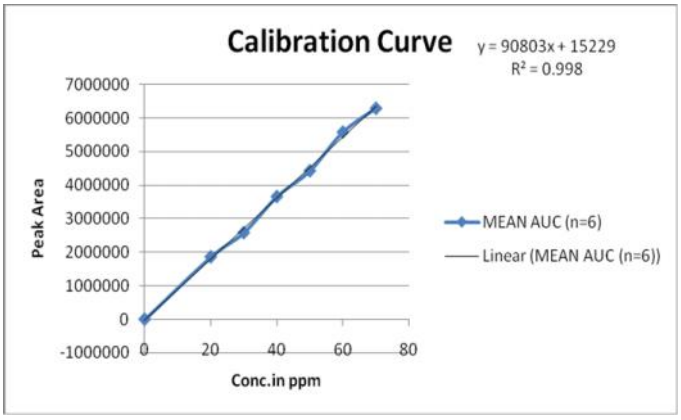

Table-6: Linearity results

CONC.(µg/ml)	MEAN AUC (n=6)
0	0
20	1861111
30	2584922
40	3659543
50	4429039
60	5584304
70	6291175

3.4. METHOD ROBUSTNESS

Influence of small changes in chromatographic conditions such as change in flow rate (± 0.1ml/min), Temperature (±2^{0}C), Wavelength of detection (±2nm) & acetonitrile content in mobile phase (±2%) studied to determine the robustness of the method are also in favour of (Table-7, % RSD < 2%) the developed RP-HPLC method for the analysis of Glibenclamide (API).

Table-7: Result of Method Robustness Test

Change in parameter	% RSD
Flow (1.1 ml/min)	0.51
Flow (0.9 ml/min)	0.57
Temperature (27^{0}C)	0.51
Temperature (23^{0}C)	0.49
Wavelength of Detection (227 nm)	0.95
Wavelength of detection (225 nm)	0.96

3.5. LOD & LOQ:

The Minimum concentration level at which the analyte can be reliable detected (LOD) & quantified (LOQ) were found to be 0.8 & 2.5 µg/ml respectively.

3.6. System Suitability Parameter

System suitability parameter test is an integral part of many analytical procedures. This test is based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. Following system suitability test parameters were established. The data are shown in Table-8.

Table-8: Dataof System Suitability Parameter

S.No.	Parameter	Limit	Result
1	Resolution	Rs > 2	9.15
2	Asymmetry	T ≤ 2	Glibenclamide=0.12
3	Theoretical plate	N > 2000	Glibenclamide=3246

4. RESULTS AND DISCUSSION

To develop a precise, linear, specific & suitable stability indicating RP-HPLC method for analysis of Glibenclamide, different chromatographic conditions were applied & the results observed are presented in previous chapters.

Isocratic elution is simple, requires only one pump & flat baseline separation for easy and reproducible results. So, it was preferred for the current study over gradient elution.

In case of RP-HPLC various columns are available, but here Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d. column was preferred because using this column peak shape, resolution and absorbance were good.

The drug was found to be Glibenclamide was found to be Soluble in ethanol (5 mg/mL), DMSO (25 mg/mL), chloroform (1:36), methanol (1:250), and DMF. Insoluble in water.Using these

solvents with appropriate composition newer methods can be developed and validated according to ICH Guidelines.

5. CONCLUSION

A sensitive & selective RP-HPLC method has been developed & validated for the analysis of Glibenclamide API and tablet dosage form.

Further the proposed RP-HPLC method has excellent sensitivity, precision and reproducibility.

The result shows the developed method is yet another suitable method for assay, purity which can help in the analysis of Glibenclamide in different formulations.

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Original Article

RP-HPLC METHOD DEVELOPMENT AND VALIDATION OF RABEPRAZOLE IN TABLET DOSAGE FORM

Dr. Shahana Banu[1], Jabeen Farhana[2]*, Safiya Begum[2], Shaik Riyyan[2], Mohammed Ishtiyaq Ahmed[2], Mohd.Tousif Pasha[2], Mohd. Nishad Uddin[2]

1. Department of Zoology, Gulbarga University Gulbarga, Karnataka.
2. Azad College of Pharmacy, Peddamangalaram, Moinabad, Rangareddy District, Hyderabad-500079, Telangana, India.

A novel, stability-indicating reversed phase high performance liquid chromatography (RP-HPLC) method has been developed for the estimation of Rabeprazole in active pharmaceutical ingredients and in its Pharmaceutical dosage form by using aDevelosil ODS HG-5 RP C_{18}, 5µm, 15cm x 4.6mm was used with a mobile phase containing a mixture of Acetonitrile and Potassium dihydrogen phosphate buffer adjusted to pH 2.5 with orthophosphoric acid in the ratio of 40:60. The flow rate was 1.0 ml/min and effluent was monitored at 282nm and a peak eluted at 3.797 minutes and column oven temperature was maintained ambient. Calibration curve was plotted with a range from 0-70 µg/ml. The developed RP-HPLC method was validated according to the current International Conference on Harmonization (ICH) guidelines for LOD, LOQ, linearity, accuracy, precision, intermediate precision and robustness. The results of the study showed that the proposed RP-HPLC method is simple, rapid, precise and accurate, which is useful for the routine determination of Rabeprazole in tablet dosage form.

Key words: Atazanavir, RP-HPLC, Method development, Method Validation, ICH Guidelines.

Correspondence Address:
Dr.Shahana banu, Azad College of Pharmacy, India

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1. INTRODUCTION

Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. It is a prodrug - in the acid environment of the parietal cells it turns into active sulphenamide form. Rabeprazole inhibits the H+, K+ATPase of the coating gastric cells and dose-dependent oppresses basal and stimulated gastric acid secretion.For the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastroinetestinalbleeds with NSAID use.

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+/K+ATPase (hydrogen-potassium adenosine triphosphatase) at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied in vitro, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds.

Rabeprazole is a 4-(3-methoxypropoxy)-3-methylpyridinyl derivative of timoprazole that is used in the therapy of STOMACH ULCERS and ZOLLINGER-ELLISON SYNDROME. The drug inhibits H(+)-K(+)-EXCHANGING ATPASE which is found in GASTRIC PARIETAL CELLS.

Rabeprazole is a proton pump inhibitor (PPI) and a potent inhibitor of gastric acidity used in the therapy of gastroesophageal reflux and peptic ulcer disease. Rabeprazole therapy is associated with a low rate of transient and asymptomatic serum aminotransferase elevations and is a rare cause of clinically apparent liver injury.

Rabeprazole is a proton pump inhibitor sold (as its sodium salt) under the brand names Aciphex and Pariet (distributed by Janssen-Cilag); Rabeprazole is a proton pump inhibitor sold (as its sodium salt) and it is used in the treatment of gastric ulcers and GERD (or heartburn). It is taken once a day along with a full glass of water (preferable 30 min before breakfast). The structure of Rabeprazole is shown in fig-1.

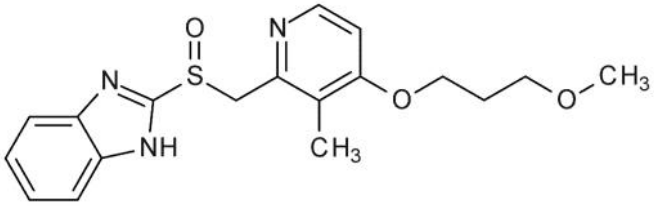

Fig-1: Structure of Rabeprazole

2. METHODOLOGY

2.1. Materials and Chemicals

The Rabeprazole working standard was received from Dr. Reddys Laboratories Pvt.Ltd, Hyderabad.Rabeprazole drug substance from AR Chemicals Pvt. Ltd.Rabeprazole Tablets 20mg, orthophosphoric acid, Potassium dihydrogen phosphate of grade AR.Acetonitrile and methanol of grade HPLC.HPLC Grade Water.

2.2. HPLC Instrumentation & Conditions:

The HPLC system employed was **HPLC WATERS**with Empoer2 Software with Isocratic with UV-Visible Detector.

2.3. Standard Solution preparation

25 mg of Rabeprazole standard was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase.

Further dilution was done by transferring 0.5 ml of the above solution into a 10ml volumetric flask and make up to volume with mobile phase.

2.4. Sample Solution preparation

25 mg of Rabeprazole sample was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase.

Further dilution was done by transferring 0.5 ml of the above solution into a 10ml volumetric flask and make up to volume with mobile phase.

Chromatographic Conditions

The analysis was carried on HPLC Develosil ODS HG-5 (C18) RP Column,15mm x 4.6 mm.with detection wavelength of 282.0nm.Injection volume of 20.0 µl and maintaining flow rate at 1ml/min.

Buffer Preparation

The mobile phase used in this analysis consists of a mixture of Phosphate Buffer (0.01M potassium dihydrogen phosphate & pH adjusted to 2.5 with orthophosphoric acid) and Acetonitrile in a ratio of 68:32.

680 ml of this buffer solution was added and properly mixed with 380 ml of Acetonitrile and a homogenous solution is achieved. This mobile phase was filled and sonicated for 15 minutes before using in the experiment.

Diluent

Mobile phase can be used as diluent.

2.5. Preparation of Standard Solution

Weigh accurately about 25mg of Rabeprazole Standard and transferred in clean and dry 25ml volumetric flask. Then add 10ml of diluent and shake it for few minutes. Then make up the volume up to the mark with diluent. Then finally make the concentration to 50µg/ml.

2.6. Preparation of Test Solution

Weigh accurately about 25mg of Rabeprazole Sample and transferred in clean and dry 25ml volumetric flask. Then add 10ml of diluent and shake it for few minutes. Then make up the volume up to the mark with diluent. Then finally make the concentration to 50µg/ml.

3. PROCEDURE FOR METHOD VALIDATION

3.1. System Suitability Parameter

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. Following system suitability test parameters were established. The data are shown in Table-1.

Table-1: Data of System Suitability Parameter

S. No.	Parameter	Limit	Result
1	Resolution	Rs> 2	9.15
2	Asymmetry	T ≤ 2	Rabeprazole=0.12
3	Theoretical plate	N > 2000	Rabeprazole=3246

3.2. Limit of Detection and Limit of Quantification (LOD & LOQ)

3.2.1. Limit of detection:

The limit of detection 7 is defined, as the lowest concentration of an analyte in a sample that can be detected, not quantified.

$$LOD = 3.3\ \sigma / S$$

3.2.2. Limit of Quantification:

The limit of quantification is defined as the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operational conditions of the method.

$$LOQ = 10\ \sigma / s$$

For the present developed HPLC method Limit of detection was found to be 0.03 µg/mL and Limit of quantification was found to be 0.09 µg/ml for Rabeprazole. LOD and LOQ were determined based on signal to noise ratio.

