MADRID 2014 ESMO congress

Complications arising with compliance

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Faculty disclosure

I have no conflict of interest to declare

1. Definitions

Compliance
Adherence
Concordance
Persistence

Definitions: compliance

Respect of physician's indications

Degree of coincidence between patient's attitude (in terms of drugs intake, dietary, lifestyle) and physician's indications

(Paternalistic view)

Definitions: adherence

Active and collaborative patient's involvement

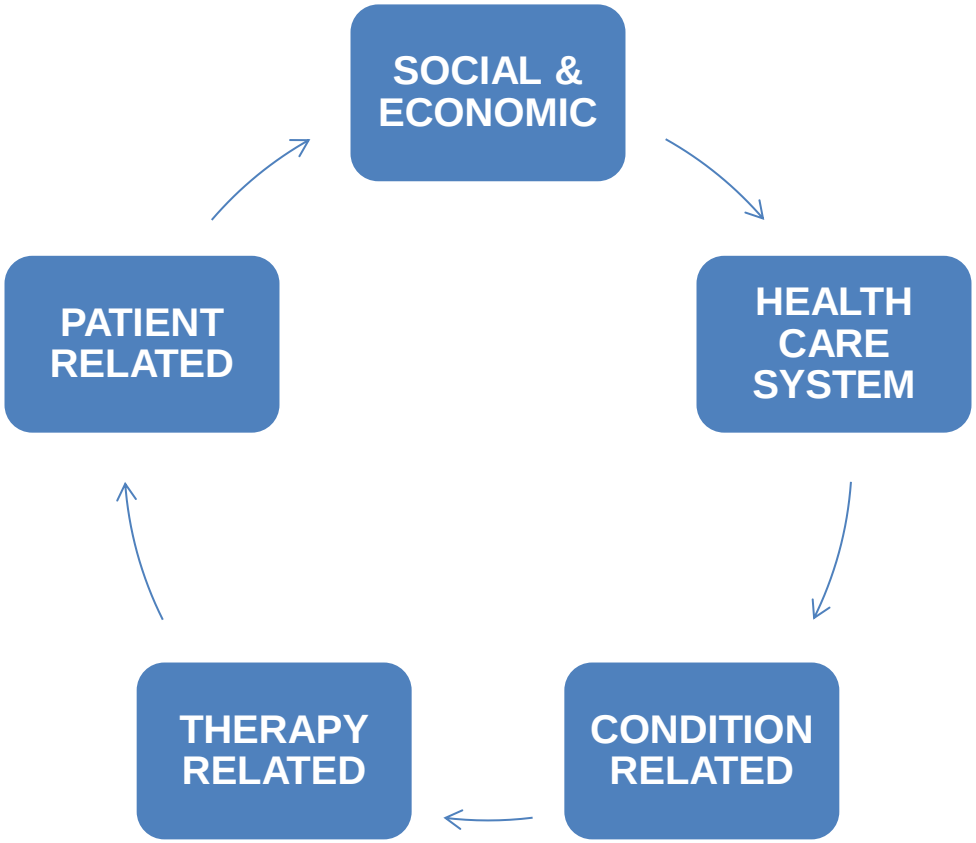
Planned and informed-based treatment ("concordance and persistence")

Defined as "***the degree or extent of conformity to the recommendations*** about day-to-day treatment by the provider with respect to the timing, dosage and frequency"

Term preferred to compliance because is generally believed to have ***a less pejorative and less judgmental connotation***

Value Health 2008

WHO's Five Dimensions of Adherence

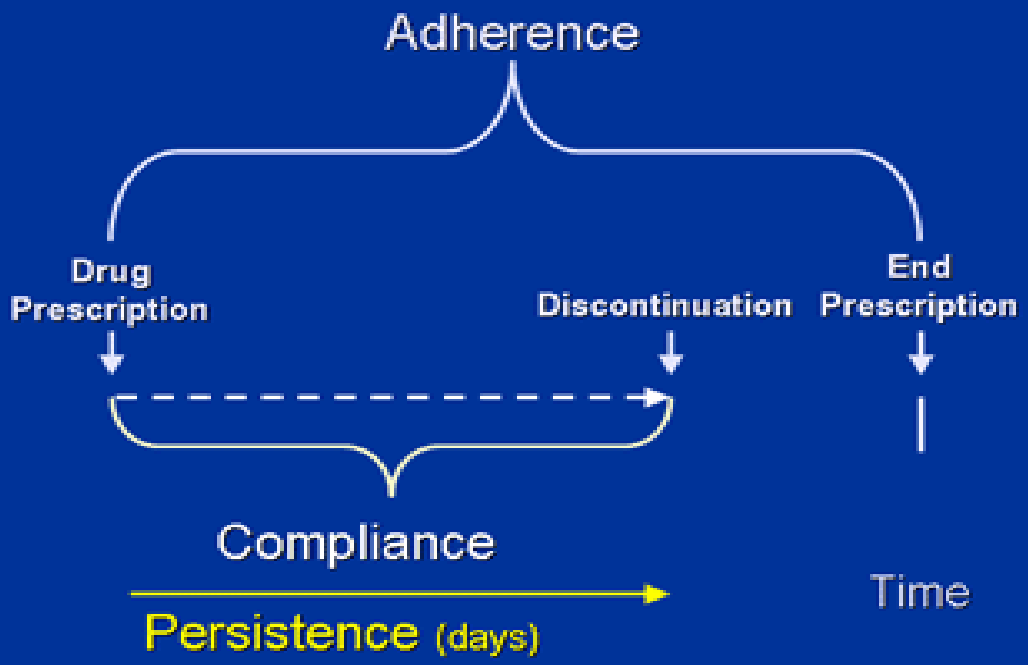


Definitions: Concordance and Persistence

Concordance: the need to reach a ***therapeutic alliance*** between physician and patient respecting both

Persistence: ***lenght of time*** in which the patient does follow recommendations

Adherence, Compliance, and Persistence



2. Factors influencing treatment's adherence

Adherence to anticancer agents has become problematic because of:

Increased ***combinations of oral (biologic/targeted) therapy*** with varying patterns of administration and duration of use

Poly-pharmacy

Older baseline age of patients with cancer

Other factors influencing treatment's adherence

Social and economics (e.g. poverty and income)

Health care systems factors (organizational structures and characteristics of healthcare professionals)

Patient (Motivation, attitude, knowledge, beliefs, perceptions and expectations)

The importance of treatment's adherence

Overestimation by patients and physicians of adherence to treatments, specifically for oral therapies

