DRUG COMPLIANCE AND ADHERENCE TO TREATMENT

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ABSTRACT:
BACKGROUND: In spite of any number of medicines will not be of use unless patient takes' them. After diagnosing the disease, the next most important step is to follow the instructions of physician in terms of treatment. The doctor's responsibility does not end with writing prescription, assuming patient will adhere to it. He/she should cross check the behavior of patient for drug compliance and see that patient follows it and get the benefit.

Non compliance is the main barrier for the effective delivery of the medical care. This will have greater implications on the economic burden on the country in terms of frequent hospitalization, use of expensive medicines in case of relapse due to non adherence.Though the terms compliance and adherence are used synonymously, they differ in the delivery of quality of the medicare as the former implicates the passive following of the physician instruction, while in the later, patient actively participates in the development of the treatment plan, which will improves outcome of the treatment. Adherence is the preferred term over compliance by WHO.
KEYWORDS: Adherence; compliance; concordance; non compliance; non adherence; treatment

INTRODUCTION: Significant advances have been made in understanding etiology of disease states, and development of new therapeutic agents made it possible to cure or provide symptomatic control. However, in many circumstances, drugs are not being used in the manner conducive to optimal benefit and safety. Efforts to maintain or improve health, fall short of the goals considered attainable, and has been attributed to patient's noncompliance or partial compliance.

Medication compliance (taking one's medicine as prescribed) is a major concern as it prevents hospitalization up to 5.5% and increase deaths by 8.48-fold to medication errors. Cost and poor understanding of the directions for the treatment are major barriers in completing treatment. WHO (World Health Organization) has estimates that only 50% of people complete long-term therapy for chronic illnesses as prescribed[1].

Half of all prescriptions for drugs to be taken on an ongoing basis are either not completed or are never filled in the first place due to cognitive issues, depression or physical problems [2-3]. Medication for asymptomatic conditions is most likely not to be taken casually,

else land up with devastating problems over a period of time, especially with conditions like diabetes, high blood pressure or high cholesterol[1]. A report from the American heart association reveals that nearly 60 percent of patients whenever taking five or more medicines gets confused while taking them.

TYPES OF PATIENTS: Based on the acceptance of diagnosis and treatment initiation, patients are categorized into four types

1.NON COMPLIERS: Those who do not accept diagnosis and need treatment.

2.PARTIAL COMPLIERS: Those who accept diagnosis and treatment but cannot fulfill the recommended actions sufficiently to reach targeted improvements in their health.

3.OVER COMPLIERS: Those who take recommended actions in excess of targeted improvements (These patients are rare).

4.ADEQUATE COMPLIERS: Those who follow health advice adequately to improve or control their disorder.

TYPES OF MEDICATION-TAKING BEHAVIOR:

COMPLIANCE: It is the conscious effort to use drugs in the manner prescribed, it is the extent to which all individuals' behavior coincides with medical & health advice. Understanding how medication should be used, with sufficient positive motivation, and intentions, looking at the perceived self benefit and positive outcome. , it can also apply to other situations such as medical device use, self care, self-directed exercises, or therapy sessions.

ADHERENCE: The extent to which a person takes medication as prescribed. WHO defines adherence as "The extent to which a person's behavior, corresponds with agreed recommendations from a health care professional". Concept of adherence is broadly viewed as related to instructions concerning medicine intake, use of medical device, diet, exercise, life style changes, rest and return for scheduled appointments[4-7].

CONCORDANCE: Consultative and consensual course of therapy partnership between the consumer and their doctor. Concordance is the process by which a patient and clinician make decisions together about treatment[8].