3.3. Linearity and Range

Weigh accurately about 25mg of Rabeprazole Standard and transferred in clean and dry 25ml volumetric flask. Then add 10ml of diluent and shake it for few minutes. Then make up the volume up to the mark with diluent.

From the above solution 2.0, 3.0, 3.0, 4.0,5.0,6.0 and 7.0ml was pipetted into 25ml volumetric flasks and made upto volume with diluent such that the resulted concentrations are 2.0,3.0,4.0,5.0,6.0 and 70µg/ml respectively.

The calibration curve showed good linearity in the range of 0 – 70 µg/ml, for Rabeprazole (API) with correlation coefficient (r^2) of 0.995 (Fig-2). A typical calibration curve has the regression equation of y = 84145x + 18258 for Rabeprazole.

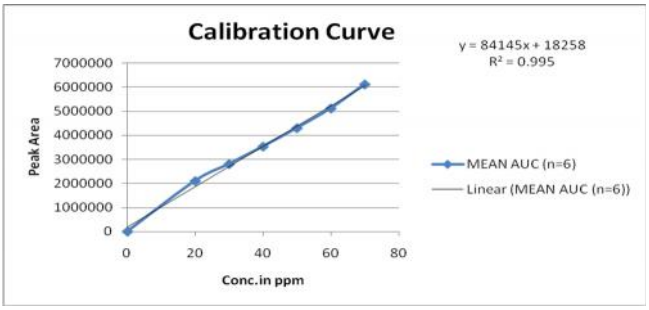

Fig-2:Calibration curve of Rabeprazole (API).

Table-2:

Linearity Results

CONC.(µg/ml)	MEAN AUC (n=6)
0	0
20	2103282
30	2809668
40	3535360
50	4302725
60	5122592
70	6123521

3.4. Accuracy: Recovery study:

To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of pure drug of RABEPRAZOLE were taken and added to the pre-analyzed formulation of concentration 50µg/ml. From that percentage recovery values were calculated. The results were shown in Table-3.

Table-3: Accuracy Readings

S. No.	Pure drug	Peak Area	Conc. Found	%Recovery of Pure drug	Statistical analysis
S_1 : 80 %	40	3423142	40.46	101.15	Mean= 101.0917% S.D. = 0.146487 R.S.D.=0.144905%
S_2 : 80 %	40	3424651	40.48	101.20	
S_3 : 80 %	40	3415214	40.37	100.925	
S_4 : 100 %	50	4251284	50.30	100.60	Mean= 100.32% S.D. = 0.341174 R.S.D.= 0.340086%
S_5 : 100 %	50	4223124	49.97	99.94	
S_6 : 100 %	50	4243414	50.21	100.42	
S_7 : 120 %	60	5124752	60.68	101.133	Mean= 100.5217% S.D. = 1.044173 R.S.D. = 1.038754%
S_8 : 120 %	60	5123654	60.67	101.116	
S_9 : 120 %	60	5032564	59.59	99.316	

3.5. Precision

3.5.1. Repeatability

The precision of each method was ascertained separately from the peak areas & retention times obtained by actual determination of six replicates of a fixed amount of drug. Rabeprazole (API). The percent relative standard deviations were calculated for Rabeprazole are presented in the Table-4.

Table-4: Repeatability readings

HPLC Injection Replicates of Rabeprazole	Retention Time	Area
Replicate – 1	3.797	10613428
Replicate – 2	3.799	10576247
Replicate – 3	3.801	10353604
Replicate – 4	3.802	10576247
Replicate – 5	3.805	10176752
Replicate – 6	3.803	10325641
Average	3.801167	10436986.5
Standard Deviation	0.002858	177195.3912
% RSD	0.075181	1.697763921

3.5.2. Intermediate Precision

3.5.2.1. Intra-assay & inter-assay

The intra & inter day variation of the method was carried out & the high values of mean assay & low values of standard deviation & % RSD (% RSD < 2%) within a day & day to day variations for Rabeprazole revealed that the proposed method is precise.

Table-5: Results of intra-assay & inter-assay

Conc. Of Rabeprazole(API) (µg/ml)	Observed Conc. Of Rabeprazole (µg/ml) by the proposed method			
	Intra-Day		Inter-Day	
	Mean (n=6)	% RSD	Mean (n=6)	% RSD
40	05.46	0.82	05.28	0.98
50	10.26	0.42	10.53	0.23
60	15.51	0.13	15.59	0.33

3.6. Method Robustness

Influence of small changes in chromatographic conditions such as change in flow rate (± 0.1ml/min), Temperature (±2^{0}C), Wavelength of detection (±2nm) &Acetonitrile content in mobile phase (±2%) studied to determine the robustness of the method are also in favour of (Table-6, % RSD < 2%) the developed RP-HPLC method for the analysis of Rabeprazole (API).

Table-6: Result of method robustness test

Change in parameter	% RSD
Flow (1.1 ml/min)	0.35
Flow (0.9 ml/min)	0.39
Temperature (27^0C)	0.06
Temperature (23^0C)	0.09
Wavelength of Detection (242 nm)	0.27
Wavelength of detection (248 nm)	0.37

4. RESULTS AND DISSCUTION

A simple, precise RP-HPLC method for the estimation of Rabeprazole in Tablet dosage form has been developed and validated according to ICH Guidelines.The drug was found to be highly Soluble in water (10 mg/ml), methanol, DMSO (~25 mg/ml), DMF (~30 mg/ml), and ethanol (~30 mg/ml). freely soluble chloroform and ethyl acetate and insoluble in ether. Using these solvents with appropriate composition newer methods can be developed and validated. The linearity of response for Rabeprazole was determined in the range of 20 to 70µg/ml. The correlation coefficient was found to be 0.995. The percentage Recovery of pure drug was found to be within the limits. The method has good precision with %RSD < 2 (0.8%). The retention time was 3.797min with run time of 5 min.

5. CONCLUSION

The developed method can be used for routine quality control analysis of Rabeprazole. A sensitive & selective RP-HPLC method has been developed & validated for the analysis of Rabeprazole API.

Further the proposed RP-HPLC method has excellent sensitivity, precision and reproducibility.

The result shows the developed method is yet another suitable method for assay, purity which can help in the analysis of Rabeprazole in different formulations.

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Original Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF GLIBENCLAMIDE

Jakir Hussain shaik * [1], Dr. Khaja pasha , Mujtaba , Ahmed , Zubair , Cameeroddin, Azmathullah, Dr. Shahana Banu [2]

1. Azad College of Pharmacy, Moinabad, Ranga reddy.
2. Department of zoology Gulbarga University, Gulbarga

The objective of present study was to develop matrix type transdermal therapeutic systems of Glibenclamide using various hydrophilic (HPMC) and hydrophobic (EUDRAGID) polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The in vitro release study revealed that F3 formulation showed maximum release in 24hrs. Formulation F3 was subjected for accelerated stability studies. The F3 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Glibenclamide has been developed. F1, F2, F3, F4 formulations showed highest cumulative percentage drug release of 98.13%, 95.50%, 98.65%, 97.21% were obtained during in vitro drug release studies after 24 hrs. The release of Glibenclamide appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F3 formulation was concluded as optimized formulation.

Key words: Glibenclamide, Ethylcellulose, Sodium alginate, Poly ethylene glycol

Correspondence Address:

Zakir, Azad College of Pharmacy, Moinabad, Ranga reddy.

1.INTRODUCTION

Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin [1,2]. The main advantages of this system are that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin [3]. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance [4,5]. Glibenclamide is a potent oral sulfonylurea hypoglycemic agent. It is currently available for treating hyperglycemia in Non insulin dependent Diabetes Mellitus [6]. Plasma half life is 4-6hrs. Which make frequent dosing necessary to maintain therapeutic blood level of the drug a long term treatment [7,8]. Therefore controlled released

Transdermal preparation of Glibenclamide was prepare to give sustain effect as compared to conventional multiple oral dosing. It is highly accepted that membrane controlled transdermal systems have the distinct advantage that the drug release rate [9], which is regulated by permeation through the rate controlling membrane, remain relatively constant as long as drug loading in the reservior is maintained at high level. Hence, the proposed work involves the development and evaluation of transdermal drug delivery systems containing Glibenclamide [10,11,12].

2.MATERIALS AND METHODS [13,14]

MATERIALS

Glibenclamide was obtained as gift sample from Hetero labs. Pvt india. Eudragit RS100 & Ethyl cellulose was procured from AR chemicals. Other excipients used were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

METHOD

Preparation of transdermal patch

Table 1: Formulation Design of Glibenclamide Transdermal Patches

S. No	Formulation code	Ingredients (gms)				
		Drug (mg)	HPMC	Ethylcellulose	Eudragit	Sodium alginate
1	F1	100	100	900	-	-
2	F2	100	900	100	-	-
3	F3	100	-	-	100	900
4	F4	100	-	-	900	100

Transdermal patches containing Glibenclamide were prepared by the solvent casting evaporation technique. The drug Glibenclamide was dissolved in methanol. Polymers HPMC, Ethylcellulose, Sodium alginate and ERS100 were taken in a boiling tube, to this add Glibenclamide drug which was previously dissolved in methanol. About 30ml of solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set aside for 4 hours to allow the polymer to swell. Polyethylene glycol was taken as a plasticizer (15%v/w of dry polymer weight), and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate ($40cm^2$) , drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation [15,16,17].

EVALUATION PARAMETERS

Physical appearance

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Glibenclamide patches are 180 – 292. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the film

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

Weight uniformity

The mean weights of all the prepared patches are shown in table 17. The weights are in the range of 401.9 – 539. The F11 formulation patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 – 101%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Glibenclamide transdermal patches.

In vitro release study

Phosphate buffer pH 7.4 containing 0.5% SLS was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of Glibenclamide patches containing different ratios of polymers HPMC, Eudragit E100, Ethylcellulose. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content. The formulations F1, F2, F3, and F4 showed the maximum release when comparing with other formulations due to the high concentration of HPMC polymer. The release was decreased as the concentration of hydrophobic polymer increase.