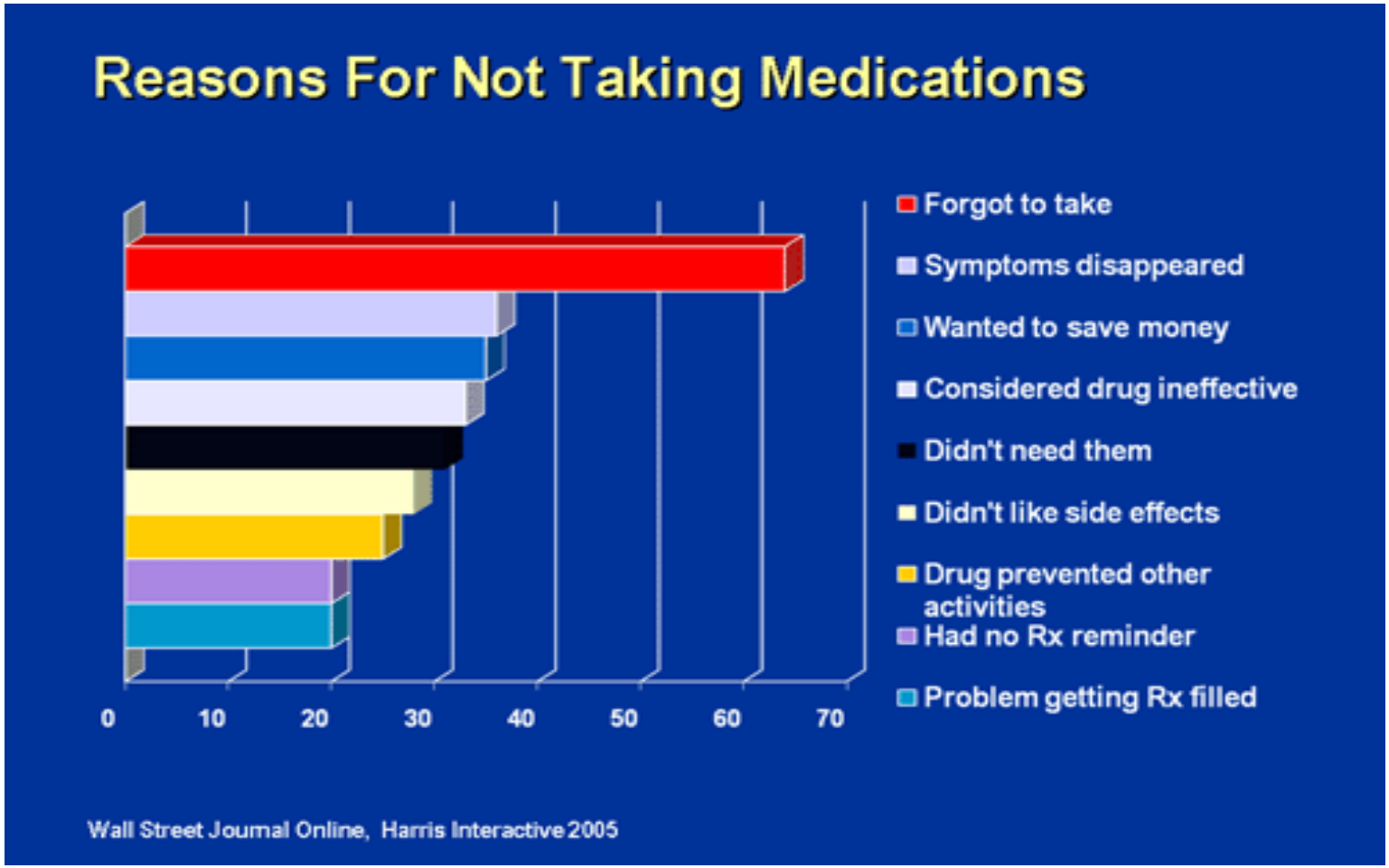
Reduced compliance gives ***increased costs*** for Healthcare system

Non adherence to treatments ***varies due to disease and phase of treatment***

Importance of evaluating strategies for improving compliance

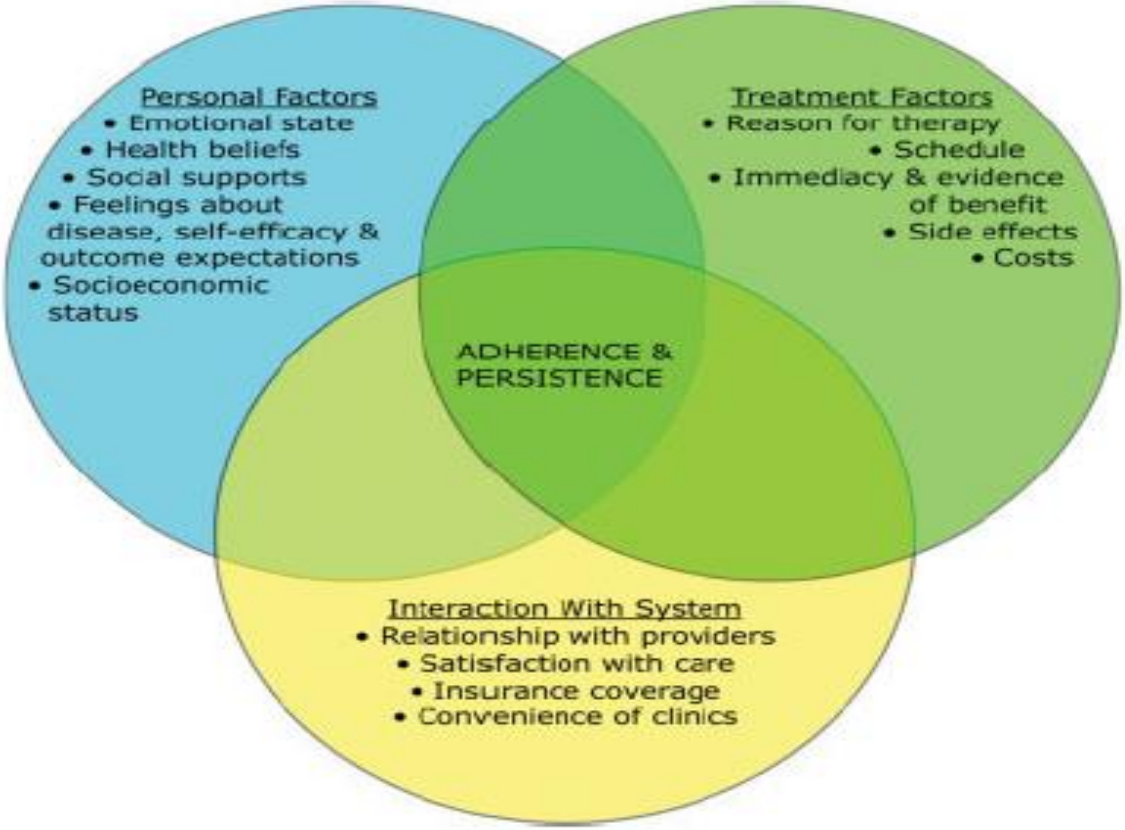
Signs and predictors of poor adherence and persistence

- Missed appointments, inadequate follow-up
- Poor patient-provider relationship
- Unfilled prescriptions
- Adverse effects from medication, medication cost
- Lack of belief in treatment
- Psychologic problems, particularly depression