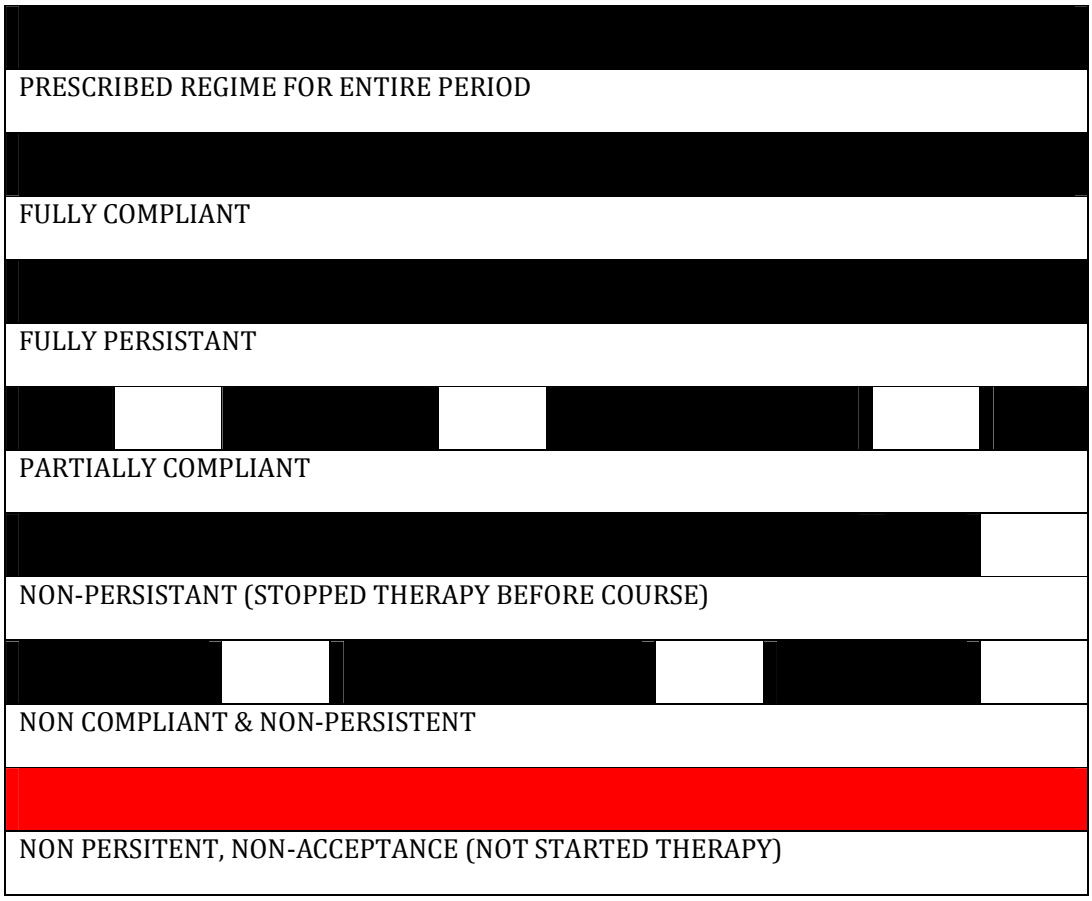
PERSISTENCE: A person's ability to continue medical advice for the intended course, which may range from few days to life long.

However the preferred terminology remains a matter of debate. In some cases, concordance is used to refer specifically to patient adherence to a treatment regimen that is designed collaboratively by the patient and physician, to differentiate it from adherence to a physician only prescribed treatment regimen[5-8], despite the ongoing debate, adherence is the preferred term for the WHO[1], the American pharmacists association[9] and the US National Institutes of Health Adherence Research Network[8,10], and is important for optimum therapeutic outcome which improves patient's quality of life.

Concordance also refers to a current UKNHS (United Kingdom National Health Services) initiative to involve the patient in the treatment process to improve compliance [11, 12]. Here patient is informed about their condition and treatment options, they are involved with the treatment team in decision making process and partially responsible for monitoring and reporting back to the team[1].

Non-compliance is a major obstacle to the effective delivery of health care. Estimates from the WHO indicate that about 50% of patients with chronic diseases living in developed countries do not follow treatment recommendations[1, 13]. Non-compliance means not following the directions for treatment due to irrational behavior or willful ignoring of instructions leading to increased morbidity, treatment failures, exacerbation of disease, more frequent physician visits, increased hospitalizations and even death (Fig.1) [6, 14, 15].