Stability studies

Optimized formulations F3 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

3. RESULTS

Table 2: Physicochemical evaluation of Glibenclamide patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)
F1	473.9±1.66	0.89±1.88	292±4.72	101
F2	430±1.58	0.86±1.72	290±2.51	99
F3	486±0.89	0.81±1.55	289±3.46	99.64
F4	501.7±2.50	0.85±0.99	291±3.18	98.86

Table 3: *In vitro* drug release profiles of Glibenclamide transdermal patch (F1-F4)

Time (hrs)	% Cumulative drug released			
	F1	F2	F3	F4
0	0	0	0	0
0.5	13.56±1.43	10.65±1.44	13.48±1.27	11.79±2.1
1	22.72±1.87	19.27±1.49	26.50±1.33	24.67±1.8
2	34.94±1.26	25.49±1.77	31.71±1.45	26.627±1.22
3	41.16±1.33	30.28±1.29	34.36±1.72	30.18±1.38
4	47.88±1.89	33.63±1.39	40.25±1.63	36.71±1.59
5	51.33±2.0	37.46±2.1	41.07±1.82	39.20±1.66
6	53.46±2.3	41.60±1.27	45.53±1.25	43.76±1.91
8	62.87±1.67	49.35±1.71	52.15±1.19	50.92±1.83
10	69.01±1.31	53.61±1.33	60.71±1.32	55.08±1.77
12	74.93±1.56	63.49±1.92	68.30±1.83	62.48±1.45
14	79.70±1.19	70.45±1.68	76.11±1.95	70.81±1.21
16	87.64±1.88	79.33±1.18	80.27±1.18	79.23±1.07
18	92.49±1.3	83.80±1.22	85.93±2.5	84.16±1.55
20	97.08±1.99	88.34±1.82	91.44±2.41	89.42±1.91
22	98..01±1.25	92.20±2.39	95.09±1.85	93.82±1.05

24	98.93±1.71	95.50±2.81	98.65±1.90	97.21±1.02

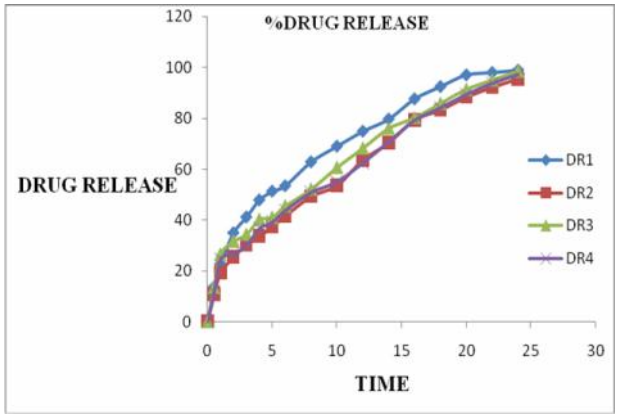

Figure 1: Drug release formulations

Stability studies

Optimized formulations F3 was selected for accelerated stability studies as per ICH guidelines.

Table 4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	98	285	No change in color	97
90	97.1	281	Slight yellowish color	96.35

4.CONCLUSION

Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F3 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Glibenclamide has been developed. F1, F2, F3, F4 formulations showed highest cumulative percentage drug release of 98.65%, 95.50%, 98.93%, 97.21% were obtained during *in vitro* drug release studies after 24 hrs. The release of Glibenclamide appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the *in vitro* dissolution data the F3 formulation was concluded as optimized formulation.

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Original Article

A STUDY ON EFFECT OF OMEGA 3 FATTY ACIDS ON ARTERIAL STIFFNESS IN PATIENTS SUFFERING WITH HYPERTENSION

Dr. shahana Banu[1], Jyothi*[2], Abeda Siraj[2], Nikhaith Anjum[2], Nusrath Unnisa Begum[2], Shaguftha Adeeb[2], Hajera Nausheen[2]

1. **Gulbarga Unversity, Gulbarga, Karnataka.**
2. **Azad college of pharmacy, Hyderabad, Telangana**

The force of blood against the wall of arteries is known as blood pressure. High blood pressure can lead to many heart diseases and it also increases the risk of heart attacks and strokes. To assessed the effects of esterified omega–3 fatty acids on PWV and serum markers of inflammation among patients with hypertension. To Assess of effect of high-dose (3.36 g) omega-3 fatty acids on PWV and secondarily high sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and serum adiponectin. Subjects were recruited from outpatient primary care clinics or a preexisting registry of hypertension patients. This cohort consisted of 52 individuals; the inclusion and exclusion criteria for this registry have been previously reported. Eligible patients were ≥18 years of age, of either Latino or non-Latino White ethnicity and had at least one other CVD risk factor including diabetes, dyslipidemia, obesity, chronic kidney disease, microalbuminuria, current smoking, or age >55 for men or >65 for women, but were excluded if they had pre-existing CVD. Sensitivity analyses were performed to assess changes in outcomes among the following subgroups: patients naïve to statin therapy, those with baseline systolic blood pressure ≥ 140 mm Hg, and diabetic patients, *P*-values <0.05 were considered statistically significant. SAS Version 9.4 (Cary, NC) was used for all statistical analyses. In conclusion, high-dose purified omega-3 fatty acids did not significantly improve arterial stiffness among hypertensive patients extending the negative results of previous studies. Given the absence of benefits of omega-3 fatty acids on CVD events in large randomized controlled clinical trials, this therapy cannot be uniformly recommended in primary prevention patients despite widespread use.

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1. INTRODUCTION

Hypertension (**HTN** or **HT**), also known as **high blood pressure** (**HBP**), is a long term medical condition in which the blood pressure in the arteries is persistently elevated.[8] High blood pressure usually does not cause symptoms.[1] Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.[2][3]

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[4] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.[4][5] Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol.[1][4] The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[4]

Blood pressure is expressed by two measurements,
the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[1] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[9] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults.[4] Different numbers apply to children.[10] Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement.[8][4]

To Assess of effect of high-dose (3.36 g) omega-3 fatty acids on PWV and secondarily high sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and serum adiponectin.

2. MATERIALS AND METHODS:

We conducted a prospective, randomized placebo-controlled, double-blind pilot study. Patients received either 4 omega-3 fatty acid capsules or identically matched corn-oil placebo. Each Lovaza capsule includes 465 mg of EPA and 375 mg of docosahexaenoic acid (DHA) for a total daily dose of 3.36 g. The treatment period was 3-months with baseline and follow-up measurements performed in the morning in a fasted state. The Colorado Multiple Institutional Review Board approved the study and it was registered with clinical trials.gov. All study participants signed written informed consent.

Subjects were recruited from outpatient primary care clinics or a preexisting registry of hypertension patients. This cohort consisted of 177 individuals; the inclusion and exclusion criteria for this registry have been previously reported [11]. Eligible patients were ≥18 years of age, of either Latino or non-Latino White ethnicity and had at least one other CVD risk factor including diabetes, dyslipidemia, obesity, chronic kidney disease, microalbuminuria, current smoking, or age >55 for men or >65 for women, but were excluded if they had pre-existing CVD.

Arterial PWV measurements were performed in the recumbent position. Supine blood pressure was measured in duplicate in the non-dominant arm. Bilateral brachial-ankle PWV was derived

from the pulse transit time between and the estimated path length between proximal and distal arterial sites expressed as cm/s. Inflammatory markers and adiponectin were also assessed while fasting. We chose hsCRP because it has incremental CVD risk discrimination beyond standard Framingham risk factors [12] and Lp-PLA2 given its specificity for inflammation localized to atherosclerotic plaque [13].

Statistical analysis

Means, standard deviations, and medians were calculated for all continuous variables. For univariate analyses, comparisons were made using analysis of variance, chi-squared or Wilcoxon rank sum tests. For change over time analyses, mixed-effects models were used to account for repeated measures within participants. Univariate associations between baseline risk markers and change in PWV were assessed, and multivariate models were fitted to assess for predictors of change. Sensitivity analyses were performed to assess changes in outcomes among the following subgroups: patients naïve to statin therapy, those with baseline systolic blood pressure ≥ 140 mm Hg, and diabetic patients, *P*-values <0.05 were considered statistically significant. SAS Version 9.4 (Cary, NC) was used for all statistical analyses.

3. RESULTS AND DISCUSSION:

Baseline characteristics of the 62 participants are shown in Table 1 and were consistent with a safety-net population. The majority of patients were receiving medication for chronic hypertension and half had diabetes. Overall, baseline characteristics were well matched; specifically, PWV values did not differ by randomization group. Among baseline variables, older age, higher systolic blood pressure, and adiponectin were significantly associated with increased PWV: 16 cm/s increase in mean PWV per year of increasing age ($p < .0001$), 7.3 cm/s increase in mean PWV per each mm Hg of higher systolic blood pressure ($p = 0.005$), and 14 cm/s per unit of adiponectin ($p = 0.008$).

		Placebo (*N* = 35) **N (%) or Mean (SD)**	**Omega-3 (*N* = 27)** **N (%) or Mean (SD)**	**Overall (*N* = 62)** **N (%) or Mean (SD)**
Age (years)		60.2 (10.8)	62.3 (9.7)	61.1 (10.3)
Female Gender		22 (63 %)	18 (67 %)	40 (65 %)
Educational Status	Did Not Complete High School	18 (51 %)	10 (37 %)	28 (45 %)
	Completed High School	9 (26 %)	10 (37 %)	19 (31 %)
	Completed College	8 (23 %)	7 (26 %)	15 (24 %)
Unemployed		28 (80 %)	21 (81 %)	49 (80 %)
Body Mass Index (kg/m2)		31.5 (7.1)	33.9 (8.6)	32.6 (7.8)
Systolic Blood Pressure (mm Hg)a		137 (16)	128 (14)	133 (16)
Diastolic Blood Pressure (mm Hg)		82 (9)	78 (10)	81 (10)
Antihypertensive Medication		32 (91 %)	21 (78 %)	53 (85 %)

Statin therapy		17 (49 %)	11 (41 %)	28 (45 %)
Total cholesterol (mg/dL)		179 (43)	179 (38)	179 (40)
Triglycerides (mg/dL)		188 (103)	173 (65)	182 (89)
HDL-C (mg/dL)		48.4 (14.9)	44.9 (12.4)	46.9 (13.9)
LDL-C (mg/dL)		97 (38)	99 (29)	98 (34)
Diabetes diagnosis		19 (54 %)	12 (48 %)	31 (52 %)
Hemoglobin A1c (%)		6.7 (1.8)	6.3 (1.3)	6.6 (1.6)
Glucose (mg/dL)		127 (61)	111 (25)	120 (49)
Smoking status	Current	12 (34 %)	6 (22 %)	18 (29 %)
	Former	23 (66 %)	21 (78 %)	44 (71 %)
hsCRP (mg/L)		3.42 (3.35)	5.63 (5.05)	4.38 (4.29)
Adiponectin (ug/mL)		10.6 (8.3)	12.2 (7.8)	11.4 (8.1)
LpPLA2 mass (ng/mL)		244 (46)	252 (62)	247 (53)
Mean PWV (cm/s)		1690 (335)	1602 (324)	1652 (330)

Changes in risk factors, inflammatory markers, and PWV are shown in Table 2. Comparative percentage change in Lp-PLA2 mass, PWV, and hsCRP were all directionally more favorable in the omega-3 arm but did not achieve statistical significance (Fig. 1). Absolute change in mean PWV was −97 cm/s in the omega-3 arm compared to −33 cm/s in the placebo group ($p = 0.36$). Reductions were also seen in mean hsCRP (−0.9 mg/L vs. 0.9 mg/L in placebo group) and Lp-PLA2 mass (−18.1 ng/mL vs. −6.1 ng/mL). Numeric mean reductions in risk markers were relatively larger within subgroups: Among 34 statin-naïve subjects, the difference in arterial PWV was larger (−82 vs. +50 cm/s), but remained non-significant ($p = 0.20$), though the reduction in mean hsCRP (− 0.8 vs. +1.6 mg/dl) achieved significance ($p = 0.03$). Among 31 diabetic subjects, PWV (−100 vs. −18 cm/s), hsCRP (−0.8 vs. +1.7 mg/L), and LpPLA-2 mass (−11.1 vs. −4.1 ng/ml) were non-significantly lower with active treatment (minimal *p*-value 0.19). Among 24 subjects with baseline systolic blood pressure ≥ 140 mm Hg PWV (−98 vs. −65 cm/s), hsCRP (−1.0 vs. +0.8 mg/L), and LpPLA-2 mass (−32.7 vs. −3.2 ng/ml) were non-significantly lower with active treatment (minimal *p*-value 0.09).