Reasons For Not Taking Medications
Forgot to take
Symptoms disappeared
Wanted to save money
Considered drug ineffective
Didn't need them
Didn't like side effects
Drug prevented other activities
Had no Rx reminder
Problem getting Rx filled
0
10
20
30
40
50
60
70
Wall Street Journal Online, Harris Interactive 2005

The complexity of non-adherence

Models of adherence and persistence



3. The history…(of adherence) and literature

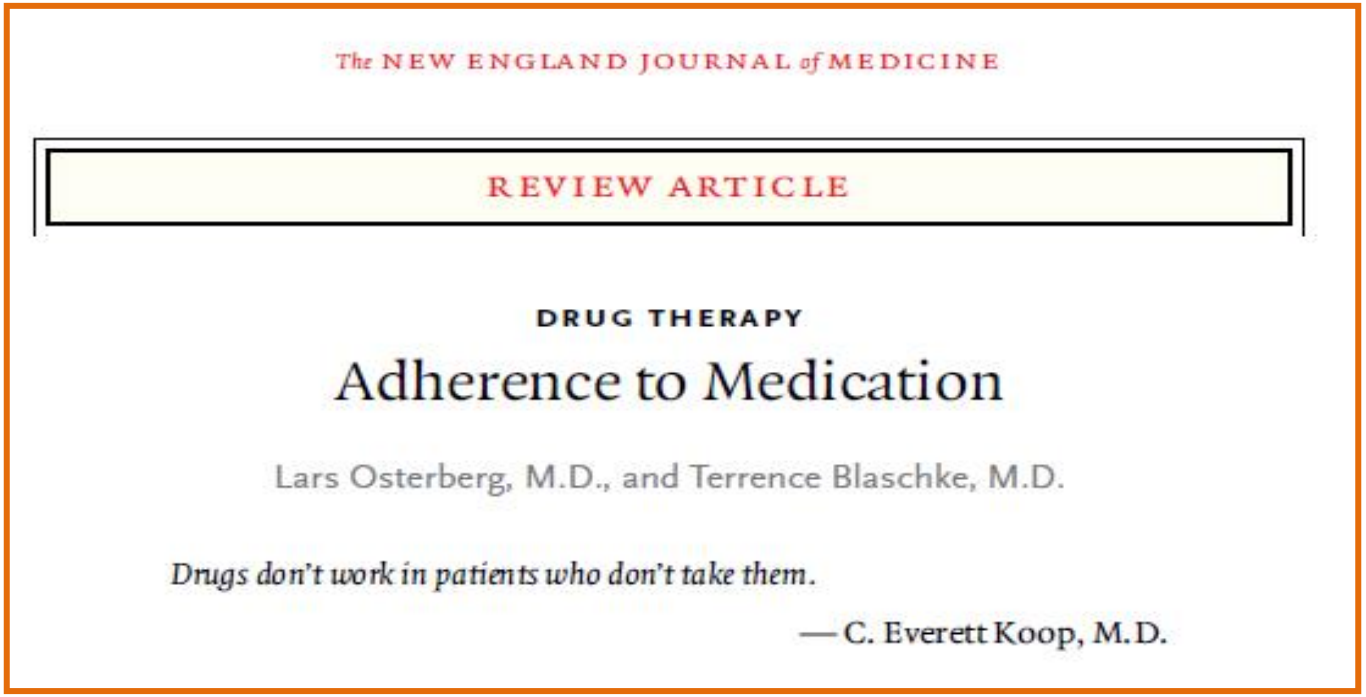
Adult populations

Adult pts with non oncological chronic disease on average take only ***half of their prescribed medications***

Adherence and persistence have been traditionally ***assumed to be better in cancer pts*** due to the perceived understanding of the risk of not taking medications as prescribed

JCO 1993, JAMA 2002, N Engl J Med 2005

Adherence and non–oncological Chronic diseases



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Adherence to Medication

Lars Osterberg, M.D., and Terrence Blaschke, M.D.

Drugs don't work in patients who don't take them.

— C. Everett Koop, M.D.

HIV, Hypertension, Psychiatric illnesses, pediatric pts

Adherence and symptoms and comorbidities Tx

- Pain
- Anorexia-asthenia
- Nausea and vomiting
- Constipation-diarrhea
- Gastrointestinal obstruction
- Ascites
- Dyspnea……

- CV and tromboembolic diseases, diabetes, psychiatric/neurologic,…

TABLE 2. Studies of Adult Adherence to Oral Antineoplastic Agents Over Time

YEAR	CANCER	NO.	ORAL THERAPY	ADHERENCE OR PERSISTENCE MEASURE	ADHERENCE OR PERSISTENCE RATE	TIME PERIOD	STUDY
1987	Hematologic malignancy	108	Prednisone and allopurinol	Serum metabolites	Prednisone: 26.8% Allopurinol: 16.8%	6 mo	Levine 1987[50]; Richardson 1988
1990	Breast cancer	51	Cyclophosphamide and/or prednisone	Self-report that 90-110% taken	53% overall with both drugs	6 mo	Lebovits 1990[21]
1992	Lymphoma	21	Chlorambucil, prednisolone, or dexamethasone	Microelectronic monitoring system (MEMS)	100% (standard deviation [SD]: 20.6%)	852 d	Lee 1992[52]
1993	Breast cancer	26	Tamoxifen	Self-report Pill count MEMS	97.9% (SD: 3%) by self-report; 92.1% (SD: 9.8%) by pill counts; 85.4% (SD: 17.2%) by MEMS	Mean of 2.92 mo	Waterhouse 1993[48]
1993	Small cell lung cancer	12	Etoposide	MEMS	93.2% (SD: 12%)	298 d	Lee 1993[53]
1996	Ovarian cancer	11	Altretamine	MEMS	97.4% (SD: 6.9%)	294 d	Lee 1996[54]
2000	Colon cancer	57	Uracil-tegafur	Self-report Physician interview Urine level	94.4% at 3 mo, 94.7% at 1 y by self-report and interview; 94.7% in range by urine testing of 38 patients at various timepoints	1 y	Sadahiro 2000[55]
2002	Breast cancer	53	Tamoxifen	Self-report	76% missed <1 dose per wk	6 mo	Murthy 2002[56]
2003	Breast cancer	2,378	Tamoxifen	Prescription refill records	77% filled prescriptions that covered at least 80% of doses over the 1st y; 50% did so by 4th y	4 y	Partridge 2003[57]
2005	Breast cancer	110	Tamoxifen	Self-report	88% adherent	Not stated	Grunfeld 2005[58]
2006	Myelodysplastic syndrome	90	Topotecan	MEMS	90%	5-10 d	Klein 2006[59]
2006	Breast cancer	131	Tamoxifen	Self-report	55% reported nonadherence to medication frequently or occasionally	Single point in time	Atkins 2006[60]
2007	Breast cancer	2,816	Tamoxifen	Prescription refill records	77.9% at 1 y; 64.8% at 3.5 y	3.5 y	Barron 2007[61]
2007	Breast cancer	1,633	Tamoxifen	Clinical notes, audit records, cancer registry data, prescription records	93% median (95% confidence interval, 84-100%)	2.4 y	Thompson 2007[8]
2008	Breast cancer	12,391	Anastrozole	Prescription refill records	78-86% of d were covered by filled prescriptions in Year 1; 62-79% of d were covered by filled prescriptions in Year 3	3 y	Partridge 2008[62]
2008	Breast cancer	161	Capecitabine	MEMS	76% took at least 80% of doses	6 cycles (14/21 d)	Partridge 2008[27]