(Fig.1: TYPES OF MEDICATION TAKING BEHAVIOR)



The most common situations associated with non adherence are

- Failure to have the prescription dispensed or renewed, not refilling prescriptions for chronic diseases states, not obtaining refills at appropriate intervals, 25% don't fill new prescriptions[16-18],
- Omission of doses most common type of non compliance and more likely to occur when a medication is to be administered at frequent intervals. Increased frequency cause more interruption of normal routine, or work schedule, especially in poly pharmacy or when treatment is needed with an extended period of time. Few patients cannot identify their own medications [18,19].
- Errors of dosage, like giving instructions in measures of tea spoon (measure range from 5ml. to 15ml.) and not following administration of medicines at night time if patient falls into sleep etc., where dose of administration is incorrect[20].

- Incorrect administration of medication: includes not using proper technique like using metered dose inhalers, wrong route of administration, such as taking vaginal pessaries orally[21].
- Errors in time of administration: in 8th hourly prescription, night dose is adjusted in the day time.
- Premature discontinuation of treatment occur most commonly with antibiotics and drugs used for chronic disorders like hypertension. American Association of Retired persons (AARP) Survey of ambulatory elderly patients reported 33% premature discontinuation of medications[22]. In a pediatric outpatient study on acute otitis media therapy 37% discontinued early. Highly priced drugs are prematurely discontinued [1, 23].
- Preference for self care other than medications, such as following other systems of medicine or indigenous remedies etc., [24, 25].
- Not completing entire course of therapy, when symptoms subside with partial usage of antibiotics or treatment regimen as seen in acute infections and treatment of tuberculosis.
- Other patient factors such as, fear of dependency, social problem like usage of diuretics causing polyuria, taking out dated or improperly stored medicines, or friends and family members' medications causes non adherence. Lowest compliance of about 20-30% is seen with life style changes [26, 27]. Addiction to alcohol and smoking has decreased compliance in conditions like asthma, hypertension and renal transplantations [28-38].

Main reasons for not filling prescriptions according to study in Americans with age 50 and above[37,] (Table No.1).

(Table No.1: prescription refill proportions in elderly patients)

Cost of the drug	(40%)
side effect of drug	(11%),
thought drug wouldn't help much	(11%)
Already taking many prescriptions	(3%)
condition improved	(4%)
don't like taking prescription drugs	(5%)
drug did not help	(6%)
didn't think i needed it	(8%),
Other reasons (physical impairments etc,.)	(12%)

NON PATIENT FACTORS ASSOCIATED WITH NON ADHERENCE ARE:

THE NATURE OF PATIENT'S ILLNESS: Patients suffering from schizophrenia has high incidence of non compliance, due to distorted reality & lack of insight do not recognize their

illness and need for treatment. Similarly in chronic disorders like hypertension, tuberculosis etc., same pattern is observed [39].

THERAPEUTIC REGIME: Multiple drug therapy like 5-6 prescribed drugs[13, 40-42] taking at different timings ,taking tablets with same color, size and shape cause more confusion[43] and skip doses. Technical difficulty in using inhalers[44-50].

DURATION OF TREATMENT: Compliance is inversely proportional to duration of treatment[27, 51, 52]. In a study of long term therapy, low compliance is observed as in bronchial asthma (50%) and hypertension (50-70%) [53-60].

FREQUENCY: Increased frequency of drug administration causes more disruption of normal routine or work schedule, hence many patients forget or inconvenienced or embarrassed. In one of the study, compliance has improved from 59% on 8thhourly regimen to 84% with once a day regimen [61-67]

ADVERSE EVENTS: Events are like deterrents; in a study on elderly patients 40% experienced side effects of this 20% stopped medications and in this only 18-19% informed their physicians about discontinuation[22]. In one of the survey, over 60% are noncompliant due to adverse events. Some drugs like Anti-Hypertensive agents, Anti depressants or Anti psychotics cause sexual dysfunction which is frequently implicated for non compliance. [68-82]

TASTE OF MEDICATION: Can be the cause for noncompliance especially in children.