	Placebo (*N* = 35) Mean (SD)	**Omega-3 (*N* = 27) Mean (SD)**
Pulse Wave Velocity (cm/s)	−33 (306)	−97 (182)
Total cholesterol (mg/dL)	−6.6 (30.4)	−0.8 (18.1)
Triglycerides (mg/dL)	−30.0 (58.1)	−17.6 (45.6)
HDL-C (mg/dL)	0.2 (8.5)	2.9 (14.6)
LDL-C (mg/dL)	−2.8 (28.6)	0.7 (18.3)
Hemoglobin A1c (%)	−0.13 (0.94)	0.06 (0.44)
Glucose (mg/dL)	−13.1 (44.0)	0.6 (23.0)
hsCRP (mg/L)	0.9 (4.4)	−0.9 (3.1)
Adiponectin (ug/mL)	0.3 (3.4)	−0.4 (2.4)
LpPLA2 mass (ng/mL)	−6.1 (31.7)	−18.1 (41.1)

In multivariate analysis accounting for baseline age, systolic blood pressure and adiponectin, no significant change in mean PWV [parameter estimate (standard error) = -22 (24), $p = 0.36$] was observed. In analysis including only time and treatment group, the reductions in hsCRP and Lp-PLA2 mass were numerically greater with omega-3 therapy, but were not statistically significant ($p = 0.08$, and 0.21, respectively).

4. DISCUSSION:

To our knowledge, this is the first prospective randomized trial evaluating the effects of prescription doses of omega-3 fatty acids on arterial stiffness in a Latino-predominant population. Short-term treatment with omega-3 fatty acids was not associated with a significant reduction in arterial PWV. Moreover, with the exception of a reduction in serum hsCRP among statin-naïve subjects, no significant improvements in markers of vascular inflammation were observed despite a high prevalence of obesity and diabetes. Given an association between the metabolic syndrome and increased arterial stiffness [14], a positive effect of omega-3 fatty acids might have been expected.

A number of possible explanations for our findings merit consideration. One potentially important factor is the dose of omega-3 utilized. In one study, PWV was assessed among overweight patients receiving 2, 4, and 6-g of omega-3 fatty acids daily [15]. Reductions in PWV were observed only in the group receiving 6-g per day. It is possible that despite the 3.36 g dose in the current study, it was still inadequate to reduce PWV, particularly if compliance was sub-optimal. Although no medication diary or formalized drug reconciliation process was utilized in our study, this is plausible given the absence of a significant triglyceride reduction observed in the active treatment arm, which may reflect medication non-adherence in our vulnerable population. Also, half of the patients in our study were already receiving statin therapy, which could limit our ability to further discern a treatment effect. In support of this possibility, a recent trial among patients with peripheral arterial disease already receiving statin therapy, found no improvement in PWV after omega-3 fatty acid treatment [16]. Our findings are in line with this possibility since the difference in PWV over time between the groups was larger among statin-naïve subjects. Analogously, an expected greater reduction in hsCRP was seen among statin-naïve subjects. One further study limitation is that fatty acid bioavailability data were not evaluated, so we don't know if there was a relationship between plasma fatty acid level and changes in PWV.

Another potential explanation for the findings in the current study is the relatively small sample size. Root and colleagues also found no reduction in PWV with omega-3 therapy in a short-term study of 57 patients [17]. In assessing sample size, approximately 100 subjects would provide > 80 % power to detect a 10 % decrease in PWV (standard deviation [SD] 350 cm/s) assuming a baseline PWV of 1700 cm/s. With 62 randomized patients, the current study had just over 60 % power under those assumptions. Although the numeric effect size in the current trial was consistent with this reduction, and the standard deviation was within assumed range, the placebo-corrected absolute reduction in PWV was only 4 %. The clinical significance of this numeric finding may be gleaned from a meta-analysis of observational data from 17,635 subjects, where a 10 % increase in PWV was

associated with a hazard ratio for CVD events of 1.07 (95 % CI: 1.02 to 1.12) [18].

In addition, the relatively short duration of therapeutic exposure, may have limited our ability to detect alterations in vascular stiffness. There was also a numeric imbalance of subjects between arms, which likely reflects a chance finding in the randomization sequence given the small sample size. This theoretically may have made a Type II error more likely. Most importantly, however, no pharmacologic therapy to date has been shown to reduce PWV independent of blood pressure reductions, suggesting the possibility that any salutatory effects of omega-3 treatment on inflammation and plaque may be inadequate to alter vessel wall physiology.

5. CONCLUSION:

In conclusion, high-dose purified omega-3 fatty acids did not significantly improve arterial stiffness among hypertensive patients extending the negative results of previous studies. Given the absence of benefits of omega-3 fatty acids on CVD events in large randomized controlled clinical trials, this therapy cannot be uniformly recommended in primary prevention patients despite widespread use.

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Formulation and Evaluation of Glimepiride Liposomal Drug Delivery System

Dr. Khaja Pasha[*1], Dr. Shahana Banu[2]

[1]Azad College of Pharmacy, Moinabad, Rangareddy.India
[2]Department of zoology Gulbarga University, Gulbarga, India

***Corresponding Author:** Khaja Pasha, Azad College of Pharmacy, Moinabad, Rangareddy, India*

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ABSTRACT

The drug release from Liposomes depends on many factors including the composition of Liposomes, the type of drug encapsulated and nature of the cell. Once it is released a drug that normally crosses the membrane of a cell will enter the cell, other drugs will not enter.

Glimepiride is a drug with narrow therapeutic index and short biological half-life. This study aimed at developing and optimizing liposomal formulation of Glimepiride in order to improve its bioavailability. In evaluation study the effect of the varying composition of lipids on the properties such as encapsulation efficiency, particle size and drug release were studied. Phase transition study was carried out to confirm the complete interaction of Glimepiride with bilayer structure of liposome. Moreover, the release of the drug was also modified and extended over a period of 8 h in all formulations. F1 emerged as the most satisfactory formulation in so far as its properties were concerned. Further, release of the drug from the most satisfactory formulation (F1) was evaluated through dialysis membrane to get the idea of drug release.

Keywords: *Liposomes, Glimepiride, bioavailability.*

INTRODUCTION

Conventional antidiabetic drugs administered either orally or parenterally have several disadvantages. The therapeutic areas of liposomes were widely extended as carriers for antidiabetics, anticancer agents, antibacterial, antifungal drugs and ocular liposomes [1,2]. These studies show that the role of liposomes in satisfying pharmaceutical considerations is unavoidable in the field of medicine. The supporting factors of liposomes include inexpensive material, straightforward and rapid method of generating liposomes, homogeneous and reproducible size distribution and different efficient techniques for loading liposomes [3,4,5]. In addition, the final liposomal formulation must be highly stable, as both the retention of entrapped drug as well as chemical and dimensional stability of the liposome themselves. For treating patients with type II diabetes mellitus, an oral antidiabetic drug, Glimepiride is commonly prescribed. Glimepiride is a sulfonylureas class drug [6,7].

MATERIALS AND METHOD

Materials

Glimepiride was a gift sample from Dr. Reddy's Laboratories, Hyderabad. phosphotidylcholine, cholesterol and chloroform were purchased from SD fine chemical Mumbai.

Methods

Preparation of Standard Graph of Glimepiride in 7.4 Phosphate Buffer

Accurately weighed amount (100 mg) of the drug was dissolved in distilled water in 100 ml volumetric flask and the volume was made up to 100ml. from this stock solution 10ml is withdrawn in to volumetric flask, made the volume up to 100ml with distilled water. From this second stock solution (100µg/ml), g/mlµconcentrations of 10, 20, 30, 40, 50 solutions were prepared and the corresponding absorbance was measured at wave length (λmax) 245 nm in a UV Visible spectrophotometer.

Preparation of Glimepiride Liposomes

Liposomes were prepared by physical dispersion method using different ratio of lipids.

In this method the lipids were dissolved in chloroform. This solution of lipids in chloroform was spread over flat bottom conical flask. The solution was then evaporated at room temperature without disturbing the solution. The hydration of lipid film form was carried out with aqueous medium phosphate buffer (pH 7.4). For this the flask was inclined to one side and aqueous medium containing drug to be entrapped was introduced down the side of flask and flask was slowly returned to upright orientation. The fluid was allowed to run gently over lipid layer and flask was allowed to stand for 2 h at 37^0C for complete swelling. After swelling, vesicles are harvested by swirling the contents of flask to yield milky white suspension [11,12,13]. Then formulations were subjected to centrifugation. Different batches of liposomes were prepared in order to select an optimum formula. All batches of liposomes were prepared as per the general method described above.

Formulation Table

Table1. *Composition of lipids for preparation of liposome*

Each formulation contain 200 mg of Glimepiride

Ingredients	F1	F2	F3
Phosphatidylcholine	200	250	300
Cholesterol	50	75	100
Solvent(Chloroform)	10	10	10
Drug(Glimepride)	100	100	100
Phosphate buffer pH 7.4	10	10	10

Evaluations of Liposomes

Drug - Excipient Compatibility Studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

Drug Entrapment Efficiency of Liposomes

Entrapment efficiency of liposomes were determined by centrifugation method. Aliquots (1 ml) of liposomal dispersion were subjected to centrifugation on a laboratory centrifuge (Remi R4C) at 3500 rpm for a period of 90 min. The clear supernatants were removed carefully to separate non entrapped Glimepiride and absorbance recorded at 245nm. The sediment in the centrifugation tube was diluted to 100 ml with phosphate buffer pH 7.4 and the absorbance of this solution was recorded at 245 nm.