NOTE: Adapted and updated from Partridge 2002.[5]

Adherence and oral anticancer Tx: imatinib

Targ Oncol (2012) 7:243–246
DOI 10.1007/s11523-012-0221-1

DAY-TO-DAY PRACTICE

Chronic therapy in gastrointestinal stromal tumours (GISTs): the big gap between theory and practice

In GIST as in CML ***adherence to Imatinib is not optimal***

Response correlated to adherence

General perception of adherence to therapy among patients, physicians and third persons (spouse, family, etc.) was uniformly ***higher than reality***

So adherence is important because…

The percentage of prescribed imatinib taken averaged 90.9% with ***71.0% of patients taking less*** (down to 29%) but also ***14.8% taking more than prescribed*** (up to 202%).

Only 14.2% were perfectly adherent with 100% of prescribed imatinib taken…"

Adherence and breast cancer hormonalTx

Table 2 Multivariate logistic regression model—factors associated with hormone use at 36 months after breast cancer diagnosis ($N = 303$)

	AOR	*P* value	Adjusted adherence rate %[a] (95 % CI)
Age	1.04	0.13	
40			86.7 (86.1, 87.3)
50			90.6 (90.2, 91.1)
60			93.4 (93.2, 93.8)
70			97.0 (96.8, 97.1)
Comorbidity (any)	3.14	0.03	97.0 (91.8, 98.9)
Partnership (no)	0.84	0.71	89.5 (77.4, 95.5)
Race/ethnicity			
Less-acculturated Latina	9.08	0.001	98.9 (96.1, 99.7)
More-acculturated Latina	3.42	0.28	97.2 (78.6, 99,7)
Other	3.74	0.06	97.4 (90.6, 99.3)
High school graduated (yes)	0.94	0.91	91.5 (77.9, 97.1)
Health insurance (no)	0.12	0.001	55.8 (26.0, 82.0)
Stage(I)	1.00	0.99	91.1 (78.0, 96.7)
Radiation therapy (yes)	0.47	0.18	82.7 (61.8, 93.4)
Chemotherapy (yes)	1.59	0.44	91.0 (76.0, 97.0)
Mastectomy (yes)	0.79	0.61	88.9 (76.8, 97.0)
Hormone side-effects (yes)	0.26	0.003	72.7(52.4, 86.6)
Financial adequacy (yes)	0.97	0.95	90.8 (80.3, 96.0)
Discussion of hormone therapy (yes)	0.95	0.92	96.7 (90.8, 98.8)
PEPPI[b] (range 0–50)	1.04	0.04	
0			71.6 (70.9, 72.3)
10			78.5 (77.9, 79.1)
20			84.1 (83.6, 84.6)
30			88.5 (88.1, 88.8)
40			91.2 (90.9, 91.4)
50			91.2 (90.9, 91.4)
Patient-centered communication (range 4–16)	1.22	0.006	
4			59.1 (55.6, 62.5)
8			76.0 (73.4, 78.5)
12			87.5 (85.8, 87.5)
16			93.8 (93.0, 94.6)

The importance of treatment's adherence: Elderly patients

reviews

Annals of Oncology

Annals of Oncology 25: 564–577, 2014
doi:10.1093/annonc/mdt433
Published online 26 November 2013

Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review

M. T. E. Puts[1*], H. A. Tu[1,2], A. Tourangeau[1], D. Howell[1,3], M. Fitch[1,4], E. Springall[5] & S. M. H. Alibhai[6,7]

The importance of treatment's adherence: elderly patients

Older adults have ***numerous comorbidities*** as well as cognitive and sensory impairment that may affect adherence

…focused mainly on women with breast cancer and adherence to adj hormonal tx

Adherence rate varied from ***52% to 100%*** and only one study asked reasons for non adherence

Non-adherence was ***common across studies*** but little is known about the factors influencing non-adherence. More research is needed….

Patient Adherence and Persistence With Oral Anticancer Treatment

Kathryn Ruddy, MD[1], Erica Mayer, MD, MPH[2], Ann Partridge, MD, MPH[3]

Adherence and persistence rates ranged from ***16% to 100%*** with different therapies and different methods of measurement.

Ca Cancer J Clin 2009

MADRID 2014 ESMO congress

The importance of treatment's adherence

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Adherence enhancing interventions for oral anticancer agents: A systematic review

Tim Mathes *, Sunya-Lee Antoine [1], Dawid Pieper [2], Michaela Eikermann [3]

Institute for Research in Operative Medicine, Faculty of Health – School of Medicine, Witten/Herdecke University, Ostmerheimer Str. 200, Building 33, D-51

Systematic review of treatment's adherence: examined studies

Adherence measurement, definition and study results.

Study	Adherence measurement	Adherence definition	Mean adherence rate (IG_n/CG (p))
Khandelwal 2012	Prescription refill	Doses taken	44.8/41.5 (0.402)
Levine 1987	Drug levels in serum (prednisone)	Drug levels in serum within individuals profile range	38.0/32.7/37.8/26.8 ($p > 0.01$ for each comparison)
	Drug levels in serum (prednisolone)	Drug levels in serum within individuals profile range	41.7/49.1/59.5/21.9 ($p < 0.01$ for each IG vs. CG; $p < 0.01$ for IG_1 and IG_2 versus IG_3)
Richardson 1987	Drug levels in serum (prednisone)	Drug levels in serum within individuals profile range	33.8/36.1/35.8/31.2 ($p > 0.05$ for each comparison)
	Drug levels in serum (prednisolone)	Drug levels in serum within individuals profile range	38.8/49.0/56.6/24.8 ($p > 0.05$ for each comparison)
Macintosh 2007	Pill count	Doses taken	81/86 (NS)
Moon 2012	NR	Doses taken	96.5/96.6 (0.958)
Simons 2011	Medication event monitoring system	Doses taken	97.9/90.5 (0.069)
		Days with correct intake (not specified)	96.8/87.2 (0.029)
		Patients with ⩾80% intake	100/79 (NR)
		Patients with ⩾90% intake	92/75 (NR)
		Days with ⩾80% intake	100/75 (NR)
		Days with ⩾90% intake	92/72 (NR)
		Irregular intake intervals (>14h or <10h)	RR = 0.51 (<0.05)
Tschida 2012	Prescription refill	Doses taken	65.7/58.0 (<0.001)

NR: not reported; NS: not significant; RR: relative risk.