Failure to comprehend the importance of therapy, as patient has limited knowledge about the illness, become non compliant if beliefs and expectations are not met with. Poor understanding of instructions also contributes to non compliance[83, 84]**.** Non compliance in elder age group is due to[2, 13, 33, 40, 41, 85 & 86]

- Adverse effects,
- Increased, or decreased sensitivity to drugs,
- Frequent change of prescriptions(prescription cascade),
- Living alone,
- Lack of social support system,
- Difficulty in opening the medication container that has flip off type of lid
- Going to pharmacist/chemist due to physical problems like (osteoarthritis)
- Cognitive impairment,
- Impaired mobility or dexterity,
- Swallowing problems,
- Financial issues like, Low income and high cost of medications,
- Everyday inconvenience in carrying and taking of medicines**.**

CONSEQUENCES OF NON COMPLIANCE: Drugs do not work if people do not take them [87]. Non-compliance is a major obstacle to the effective delivery of health care. National Council on Patient Information and Education designated it as America's other drug problem[88, 89]. Under use is very common, depriving the patient of anticipated therapeutic benefits and resulting in progressive worsening of the condition or increased complications as in hypertension. overuse

of medication is also common, where in patients increase dose or frequency of medications anticipating extra benefit or quick action and remission of symptoms and some times it can be an extra dose due to forgetfulness as in elderly age groups, causing increased adverse reactions, leading to unnecessary use of medical resources such as

- Physician Consultations
- Emergency Department visits,[90]
- Unnecessary additional laboratory tests and
- Treatments which are preventable

(Table No. 2: Consequences of non adherence to treatment in elderly patients[39, 91-93])

Cause	Proportion of hospitalization
due to non compliance	10-33%[9]
inability to self-administer	23% of nursing home admissions

Studies on HIV/AIDS have revealed higher viral loads in patients with 10- days drug holiday or 20% of missed doses of Anti retroviral agents, who are otherwise had nearly undetectable viral loads[94]. Non compliance with anti psychotics in schizophrenia had relapses with violent behavior. Similarly in Epileptics unexpected deaths are due to low the4rapeutic concentrations of antiepileptic drugs[95]. Deaths in transplant patients who have waited for years to get donor organ are because of organ rejection resulting from noncompliance in using immunosuppressants[96]

Low rates of adherence to therapies for asthma, diabetes, and hypertension are thought to contribute substantially to the human morbidity, mortality and economic burden of those conditions[1, 14]. In asthma non-compliance incidence is 28-70% worldwide, increasing the risk of acute severe asthmatic attacks requiring hospitalization. Non compliance to Anti Hypertensive agents is very common even in developed countries, and it is the main cause for hypertension related complications like heart diseases and strokes. In united States, it is estimated that drug related morbidity & mortality expenditure exceeded $177.4 billions[97]

Compliance rates are often high or over estimated in a formal clinical trial but drops off in a "real-world" setting. In a study, compliance rate for statins is 97% at the beginning, and dropped to 50% after six months[98].

ASSESSMENT TOOLS FOR MEDICATION ADHERENCE: Detection of non compliance is as important as diagnosis of a medical condition Compliance or non compliance is not stable; it may change over time, necessitating regular use of detection methods to measure the behavior as part of assessment for therapeutic efficacy[99].

Structured interviews using highly skilled and refined techniques, like Morisky scale which is validated scale estimating the risk of medication non-adherence, is cited in numerous articles since 1986 used for many different disease such as, hypertension, hyperlipidemia, asthma and HIV.

Compliance or non compliance is not stable; it may change over time, necessitating regular use of detection methods to measure the behavior as part of assessment for therapeutic efficacy[99].