Amount of glimepiride in supernatant and sediment gave a total amount of glimepiride in 1 ml dispersion.

% entrapment of drug was calculated by the following formula

$$\% \text{ Drug Entrapped (PDE)} = \frac{\text{Amount of drug in sediment}}{\text{Total amount of drug}} \text{ X } 100$$

Particle Size Analysis

All the prepared batches of liposomes were viewed under microscope to study their size. Size of liposomal vesicles from each batch was measured at different location on slide by taking a small drop of liposomal dispersion on it and average size of liposomal vesicles were determined.

In Vitro Drug Release Study

The release studies were carried out in 10 ml Franz diffusion cell containing 10 ml Phosphate buffer. Phosphate buffer pH 7.4 (10ml) was placed in a 10 ml beaker. The beaker was assembled on a magnetic stirrer and the medium was equilibrated at 37 ± 5^0C. Dialysis membrane was taken and one end of the membrane was sealed. After separation of non entrapped Glimepiride liposomal dispersion was filled in the dialysis membrane and other end was closed. The dialysis membrane containing the sample was suspended in the medium. 1sml of aliquots were withdrawn at specific intervals, filtered after withdrawal and the apparatus was

immediately replenished with same quantity of fresh buffer medium.

Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

The prepared Glimepiride liposomes were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 30 days.

RESULTS AND DISCUSSION

Standard Graph of Glimepiride

Standard Solution of Glimepiride Prepared with Phosphate Buffer Saline of Ph 7.4

Table2. *Absorbance of various concentrations of the standard solution prepared with phosphate buffer saline of pH 7.4*

S.No.	Concentration (µg/ml)	Absorbance (245nm)
1.	10	0.146
2.	20	0.216
3.	30	0.347
4.	40	0.498
5.	50	0.590

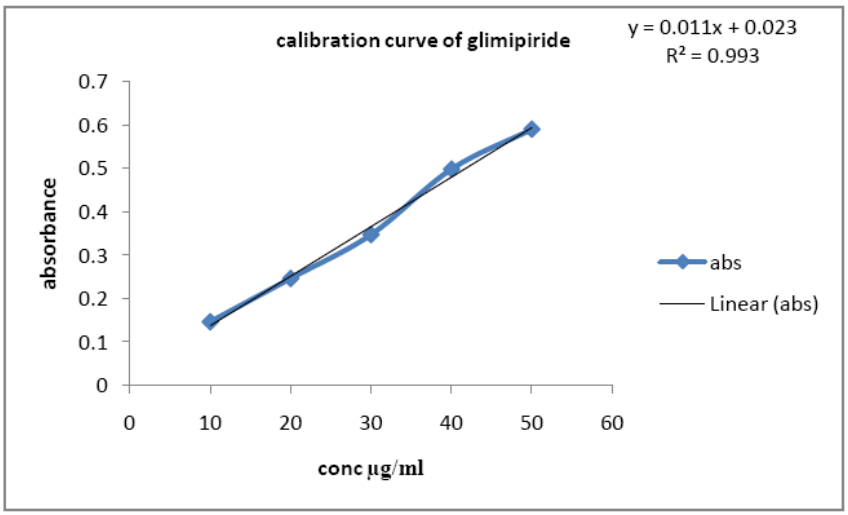


Figure1. *Standard graph and regression value of the standard solution with pH 7.4*

Drug - Excipient Compatibility Studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method.

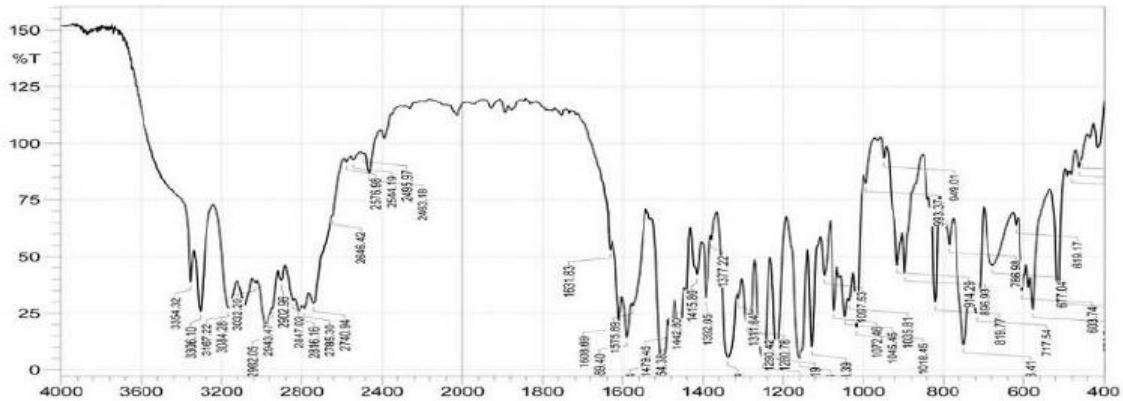


Figure2. *FTIR spectra data for pure Glimepiride*

Table3. *FTIR spectra data for pure Glimepiride*

S. No	Functional Groups	Ftir Absorption Band of Pure Decitabine
1	C-N	1213
2	CH(Alkane)	2863
3	N-H(Bending)	1620
4	OCH_3	1250
5	C=C	3205

Entrapment Efficiency

Table4. *Results of entrapment efficiency of liposomes of formulations*

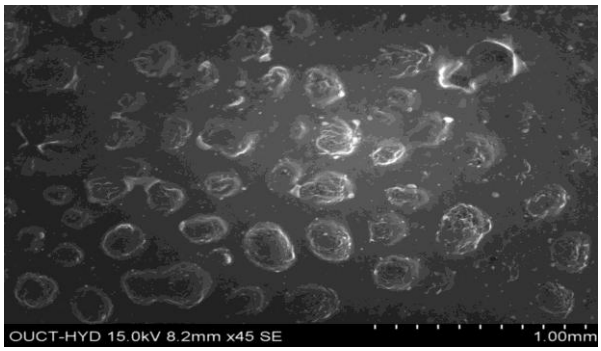
Observations	Batch Code		
	F1	F2	F3
1	49.12	47.50	46.47
2	44.59	47.69	49.14
3	47.70	45.80	46.62
Mean	48.33	46.70	48.07
Mean ± S.D.	48.33±1.000	46.70±0.566	48.07±1.525

Now, let H_0 be the hypothesis that there is no significant difference between the batches.

Particle Size

Vesicle Shape

Vesicle shape of the prepared formulation was found to be spherical from the SEM(scanning electron microscope) analysis at 15.00kV



Vesicle Size

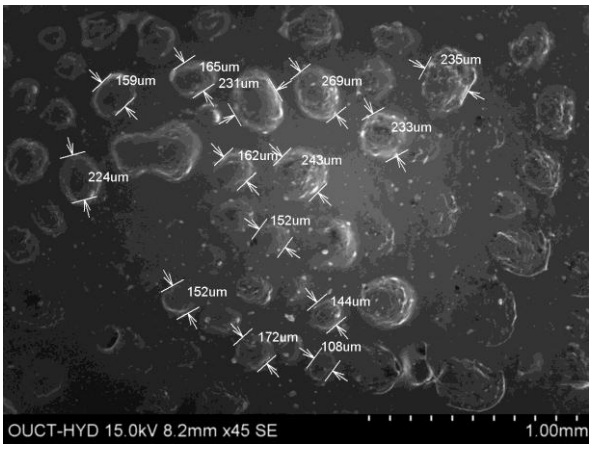


Figure3. *Particle size of Glimepiride liposomes*

Table5. *Vesicle Size*

Formulation	Size (µm)
F1	125
F2	119
F3	212

Table6. *Results of particle size of liposomes*

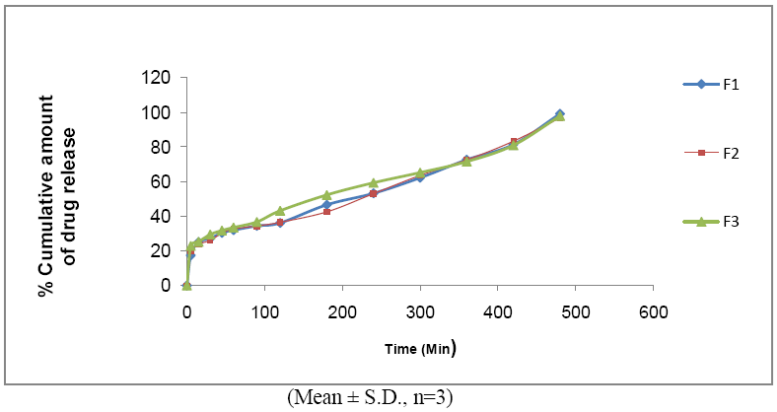
Observations	Batch code		
	F1	F2	F3
1	6.22	7.20	6.07
2	7.12	6.72	7.19
3	6.62	7.32	6.69
Mean	6.68	7.20	6.4
Mean ± S.D.	6.76±0.096	7.24±0.049	6.6±0.062

Now, let H_0 be the hypothesis that there is no significant difference between the batches.

Drug Release Studies

Table7. *Cumulative percentage drug release from verious formulation of liposomes*

Time (Min)	Batch code		
	F1	F2	F3
0	0	0	0
5	17.35±1.04	19.85±1.16	22.60±1.58
15	23.05±2.26	23.63±3.52	24.18±0.52
30	25.13±0.78	26.10±0.23	27.30±2.22
45	30.38±1.20	29.32±0.10	31.32±1.60
60	31.81±1.08	31.52±0.39	33.24±1.20
90	32.40±1.02	34.23±0.12	35.52±1.04
120	36.16±0.86	35.12±3.50	43.08±0.72
180	45.50±1.42	42.43±0.51`	51.10±0.88
240	52.19±0.77	52.10±3.00	57.25±.80
300	59.18±1.18	60.59±2.12	65.09±1.48
360	78.62±0.79	72.21±9.81	72.38±1.36
420	85.32±1.6	85.33±6.89	80.87 ±0.7
480	98.16±0.30	95.70±2.50	97.63±1.02



(Mean ± S.D., n=3)

Figure4. *In vitro drug release of various formulations*

All the three batches of formulation F1 were found to release the drug in 8 h. The cumulative percentage release was found to be 98.16%.

Stability Studies

Stability studies were carried out for a period of two month at 4±2^{0}C, 25±2^{0}C and 37±2^{0}C. The entrapment efficiency was estimated at an interval of 15 days. The results of stability studies are shown in table.