Cancer Treat Rev 2013

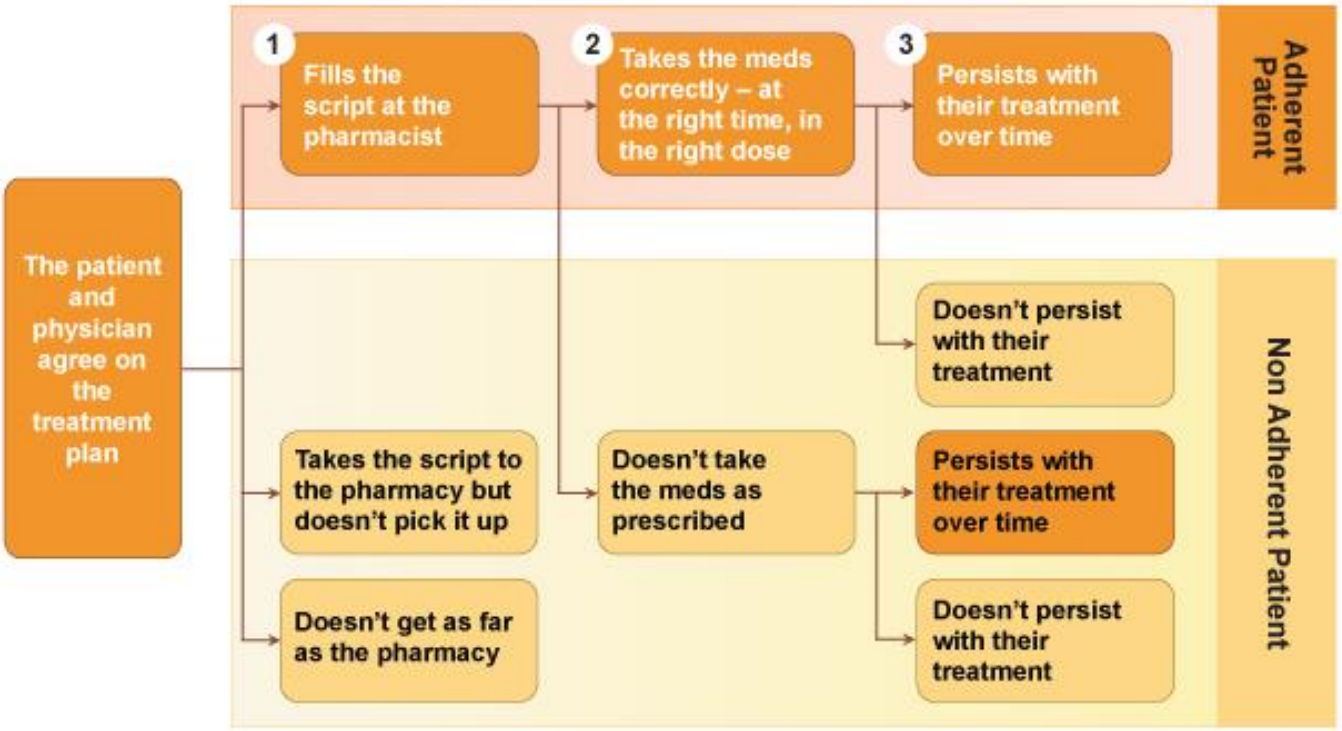
Systematic review of treatment's adherence: conclusions

Adherence enhancing interventions could have a promising effect ***(educational and counseling → mostly target several of the adherence dimension….)***

Crucial point: baseline adherence when choosing patients to avoid ceiling effects

Limited evidence: lack of sufficient studies and partly inconsistent results

Cancer Treat Rev 2013


The patient and physician agree on the treatment plan
1
Fills the script at the pharmacist
2
Takes the meds correctly – at the right time, in the right dose
3
Persists with their treatment over time
Adherent Patient
Doesn't persist with their treatment
Takes the script to the pharmacy but doesn't pick it up
Doesn't take the meds as prescribed
Persists with their treatment over time
Doesn't get as far as the pharmacy
Doesn't persist with their treatment
Non Adherent Patient

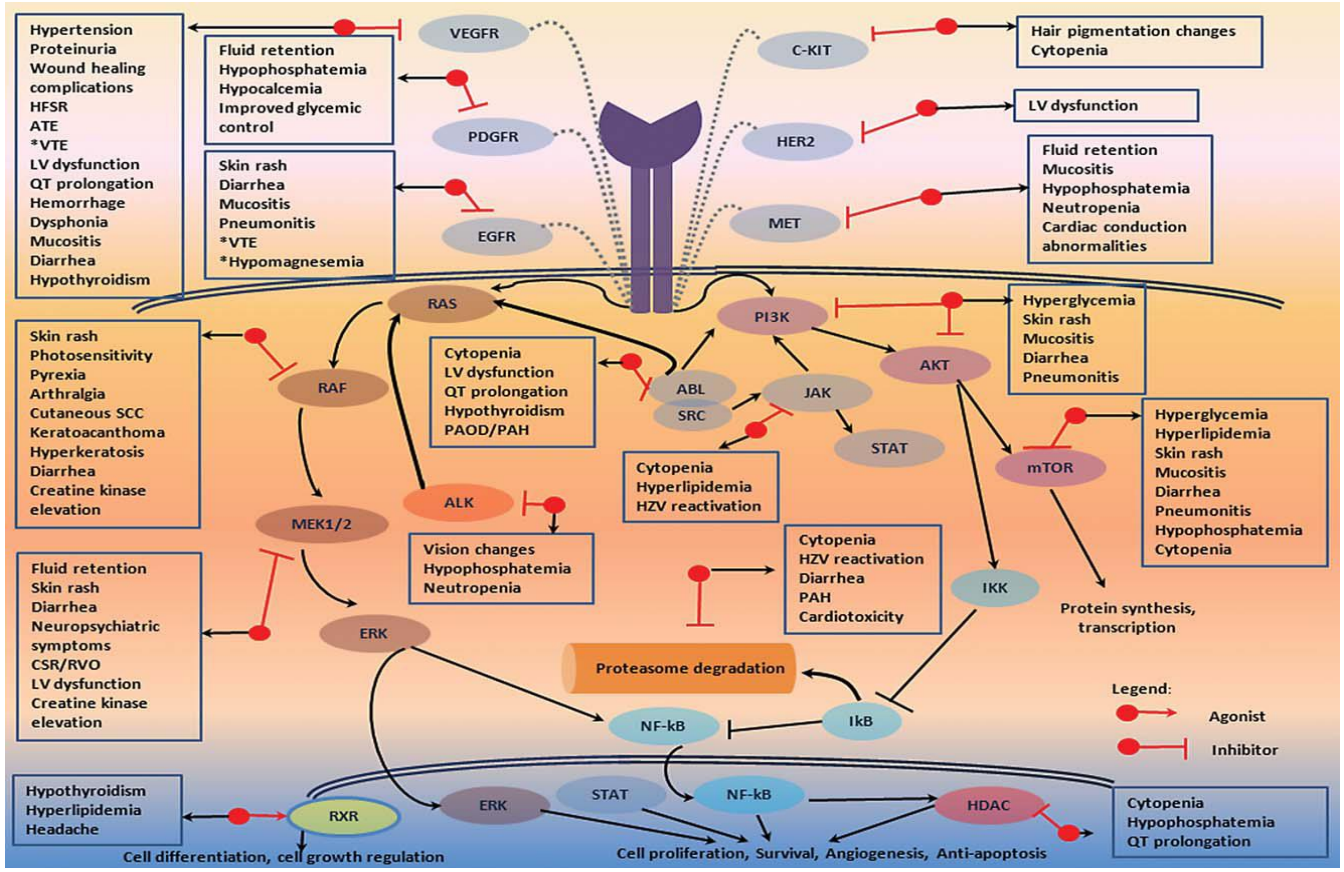
4. Complications arising with compliance (adherence)