As such there are no gold standards for Assessment for medication adherence; the ideal detection would measure compliance at the time and place of medication taking event. Direct observation of the patient would come closest to providing this ideal measure of adherence.[100]. Indirect methods of monitoring compliance other than Electronic event monitoring (EEM) are;

- Pill counts,
- Medication refill records,
- Patient self report,
- Structured interviews using highly skilled and refined techniques,
- Change in weight of meter dose inhaler canisters, ,
- Medication event monitoring using computer are most commonly used.
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Pill count is often used in clinical trials, it measures the difference between the dosage units initially dispensed and number remaining on return visit or unscheduled home visit, but pill dumping and medication discard misrepresents compliance[101, 102]

Structured interviews using highly skilled and refined techniques, like Morisky scale which is validated scale estimating the risk of medication non-adherence, is cited in numerous articles since 1986 used for many different disease such as, hypertension, hyperlipidemia, asthma and HIV. It is a structured four item self reported adherence measure that addresses barriers to compliance and permit health care provider to reinforce positive adherence behavior [103]

Sometimes achievement of treatment goals are used as a measure for compliance, like normal blood pressure in hypertensive, normal blood glucose levels in diabetics, after eliminating " tooth brush effect" (like people brushing their teeth before seeing a dentist) where patients load up medication just before their return visit to physician. Electronic event monitoring is a recent and reliable computerized compliance monitoring, here medication container cap is housed with microprocessor which records date and time of opening the cap and data can be retrieved by connecting the micro processor to computer, the disadvantage being no data is provided regarding actual amount of drug taken, It helps when supplemented with other methods of measurements[104].

Direct methods to measure adherence is by using biological markers and tracer compounds like measurement of glycosylated hemoglobin which provides objective assessment of metabolic control in preceding three months in Diabetics. Small amounts of tracer compounds with long half- lives, like Phenobarbital or digoxin are added to the medications and these tracers are measured in biological fluids.

Therapeutic drug levels monitoring in biological fluids is another direct method of compliance assessment but draw backs are individual pharmacokinetic variations, and tooth brush effect invalidate this type of measurement as data do not provide timing of doses[10]

(Table: 3 Comparison of different methods for the measurement of adherence)

DIRECT METHODS	INDIRECT METHODS
They are more sensitive and specific	They are less sensitive and specific
They are direct pharmacologic indicators of medication adherence	Tooth brush effect can not be ruled out
Limitations: i) Legal and ethical issues ii) Individual pharmaco-kinetic variations of drugs	They are better measure of detection if two different indirect methods are used and correlated; Eg: Pill count and electronic event monitoring device.

HOW TO IMPROVE COMPLIANCE/ADHERENCE: Effective ways to help people follow medication regimes could have far larger effects on health than any other treatment"-Haynes et al. 2005[106]. Patient should be evaluated before changing therapeutic regimen as non adherence is most common missed diagnosis.

Demographic factors such as age, marital status, sex, race, income, occupation, number of dependents, intelligence, level of education, or personality type have been shown to be marginally related to noncompliance[107-111]. Based on behavioral principles patient-centered compliance models are described, taking into consideration of socio behavioral determinants[112] which includes health belief models and health decision models , former is related to a preventive health behavior and latter focusing more on health decisions which combines the health belief model and patient preferences with comprehensive cognitive behavioral and affective components for advocated behavior[5, 113, 114].

Patient prerequisites for adherence:

- Understand diagnosis and potential impact
- Believe that treatment will be beneficial
- Treatment favors benefit over cost
- Confidence in health care practitioners

Patient factors for improved compliance include:

- Quick relief of symptoms
- Becomes quickly ill without therapy
- Treatment involving expensive procedure
- Recurrence if treatment is stopped
- Increased disability as a consequence with out treatment

HEALTH BELIEFS: To achieve compliance patient should believe that, he/she actually have illness which is diagnosed, and with treatment, severity of condition is reduced. Patient education & counseling should be designed to encourage health beliefs[115-118].

Patient physician interaction also affects compliance or adherence. Patient who has respect towards treating physician and is well known, giving information, assurance and psychological support, showing empathy, improves compliance or adherence. The interaction should be a negotiation between two active and equal participants with goal/strategy "to put ill

at ease".[119-124]. As recommended by NCPIE (National Council for Patient Information and Education) physician should respond to patient's queries regarding treatment and other related topics.