Table8. *Stability studies for the formulation F1*

Sampling Intervals (Days)	% Drug Entrapped at		
	4 ± 2^{0}C	25 ± 2^{0}C	37 ± 2^{0}C
0	46.72	46.72	47.72
15	47.65	47.65	46.21
30	48.32	42.42	42.12
45	46.05	42.60	38.92
60	47.70	38.12	35.09

CONCLUSION

From the performed work it was concluded that:

1. Glimepiride possesses all requisite qualities required for liposomal drug delivery.
2. Among the various formulation, the combination F1 was found to be most suitable because of high encapsulation efficiency with smaller particle size.
3. The formulation F1 comprising phosphatidylcholine, cholesterol 9:1 ratio, fulfills the requirement of good liposomal formulation. *In vitro* drug release upto 8 h and more than 98.16% drug released. Follows peppas model in release studies. It shows encapsulation efficiency of 48.33% and particle size of 6.76 µm.

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Formulation and Evaluation of Ambroxol Hydrochloride Sustained Release Microspheres

Dr. Khaja Pasha[1]*, Dr. Shahana Banu[2]

[1]Azad College of Pharmacy, Moinabad, Rangareddy, India
[2]Department of zoology Gulbarga University, Gulbarga, India

***Corresponding Author:** Khaja Pasha, Azad College of Pharmacy, Moinabad, Rangareddy, India*

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ABSTRACT

Sustained release microspheres of Ambroxol Hcl, It used as a Recipiratory Disease Ambroxol Hcl is water soluble drug, having low oral bioavailability (33-55%) due to complete metabolism of drug available in market were having daily administration. The present study was formulate and evaluate Ambroxol Hcl microspheres to increase oral bioavailability, decrease the frequency of drug administration, and improve patient compliance. In this study, Ambroxol Hcl microspheres was prepared by Ionotropic gelation technique using Sodium alginate, HPMC and Ethylcellulose as polymers and these prepared Ambroxol Hcl microspheres evaluated were percentage yield, particle size, drug entrapment efficiency and in vitro drug release studies. These microspheres results showed that percentage yield, entrapment efficiency, particle size and drug release studies were influenced mainly by concentration of polymer, type of polymer and stirring speed also. The results of in vitro drug release studies shows that the desired release rate is achieved by optimized formulation are releasing the drug up to 11 hrs. Optimized Ambroxol Hcl microspheres showing discrete, spherical microspheres.

Keywords: *Ambroxol Hcl, HPMC, Ethylcellulose, Ionotropic gelation technique*

INTRODUCTION

Ambroxol Hcl is a metabolite of bromohexine which possess muco kinetic and secreteolytic properties [1]. It is used in the treatment of respiratory tract disorders such as chronic bronchitis and management of cough. Adverse effects produced such as gastrointestinal disorder, headache, dizziness, sweating, rhinorrhoea, lacrymation and allergic reactions [2, 3]. Due to short biological half-life (4-6 hr), frequent daily dosing (2-3 times) of Ambroxol hydrochloride is required. Therefore its formulation in sustained microspheres is advantages [4,5]. The simplest and least expensive way to control the release is to dispense it with in an inert polymeric matrix [6]. Bitter after taste of many drugs which are orally administered often contributes to patient non compliance in taking medicines [8, 9].

Microspheres are characteristically free flowing powders consisting of protein or synthetic polymers which are biodegradable in nature and ideally having particle size less than 1000µm [7]. Micro particles play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects [10]. The objective of the present study was to develop microspheres of Ambroxol Hcl by Ionotropic Gelation Technique using hydrophilic carrier to sustain the release so as to reduce the frequency of dosing and to improve patient compliance.

MATERIALS AND METHODS

Materials

Ambroxol Hcl was obtained as gift sample from orchid pharma private limited, Chennai, Gelatin from aurobindo Pharma Pvt. Ltd., Hyderabad. HPMC, Sodium alginate from aurobindo Pharma Pvt. Ltd., Hyderabad. Methanol, Calcium chloride from AR chemicals.

Method

Ambroxol hcl Microspheres were prepared by using ionotropic gelation technique and by using Sodium alginate, Eudragit S100 and calcium chloride solution. Weighed Equal quantity of drug and polymer were added to 100 ml of sodium alginate solution with stirring at about 400 rpm [12,13]. The resultant solution was then

added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 30 or 40 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 6 hours at 40°C. Preparation of microspheres was optimized based on entrapment efficiency and drug release studies [14].

Table1. *Formulation table of Glipizide microspheres*

Ingredients	F1	F2	F3
Drug	500	500	500
Sodium alginate	1000	1000	1000
HPMC	500	500	-
Ethylcellulose	-	500	500
Methanol	5	5	5
Cacl $_2$	2%	2%	2 %

Evaluation Parameters [15,16,17]

The prepared Ambroxol Hcl microspheres were evaluated for various parameters such as percentage yield, particle size, drug entrapment efficiency and in vitro drug release studies.

A. Yield of Microspheres

The yield of microspheres was calculated from the amount of microspheres obtained divided by the total amount of all non-volatile components

$$\% \text{ Yield} = \frac{\text{Actual weight of the microspheres}}{\text{Total weight of all non-volatile components}} \times 100$$

B. Particle Size and Shape

The particle size of the microspheres was measured by optical microscopy. The eyepiece micrometer was calibrated using a stage micrometer and the calibration factor was used further in the calculation of the size of microspheres. The microspheres were finely spread over a slide and visualized under an optical microscope using an eyepiece micrometer. About 50 readings were taken at random and the mean ± standard deviation was calculated. The shape of the microspheres was visualized and the photographs were taken with the aid of a binocular microscope.

C. Surface Morphology

The surface morphology of the prepared microspheres was examined with the aid of a Scanning Electron Microscope (SEM).

D. Drug Entrapment Efficiency (DEE)

The amount of drug entrapped was estimated by crushing 50 mg of microspheres using mortar and pestle, and extracting drug with aliquots of 7.4 pH buffer repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 7.4 pH buffer. The solution was taken in a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectro photometrically at 247 nm against an appropriate blank.

The amount of drug entrapped in the microspheres was calculated using the following formula –

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

E. In Vitro Drug Release Study

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Ambroxol Hcl were poured into 5 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions.

The necessary dilutions were made with 7.4 pH buffer and the solution was analyzed for the drug content spectrophotometrically using UV-Visible spectrophotometer at 247 nm against an appropriate blank. Three trials were carried out for all formulations. From this cumulative percentage drug release was calculated and plotted against function of time to study the pattern of drug release.

RESULTS AND DISCUSSION

The prepared sustained release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size and in vitro drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of Ambroxol Hcl from sustained microspheres were also studied.

Table1. *Evaluation parameters of microspheres*

Formulation Code	%Yield	Particle Size	Drug Entrapment Efficiency	Drug Release Studies
F1	75.85	88.39	70.53	87.519
F2	79.55	93.64	82.22	*92.251*
F3	88.33	96.72	85.23	99.826

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases viscosity; this influences the interaction between disperse phase and dispersion medium that affects the size distribution of particle. And F3 formulation shows good results when compared to other formulations.

Table2. *Cumulative %drug release*

TIME (hours)	F1	F 2	F3
0.5	63.519	35.185	37.449
1	69.471	52.680	53.109
2	75.628	76.452	57.949
3	86.990	84.521	63.232
4	91.907	85.845	65.664
5	94.432	87.997	68.725
6	97.520	90.159	70.979
7	99.826	91.508	73.656
8	----------	95.743	80.256
9	----------	96.707	92.243
10	----------	101.995	95.451
11	----------	----------	99.087
12	----------	----------	----------
13	----------	----------	----------

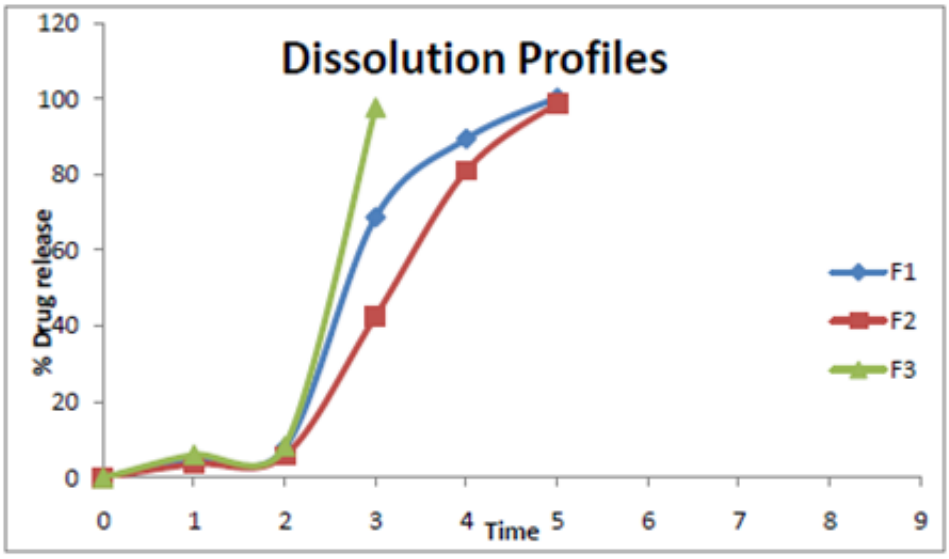


Figure1. *Percentage drug released Vs Time Curves of microspheres F 1 – F 3 in P^H 7.4 buffer.*

Conclusion

Above graph indicates that % Drug release of F3formulation shows better drug release when compared with other formulations

Kinetic Models

The mechanism of Ambroxol Hcl release from microspheres was studied by fitting the data obtained from *in-vitro* release studies into zero-

order, first-order, Higuchi's, korsermeyer peppas kinetic models.