Complications arising with adherence

About ***one quarter*** of newly developed anticancer agents could be taken orally

Adherence is ***lower*** in patients taking oral anticancer agents compared to patients taking intravenous chemotherapy

New toxicities…



CA Cancer J Clin, 2013

How to monitor adherence (toxicity, dose reductions, drug interactions)

TABLE 3. Methods Available To Monitor Adherence[1,2,15]

Direct Methods	Advantages/Disadvantages
Direct observation of therapy	Seemingly most accurate, but patients can hide pills in their mouth and discard later; requires office visits
Measurement of medicine levels (or a metabolite) in the blood	Objective, but there can be variations in metabolism; expensive; only indicates recent adherence
Measurement of a biologic marker in the blood	Objective, but requires office visits for collection of bodily fluids; expensive
Measurement of physiologic markers	Usually easy to perform, but can be affected by metabolism
Assessment of clinical response	Simple to perform, but can be affected by factors other than adherence
Indirect Methods	
Questionnaires/self-reports	Simple and inexpensive, but subject to errors or distortion with increased time between visits
Diaries	May prevent "poor recall" issues encountered with questionnaires, but can be altered by patients
Pill counts	Objective, quantifiable, and simple; however, patients can dump pills
Prescription refill records	Objective and data are easy to obtain; but refills do not confirm pill ingestion
Microelectronic monitoring devices (MEMS)	Precise and quantifiable; expensive and requires office visits and downloading from medical vials

Drugs and adherence

There are little data in oncology published to date regarding the effects of non-adherence and non-persistence.

The importance of non-adherence likely varies from drug to drug.

VOLUME 30 · NUMBER 32 · NOVEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Evidence for Therapeutic Drug Monitoring of Targeted Anticancer Therapies

Bo Gao, Shang Yeap, Arthur Clements, Bavanthi Balakrishnar, Mark Wong, and Howard Gurney

Diagnosing Toxicity

In many cases, drug toxicity can be diagnosed clinically.

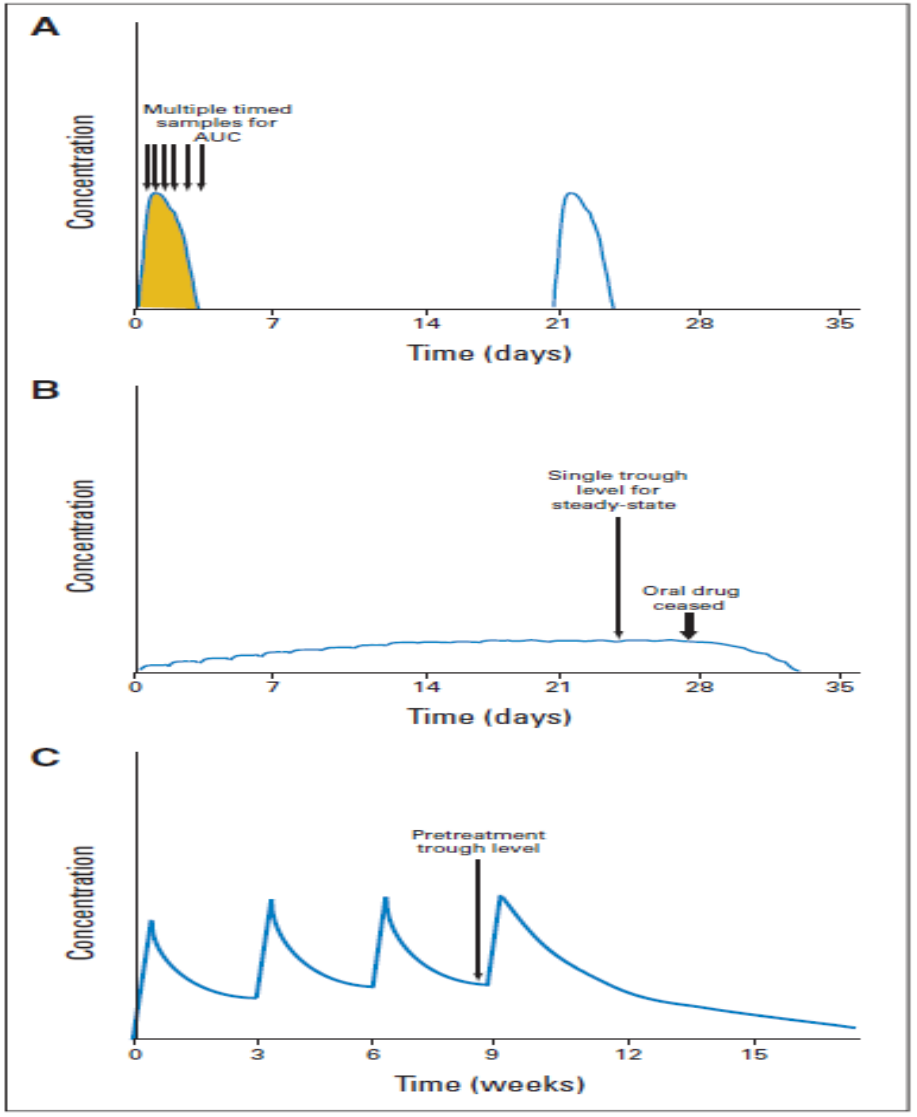


Fig 1. Representation of the blood concentration over time of various anticancer agents with differing pharmacokinetics profile. (A) Traditional cytotoxic agent given by three weekly intravenous injections. The description of systemic exposure requires multiple timed blood samples to define the area under the time-concentration curve (AUC). (B) Targeted agent given orally daily. Steady state can be described by a single trough sample. (C) Monoclonal antibody (mAB) given by intermittent infusions. Owing to the long half-life of most mABs, a pretreatment trough level may adequately describe drug exposure.