IDENTIFICATION OF RISK FACTORS FOR NON COMPLIANCE: As it is difficult to identify a non coplier, every patient is assumed a potential defaulter [125]. By recognizing individuals who are at risk, treatment is planned with simplest regimen compatible with patient's normal activities, such as avoiding expensive medicines, unnecessary medication, using long acting formulations and combination medications, to decrease frequency of administration

Prescribing low cost medicines as high cost medicine prescription fill rates are low, even if they buy reluctant to use entire prescribed quantity. Medication-flavoring formulary system developed about three dozen flavors, to overcome taste problems in medications especially in children

In cases with mental illness discuss with patients or family members regarding delayed onset of therapeutic effects, and the need for prolonged treatment by prescribing medicines with least side effects.

With physical disabilities such as visual impairment, communicate with patient verbally or use tape record instructions, increase font size or color code medication bottles, advise pre-measure and pre-cut medications. With hearing impaired patients the problem is solved by using interpreter, or speaking to better ear using regular voice volume and lip movement with eye contact maintained, repeat instructions when necessary, supplement with written information, and turn up hearing aids[2-3]

In cases with reduced mobility and dexterity advise patients to store medications in easily accessible location, using pre-cut, pre-measured medications or easy open tops that are easy to administer. Foiled backed wrappers are avoided in patients with arthritis or tremors. Wherever difficulty in swallowing is seen use alternative dosing formulations like liquids, trans-dermal patches, crushable tablets or capsules that can be opened and mixed with soft foods.

DEVELOPMENT OF TREATMENT PLAN: Hippocrates: "decisions to deviate, un aware of physician intentions keep watch also on the fault of patients which often makes them lie about the taking of things prescribed". Develop a simple plan on individual basis, involving patient in deciding treatment with minimal inconvenience and overcome forgetfulness by timing doses corresponding to regular activities in patient's daily schedule. Do not write twice or thrice a day instead of writing time in am/pm. in instructions[44, 126]

Health literacy is the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions (world health organization, 2003)[127]. Patients with low health literacy were reported to be less compliant with their therapy[128]. Written instructions and pictograms on medicine labels has proven to be effective in improving patient's compliance[129].

PATIENT EDUCATION: Best way to improve compliance. Decide what information is necessary for about illness and treatment[130]. Too much details/inappropriate presentation of adverse events may alarm patient & decrease compliance. Involve patient in decision-making process. Make patient understand benefits of treatment and importance of compliance without using complex technical terms. Patient is asked to repeat the instructions. Encourage patients to ask

questions. Patient education regarding asymptomatic hypertension, glaucoma, asthma, and diabetes mellitus removes non adherence [64].

PHYSICIANS FACTORS: Asking few questions, occasional eye contact not understanding language spend little time, giving large information in short time, lack of concern also effect compliance[131].

Physicians liability for non compliance is often over looked as they prefer pointing deficiencies of the patients rather than themselves. Physician's compliance is the extent to which the behavior of doctor fulfills their professional duty like not being ignorant, adopting new advances when they are sufficiently proved, writing prescription accurately and legibly, warning patients about side effects or adverse effects, and counseling them to use medicines effectively and safely.[132-136]

ORAL COMMUNICATIONS: Oral communication / counseling in a room with privacy[137] and free of distractions to give patient an opportunity to raise questions- supplemented by written instructions. Studies indicate that counseling has improved adherence in hypertensive patients[138]. Compliance clinics run by Pharmacists in western countries have improved adherence by reducing hospitalizations when pre & post clinics are compared[139, 140].

WRITTEN COMMUNICATION: Write timings and supplementary information regarding illness & treatment, especially for acute conditions (e.g. antibiotics) compared to chronic conditions[141]. One way communication is disadvantageous with illiterate. In a study 42% patients unable to comprehend instructions[142]**.** So combine both oral and written and encourage patient to put questions.