On application of different release kinetic models mentioned earlier, it was found that optimized formulations showed better fitting with the zero-order release and korsermeyer peppas model. Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table3. *Kinetic Models*

S.no	Time	log T	Square Root of Time	%CR	%Drug Remaining	log %CR	LOG% DRUG Retained	Cube Root of % Drug Remaining
0	0	0	0	0	100	0	2	4.642689
1	1	0	1	5.73	92.17	0.765668	1.973813	4.549564
2	2	0.30102	1.413214	6.21	94.79	0.857835	1.966501	4.527242
3	3	0.467121	1.632051	8.4	96.4	0.929417	1.961411	4.516064
4	4	0.60306	2	9.52	92.27	0.987566	1.954592	4.476037
5	5	0.69797	2.235068	10.31	88.6	1.013837	1.953792	4.37542
6	6	0.768151	2.44849	62.4	26.5	1.859729	1.440809	3.12206
7	7	0.835098	2.64751	79	10	1.94839	1.061393	2.23298
8	8	0.91329	2.828326	98.6	0.6	1.987259	-0.39674	0.736706

Table4. *Correlation coefficient values for release kinetics of sustained release microspheres*

Drug Kinetics	Optimised Formula
First-Order	0.689
Zero-Order	0.762
Higuchi	0.561
korsermeyer peppas	0.657

Zero Order Kinetics

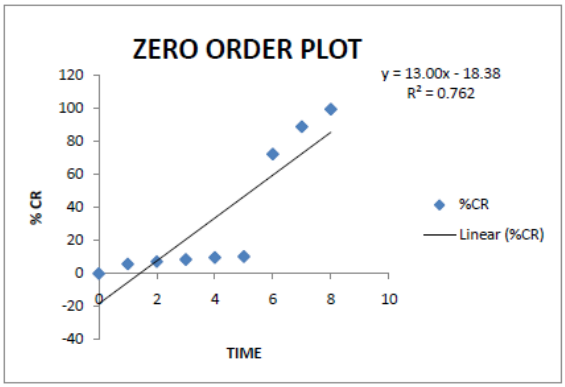


Figure2. *Zero Order Plot For Optimized Formulation*

First Order Kinetics

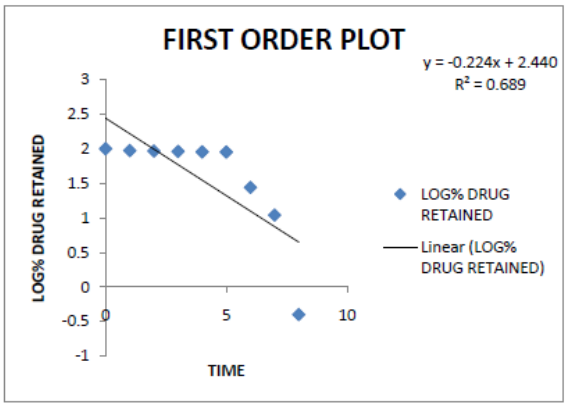


Figure3. *First Order Plot for Optimized Formulation*

Higuchi Model

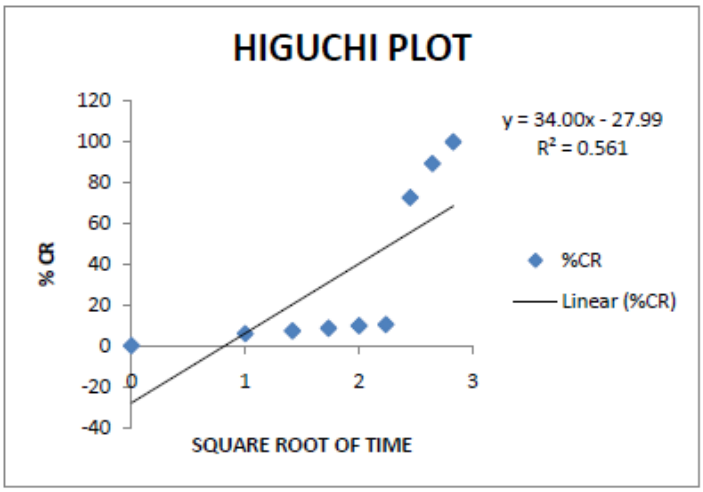


Figure4. *Higuchi Plot for Optimized Formulation*

Korsmayer Peppas Equations

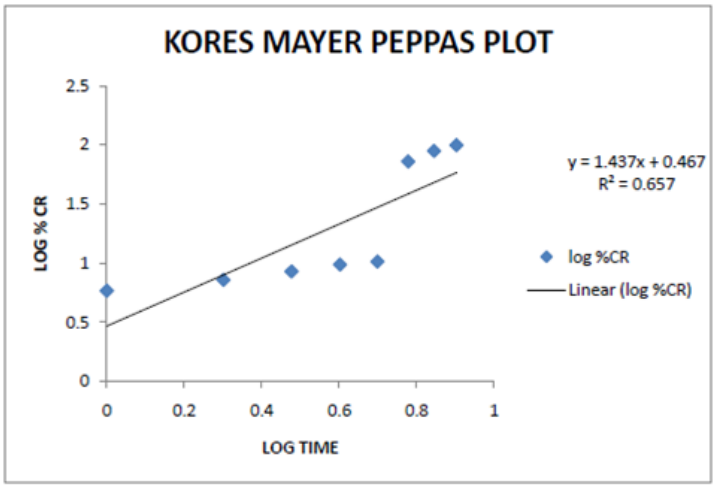


Figure5. *Kores Mayer Peppas Plot For Optimised Formulation*

Hixon Crowell Erosion Equation

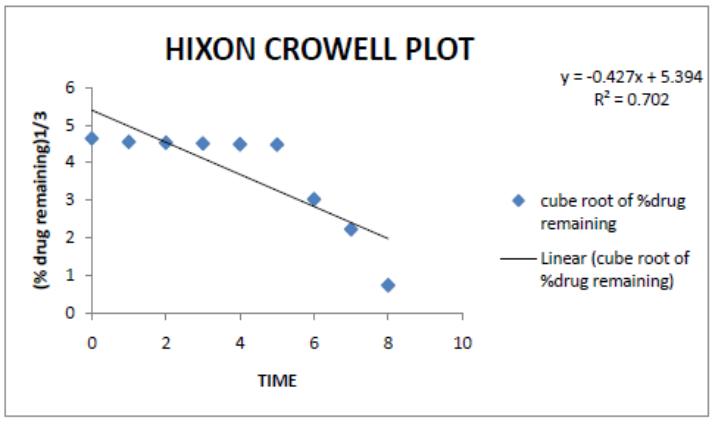


Figure6. *Hixson Crowell Plot for Optimized Formulation*

Stability Study

There was no significant change in physical and chemical properties of the formulation of F-3 after 3 Months. Parameters quantified at various time intervals were shown;

Table5. *Results of stability studies of optimized formulation F-3*

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25^0C/60%RH % Release	99.61	99.52	99.52	99.50	Not less than 85 %
F-3	30^0C/75% RH % Release	99.46	99.54	99.53	99.50	Not less than 85 %
F-3	40^0C/75% RH % Release	99.60	99.55	99.54	99.75	Not less than 85 %
F-3	25^0C/60% RH Assay Value	99.85	99.87	99.73	99.80	Not less than 90 % Not more than 110 %
F-3	30^0C/75% RH Assay Value	99.78	99.88	99.82	99.92	Not less than 90 % Not more than 110 %
F-3	40^0C/75% RH Assay Value	99.97	99.85	99.74	99.95	Not less than 90 % Not more than 110 %

Table6. *Stability dissolution profile of F-3 for 1st, 2nd & 3rd months*

S.NO.	TIME(Hrs)	F-3 1M	F-3 2M	F-3 3M
1	0	0	0	0
2	1	5.73	4.70	5.68
3	2	7.22	6.30	6.20
4	3	8.6	8.27	8.54
5	4	9.62	9.76	9.75
6	5	10.2	11.26	10.34
7	6	72.3	73.36	72.30
8	7	79	87.8	84.4
9	8	98.55	98.52	96.52

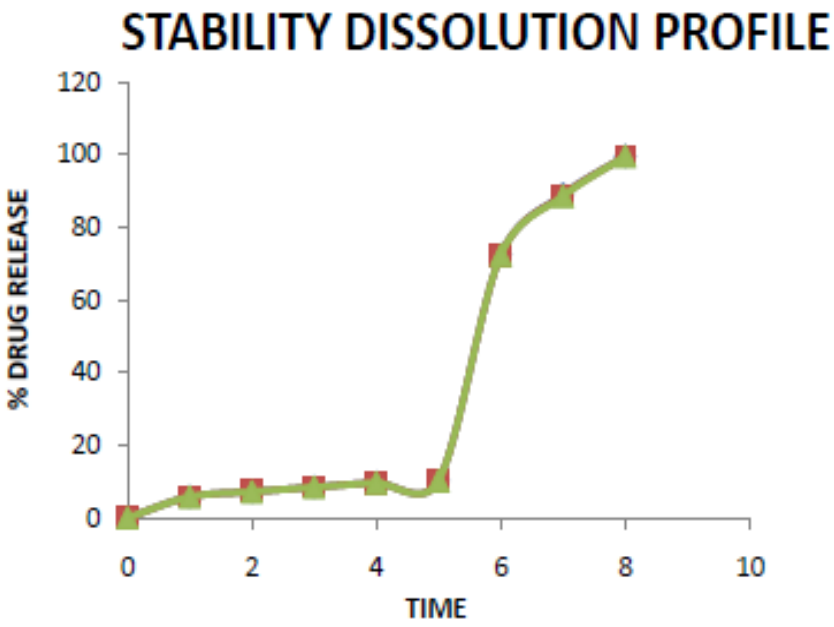
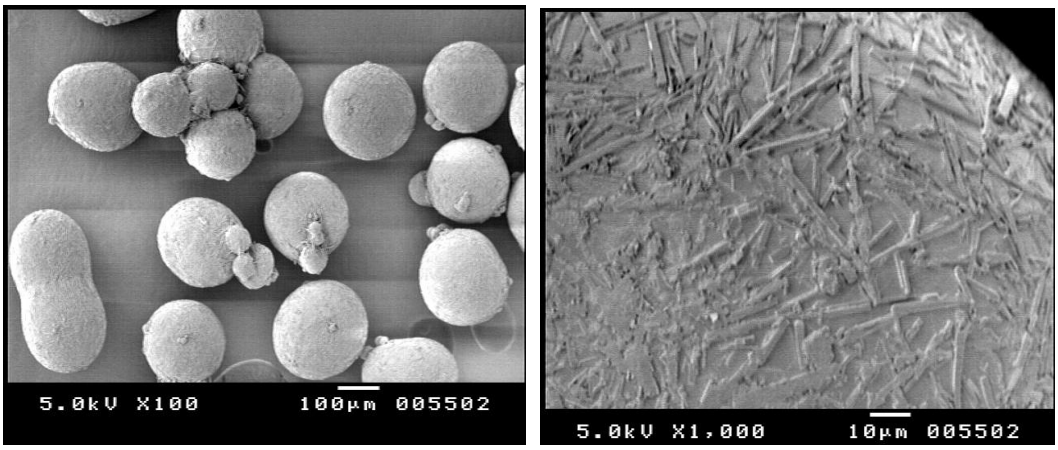


Figure7. *Stability dissolution profile of F-20 for 1st, 2nd & 3rd months*

Surface Topography by Scanning Electron Microscopy (SEM)

SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of entrapped drug in dispersion medium.



A. **B.**

Figure8. *SEM photograph of Ambroxol Hcl at 100x and 1000x magnification.*

CONCLUSION

Rationale of the present study was to prevent extensive metabolism of the drug and consequently to increase the oral bioavailability of the drug in the form of sustained.

Attempt has been made to prepare sustained release microspheres of Ambroxol Hcl , a water soluble drug. The microspheres were prepared by Ionotropic gelation method using Ethylcellulose, Eudragit, Sodium alginate polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microspheres morphology was evaluated by SEM.