Diagnosing Toxicity

On the other hand, ***some adverse effects*** such as lethargy, anorexia, and diarrhea ***are non-specific***, and the causality of which can be difficult to differentiate from malignancy or complicating treatments, including antibiotics and analgesics.

Drug concentration monitoring may be useful in delineating whether these symptoms are related to the targeted agent or to other causes

Monitoring Dose Reductions

Although dose reductions of TKIs as a result of toxicity are common, ***determination of the appropriate extent of dose reductions*** to prevent an ineffective dosage is often difficult.

Importance ***to prevent an "overshoot"*** and also provide important reassurance to patients and oncologists about appropriate dosing.

Detecting Drug Interactions

Polypharmacy is common in patients with cancer who often commence new drugs during anticancer treatment.

Potential drug interactions (especially with CYP3A4 and ABCB1 inhibitors and inducers, have been shown to affect TKI exposure)

It becomes increasingly ***important to identify patients who require dose modifications*** to achieve adequate therapeutic drug exposure while minimizing risk of toxicity.

Effects of non-adherence

Non adherence can contribute greatly to:

Variability observed in drug's therapeutic effect

Erroneus conclusions with unnecessary diagnostic testing, hospitalizations and cessation of an active treatment

Over-adherence to self-administered medications
Patient's "more is better" approach or confusion led to overdosing and to substantially increased toxicity

"Economic effects" of non-adherence

50%

On average 50 percent of patients do not take their medications as prescribed and 33 percent never even fill their first prescription.

700 THOUSAND

Each year, an estimated 700,000 Americans experience adverse reactions to prescribed drugs that require an emergency room visit.

$290 BILLION

The estimated annual cost of patients not taking their medications as prescribed approaches $290 billion.

Annual U.S. cost estimates for non-adherence range from

$100-$300 billion

Effects of non-adherence: clinical case -1

56 yrs old pts with metastatic breast cancer (bone, liver SNC)
Second line CT with oral Navelbine and Capecitabine + Denosumab
4 consecutive days of oral NVB (instead of 1!!!)
For this patient probably the i.v. drugs should be better…. ("cognitive impairment due to brain mts treated with RT")

Effects of non-adherence: clinical case -2

66 yrs old pts with metastatic renal cancer
Second line therapy with Sorafenib at a reduced dose (50%)
Grade 1-2 diarrhoea with loperamide therapy and continuation of treatment → 4 kg weight loss, severe astenia and anorexia → ***stop Tx***

Effects of non-adherence: clinical case -3

Case Study

A 50-year-old woman with metastatic breast cancer is prescribed capecitabine 1250 mg/m² by her medical oncologist. The physician instructs her to take four 500 mg tablets in the morning and four 500 mg tablets in the evening for 14 days, take 7 days off, return to the clinic in 3 weeks for a follow-up appointment, and to call if she has any problems.

Three weeks later the patient returns to the clinic with painful erythema and swelling of the hands along with diarrhea which caused her to miss several days of work. She also complained of nausea. She said she began taking antacids with her medication to help the nausea but it did not improve. She stated that she stopped taking her capecitabine with four days left to go because she felt so miserable. When asked why she did not call the clinic, the patient stated "I did not want to bother anyone and I thought everyone gets sick with chemotherapy."

Oncology Issues, *2008*

5. Strategies to improve compliance (adherence)

Strategies to improve adherence

Protection of Patients, Family, and Caregivers

Patients should be educated about any requirements for storage, such as temperature or light-resistant needs.
The ***patient, family, and caregiver also should be instructed*** on safe practices with administration of oral chemotherapy, adjustments in dosing, or return of drug to the pharmacy or oncology clinic.
Patient education sheets should be available to enhance verbal instructions with reinforcement that oral anticancer agents are toxic substances

Moody & Jackowski, 2010

Prescribing Precautions

The importance of ***detailed education by the oncology*** team, including simple calendars and detailed written instructions for disposal of hazardous medication.

Accuracy

For each drug, ***major steps*** are focused on the ***prescribing, dispensing, administering, and monitoring*** stages of medication use

Weingart et al., 2011

Side-effect reporting

A mechanism of side-effect reporting is essential to capture patient-reported outcome data and may include a simple diary

Patients may minimize experienced symptoms over a two- to three-week period;

If the clinic visit interval is greater than three weeks, patients may possibly forget symptoms.