AUDIO VISUAL AIDS: help in visualizing the nature of illness, how a medicine has to be administered eg; metered dose inhalers and how they act. Many health care professionals are using very effectively by placing them in waiting room or consultation room and answering questions patients may have.

CONTROLLED THERAPY: Hospitalized patients are entrusted to self medicate before discharge, under direct supervision of health care professionals so that latter; can identify situations that undermine compliance that are corrected by answering questions [143]

Special programs and devices: In some situations highly structured programs are developed to improve compliance eg; behaviorally oriented program for training medication management skills in schizophrenia patients which increased compliance from 63% to 81%.Similar programs are needed for vision and hearing impairment subjects by producing prescription labels in Braille, and hearing aids respectively.

PATIENT MOTIVATION: For achieving optimum benefit, information is provided to the patient in a manner that is not coercive, threatening or demeaning, by counseling, providing written materials, supplying cues for appropriate behavior. Cues may be verbal or non verbal in latter case using special packaging or reminders, Negotiable physician- patient interaction [123] with respect and positive attitude, and realistic appraisal of the circumstances ,or development of contracts [144,145] or paying incentives in the form of monitory and non monitory like gifts, vouchers etc., to achieve agreed upon treatment goals.[146,147] Mass programs like sterilization

and immunization, wherein patients are positively motivated by beneficiaries and neighbors also improve compliance [3,148]

TIME COMMITMENT: Patients may not be able to take time off work for treatment; as a shorter traveling time between residence and healthcare facilities could enhance patient's compliance. Housewives more compliant to therapy they adapt well to clinic appointment times and treatment [3, 149-151].

COMPLIANCE AIDS: The accuracy and specificity of information on the label of prescription container and Auxiliary labels that provide additional information regarding the use, precautions, and storage of medicines also help in improving adherence.

Medication Calendars and Drug Reminder Charts are designed and developed to assist self administration of drugs by patients. Special medication container like 28- compartment (MEDISET) container are designed to help patient organize their medications on weekly basis. fig Specially designed caps for prescription container like The Prescript Time Cap; containing digital time piece display time and date of last dose taken. They are effective in improving adherence by patients who forgets doses or who are confused by the complexity of regimen.

Medication packaging also influence the patients adherence. Compliance Packs are developed which are pre-packed units, which provides one treatment cycle of medication in a ready to use package[152]. New dosage forms are developed to overcome non adherence due to increased frequency, in the form of long acting and controlled release preparations. Similarly Trans- dermal drug- delivery systems also permits less frequency of drug administration.

MONITORING THERAPY: 1. Self Monitoring-Patient should be appraised of the importance of monitoring their own treatment and assume personal responsibility of adherence to treatment.

Pharmacist or physician monitoring. ".brown bag program was conducted by NCPIE &The Administration on ageing in which patients are encouraged to put all their medicines in a bag for personalized medicine review in geriatrics.

D.O.T (directly observed therapy.[153-154] It is the ideal way to monitor therapy, especially in cases of prolonged drug intake.

"French saying- 5 centuries back about patient care "To care sometimes, to restore often, and to comfort always"

Summary: Valuable resources like time, effort and expenses put on diagnosis of illness with the aim of developing treatment plan for cure, control or increased survival are not achieved, unless patient complies to treatment. Non adherence is responsible for missed diagnosis, treatment failures and changing prescriptions with more potent, expensive and toxic drugs.

Adherence to medication is not routinely measured in clinical practice, for reasons as busy practice and depriving patients on close attention and monitoring therapy are not acceptable[155]. The highest priority should be given for patients adherence problems.

Improved adherence benefits every body (patient, physician, pharmaceuticals, pharmacist & community). For patient there will be increased efficacy and safety of treatment and decreased physician and hospital visits. For pharmacist increased recognition and respect for advise and services. Pharmaceuticals by manufacturing drugs suitable to the patients need, like blister pack, increase sales of drugs. Finally society at large and health care system gets benefit as a result of few problems with non compliance.

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