According to the results of SEM analysis, no drug interaction occurred with polymers and Ambroxol Hcl. And SEM photographs of optimized formulations showed discrete, spherical microspheres.

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Original Article

FORMULATION AND EVALUATION OF CONTROLLED RELEASE OSMOTIC TABLET OF GLIPIZIDE

Syed Gouse Feroz * [1], Dr. Khaja pasha , Heena Begum , Farheen , Syeda safoora naaz , Afreen Fatima, Jahan Ara, Dr. Shahana Banu [2]

1. Azad College of Pharmacy, Moinabad, Rangareddy.
2. Department of zoology Gulbarga University, Gulbarga

Controlled porosity osmotic pump tablets of Glipizide were prepared and final formula is optimized after formulating four formulations by using different polymers, two factors, osmogent ratio and coating percentage are varied and evaluated based on their effects on drug release rate. Tablets of all formulations are prepared by Direct compression method. As the osmogent concentration and pore former increases, drug release increases in the present work, four fomulations are prepared and F3 formulation is optimized.

Key words: Osmotic drug delivery, osmosis, coating, zero order release.

Correspondence Address:

Syed Gouse Feroz**,** Azad College of Pharmacy, Moinabad, Rangareddy

1. INTRODUCTION

Oral route is the most commonly used route for drug administration. Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device [1,2,3]. Osmosis is an aristocratic bio phenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilize the principles of osmotic pressure for delivery of drug**.** Chronic diseases such as diabetes, asthma and heart diseases are often treated using multi-drug therapies, which are vulnerable to incidence of side-effects, poor patient compliance and slow improvement of patients [4,5]. Though controlled drug delivery systems have been available separately for these drugs, a system that can deliver these drugs at a prolonged rate may ensure improved patient compliance and reduce the problems associated with the multi-drug therapy [6]. Elementary osmotic pump, [EOP] essentially contains an active agent having suitable osmotic pressure, contained into a tablet coated with a semi permeable membrane usually of cellulose acetate [CA] [7]. A small orifice is drilled through the coating by LASER or high-speed mechanical driller. When exposed to an aqueous environment, the soluble drug within the tablet draws through the semi permeable coating, resulting in the formation of a saturated aqueous drug solution within the device [8,9]. The membrane is non-extensible and increase in volume due to imbibitions of water raises inner hydrostatic pressure, eventually leading to flow

of saturated solution of active agent out of the device through the small orifice [12].

Glipizide is poorly water-insoluble oral hypoglycemic agent belonging to class-II of biopharmaceutical classification system and is one of the most commonly prescribed drugs for the treatment of patients with type-II Diabetes Mellitus [13,14]. It is practically water-insoluble, but its absolute bioavailability is close to and its dissolution is considered to be rate limiting step [i.e., an effective factor] in its absorption from gastro intestinal tract [15]. It also has a relatively short elimination half life of 2-4 hours, thereby requiring twice daily dosing in large number of patients, which often leads to noncompliance [16]. The present study was aimed towards the development of swellable elementary osmotic pump tablet of a poorly water insoluble drug [17].

2. MATERIAL AND METHOD

Glipizide were gift from Lupin research pune india, HPMC, Lactose monohydrate, cellulose acetate, polyethelene glycol 400, Sodium chloride, ethyl cellulose, magnesium stearate, acetone, methanol, potassium dihydrogen phosphate, sodium hydroxide used were of pharmaceutical grade

Formulation and development

Drug layer composed of glipizide. Lactose, HPMC are weighed accurately and passed through 40#. Pass Sodium chloride through 60# and mixed properly. The mixed powder was lubricated with Magnesium stearate which is passed through 60#. Blend it in a blender for 5 minutes. The prepared blend was placed in die cavity and compressed with hardness 3.2-4 kp with diameter 3.68 mm by 8 mm round standard concave punches [18].

Coating of tablets

Preparation of coating solution

The tablet coating were applied using dip coating process. The tablet were dip coated in polymer solution consisting of Cellulose acetate phthalate (CAP) dissolved in a solution of Acetone and a non solvent. Typically, The Polymer-coating solution consisted of 15% CAP and dissolved in acetone [1S9]. After the tablets were coated with polymeric coating solution, they were air dired for 5 sec and then immersed in water bath for 3 min. After removal from the water bath the tablets were then air dired under ambient conditions for at least 12 hrs [20].

Dry tablets are weighed and the average weight was determined. The % of weight gain was calculated by following equation.

% weigh gain = (Wt-Wo/ Wo) *100

Where,

Wt = weight of tablet after coating

W_o = weight of tablet before coating

EVALUATION OF PREPARED CORE TABLETS

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, thickness, weight variation, hardness, and friability.

Appearance

The core tablets were checked for presence of cracks, depressions, pinholes, uniformity of the color, smooth polish on the surface of tablet etc if any.

Dimensions

Thickness and diameter of core tablets were measured using Verniar calipers. These values were checked and used to adjust the initial stages of compression.

Uniformity of Weight

20 tablets were weighed individually and average weight was calculated from the total weight of 20 tablets. The individual weights were compared with the permissible limits (±5 %). The percent deviation was calculated using the following formula.

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Hardness test

Six tablets were randomly selected from each batch and hardness of each tablet was determined by using Pfizer hardness tester.

Friability test

It is the ability of tablets to withstand mechanical shocks during handling and transportations 6.5gm of tablets were picked from each batch and weighed and placed in the Rochae friability test apparatus and operated at rate of 25 RPM for 4 minutes (or up to 100 revolutions), tablets were de-dusted and weighed again. The loss of tablet weight due to abrasion and fracture was measured in terms of % friability (A value of **<1%F** is acceptable).

$$F = \frac{\text{Initial wt} - \text{final wt}}{\text{Initial wt}} \times 100$$

Drug content estimation

The Glipizide tablets were tested for their drug content. Five tablets were finely powdered required quantities of the powder equivalent to 10 mg of Glipizide were accurately weighed and transferred to a 100ml of volumetric flask. The flask was filled with Phosphate buffer (pH 7.5) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 200 ml with Phosphate buffer (pH 7.5) and measure the absorbance of the resulting solution at the λmax 222 nm using a UV spectrophotometer. The linearity equation obtained from calibration curve as described previously was used for estimation of Glipizide in the tablet formulations.

Formula-tion code	Bulk density (g/ml)	Tapped density (g/ml)	Carr`s index (%)	Hausner`s ratio	Angle of repose
F1	0.416	0.463	10.1511	1.112	25
F2	0.403	0.465	13.3333	1.1414	27
F3	0.402	0.448	9.4803	1.114	25
F4	0.430	0.467	7.905	1.086	23

In-vitro Dissolution studies

In vitro drug release studies of the prepared tablets were conducted for a period of 16 hours using an eight station USP type II apparatus (LAB, India) at 37±0.5 ^{0}C the paddle speed was 50 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH 7.4 at different intervals, 10 ml of samples were withdrawn and filter through a whatsman filter paper. The equivalent volume of the medium was added to the dissolution flask.

3. RESULTS AND DISCUSSION

Table 1: Flow properties of Glipizide

S.no	Parameter	Value	Type of Flow
1	Bulk density	0.144	----
2	Tapped density	0.263	----
3	Carr`s index	44.07	Very very poor
4	Hausner`s ratio	1.810	Very very poor
5	Angle of repose	42	Very very poor

Table 2 : Average values of pre-compressive parameters of tablet blend:

Evaluation of core Tablets

The tablet formulations were subject to various post-compressive evaluation tests, such as, Hardness, Friability and Weight variation, drug content uniformity.

Weight variation test

It was carried out as per official method and the average percentage deviation of all the formulation

was found to be within the limit (as per USP standard).

Content uniformity

It also carried out as per official method and it was found that all batches shows good content uniformity. The values for all the formulations were in the ranges from 93.12 **to 98.23%.**

Hardness test

States that all the formulations were found in the **range 8to 10 kp.**

Friability test

Compressed tablets have lose less than **1 %** of their weight are generally considered acceptable. All the formulations have less than 1% friability.

Table 3: Evaluation results of the compressed tablets

Formulation code	Thickness (mm)	Weight variation (mg)	Hardness test (kp)	Friabil-ity test (%)	Content uniformity
F1	4.71± 0.04	340.2 ± 2.47	9.11± 0.26	0.3	94.15 ± 0.48
F2	4.69 ± 0.03	338.7 ± 2.30	9.12± 0.33	0.1	95.03 ± 2.15
F3	4.70 ± 0.01	340.1 ± 2.62	8.82 ± 0.26	0.2	98.23 ± 2.32
F4	4.67 ± 0.01	339.7 ± 3.26	9.18 ± 0.33	0.4	97.4 ± 1.51

The tablets of 4 formulations were tested and analysed for thickness, weight variation, hardness, friability, content uniformity

Table 4: Cumulative % of drug release

Time(hr)	F1	F2	F3	F4
0	0	0	0	0
1	100	12.12	16.19	19.11
2		14.96	24.96	22.58
4		26.78	36.78	46.12
6		36.79	56.81	52.51
8		58.59	79.14	69.1
10		81.54	99.23	89.23

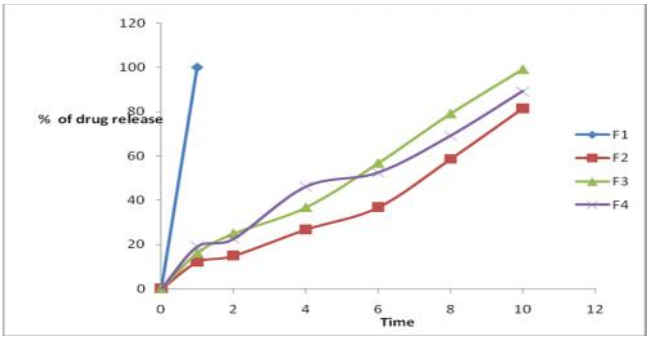

Figure 1: Invitro drug release of all formulations

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 30 days. Parameters quantified at various time intervals were shown;

Table 5: Stability studies of optimized formulation

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-3	**25^{0}C/60%RH % Release**	**99.59**	**99.50**	**Not less than 85 %**
F-3	**30^{0}C/75% RH % Release**	**99.42**	**99.52**	**Not less than 85 %**
F-3	**40^{0}C/75% RH % Release**	**99.60**	**99.54**	**Not less than 85 %**

Table 6: Results of stability studies of optimized formulation F-3

S.NO.	TIME(Hrs)	F-3 1M

1	0	0
2	1	5.71
3	2	7.20
4	3	8.5
5	4	9.60
6	5	10.1
7	6	72.2
8	7	78
9	8	99.60

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