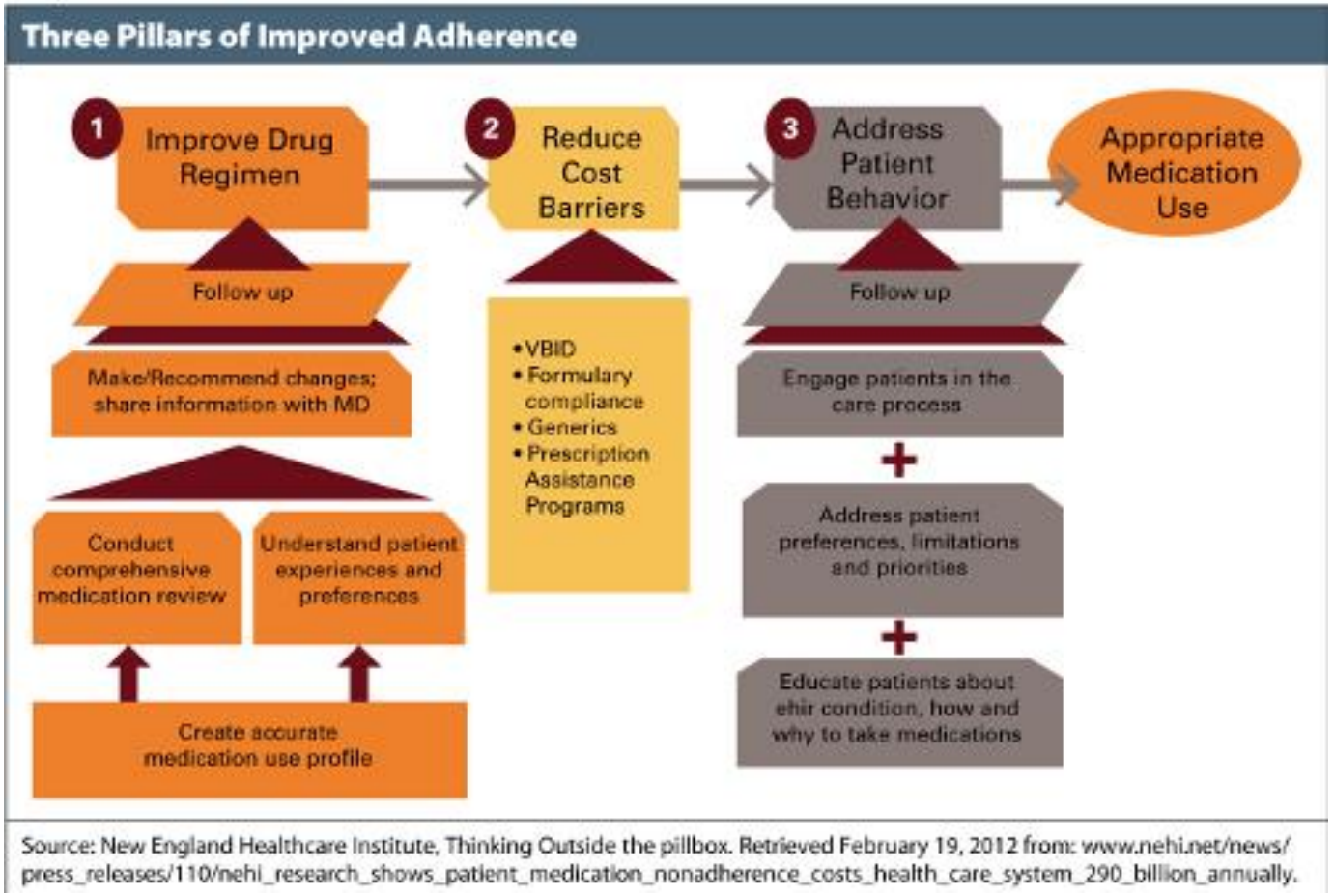
Strategies to improve adherence

Made by patient:
Patient's support programs
Computerized" Drug alerts"

Made by physician:
Improving of patient-physician's communication
Regimen's semplification
Increase of follow up visits
Frequent phone contacts

Other strategies to improve adherence

Figure 1



Source: New England Healthcare Institute, Thinking Outside the pillbox. Retrieved February 19, 2012 from: www.nehi.net/news/press_releases/110/nehi_research_shows_patient_medication_nonadherence_costs_health_care_system_290_billion_annually.

Strategies to improve adherence: the role of Supportive Care Units

Implementing Supportive Medical therapy for patient, from diagnosis and all across the route of care (adjuvant/palliative), for the cure of adverse events, toxicities and co-morbidities, to mantain ***psyco-physical well-being and improving adherence to care protocols or treatment*** in terms of dose intensity and interval of administration.

6. Open questions and discussion

Discussion

Many new drugs (targeted and non) with a lot of new and (probably) under-described toxicities

Small data about long-term safety of new drugs

Two suggested lines for improvement:

1. **Scientific** (ad hoc designed studies for adherence evaluation)
2. **Managerial** (empowerment of supportive care programs and services)

Open questions: scientific

Tools to better evaluate adherence

Who does judge toxicities? Patient or physician?
With new targeted: are we using the ***correct toxicity scale?***

Fast track drug approval conditioning adequate toxicity reports (specific populations–***third toxicity axis*** – late adverse events)

Studies regarding the impact of the better supportive care and its impact in adherence and outcome improvements

Open questions: scientific

Internal guidelines for each center to define patient's adherence

Prospective studies as tools of patient's toxicity/adherence evaluation, mHealth

Need of ***prospective, observational/interventional studies*** about adequate supportive care

Discussion

Difficult to Swallow: Issues Affecting Optimal Adherence to Oral Anticancer Agents

Winson Y. Cheung, MD, MPH

OVERVIEW

The number of anticancer drugs currently available in oral formulation has increased dramatically over the past 15 to 20 years, especially with the recent development of new hormonal and targeted therapies.[1,2] At present, approximately 25% of all cancer drugs are available in oral formulation, with numbers expected to increase exponentially in the coming years.[1,3,4] The convenience associated with the self-administration of oral therapy, the requirement of fewer trips to the physician's office, and the lack of infusion reactions are all benefits for patients, allowing them to potentially maintain their relative independence while undergoing active anticancer treatment. On the other hand, there are growing concerns regarding patients' poor adherence to oral therapy as well as the challenges of monitoring patient compliance when treatment administration does not occur in the presence of health care professional (HCPs). More importantly, poor adherence to proven therapies may detrimentally affect the patients' clinical outcomes, such as survival. Thus, there is an urgent need to identify more effective strategies to measure and monitor adherence to oral anticancer agents in an effort to maximize their therapeutic benefits.

ASCO 2013

Open questions: managerial

Need of organizative models to better follow patients during anticancer Tx (***Supportive Care Units***)

Effectiveness of these models not only in Cancer referral centers but also in Secondary and Tertiary Hospitals

Open questions: managerial

Opportunity to improve adherence to Tx and reduce costs for toxicities and drug-non assumption, giving the chance to create a ***"Sustainable Model of Care***" (cost savings for complications and investment for new high cost drugs)

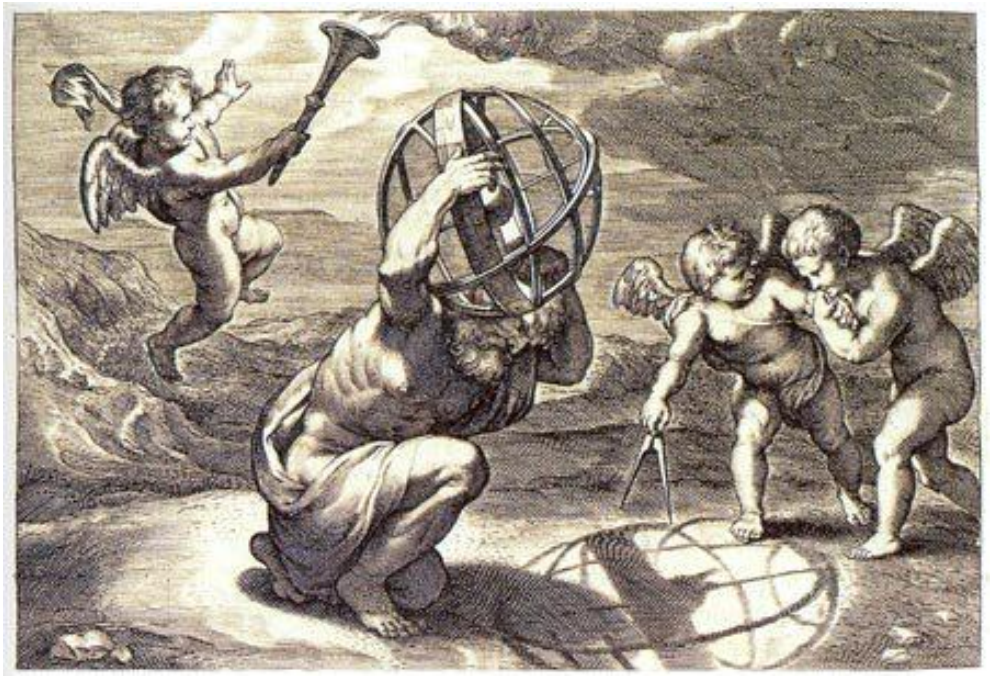
Scientific's Society warranty (ESMO, MASCC, ASCO,….)

Dedicated working groups

Discussion

Increasing the effectiveness of
ADHERENCE INTERVENTIONS
may have a far ***greater impact on the health*** *of the population* ***than any improvement in specific medical treatments.***

Thank you for your attention



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