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Evaluating Drug Utilization and Quality

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Outline

- ▶ Adherence and persistence
- ▶ Off-label use
- ▶ Explicit quality indicators
- ▶ Implicit quality indicators
- ▶ Methods to improve pharmacotherapy



Adherence and Persistence

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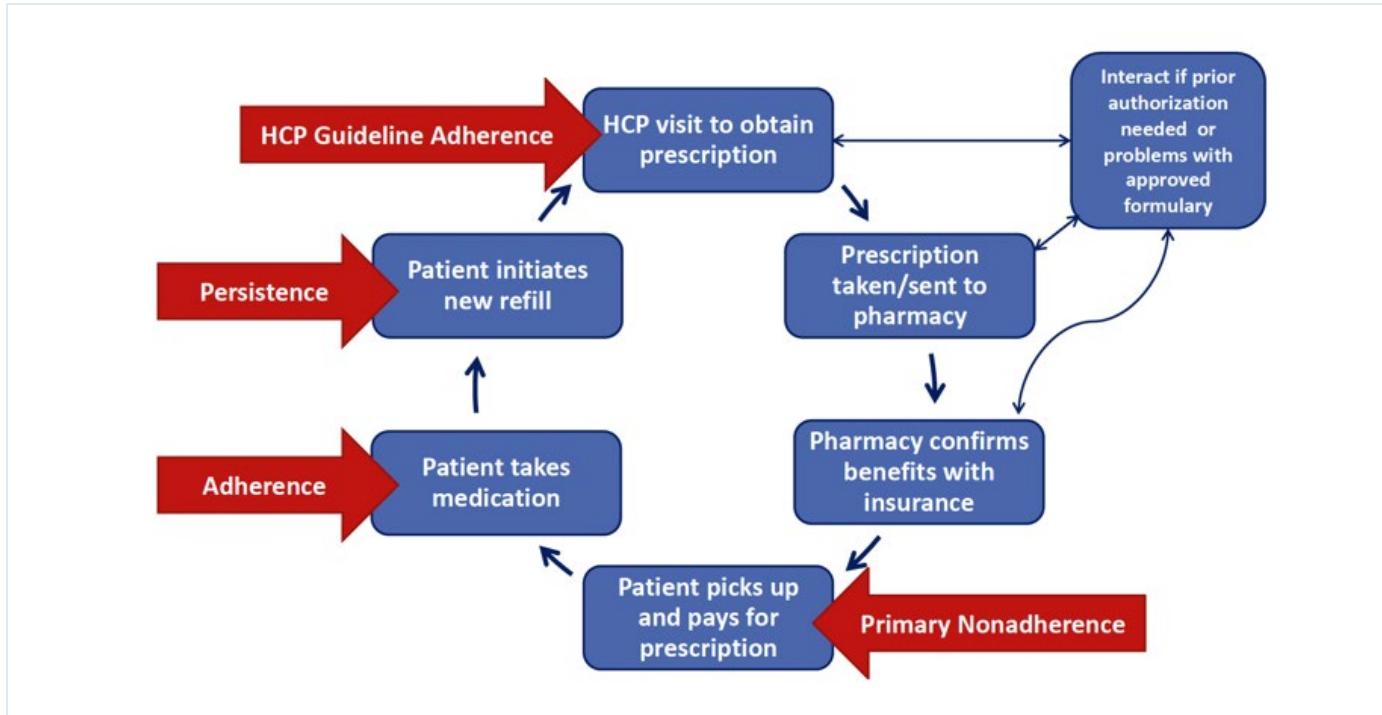
Definitions

- ▶ Adherence: “the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen”

- ▶ Persistence: “the duration of time from initiation to discontinuation of therapy”



Process of Adherence and Persistence



Nonadherence Is Common

- ▶ Average rate of nonadherence among individuals with chronic conditions is an alarming 50% in developed countries such as the US (World Health Organization)
- ▶ Primary nonadherence, in which patient never fills first drug for a prescribed medication, varies across settings and drug classes but can be as high as 25%—in one meta-analysis of 24 articles examining hypoglycemics, anti-hypertensives, lipid-lowering, and antidepressant agents, primary nonadherence was ~15% based on pooled estimate
- ▶ There are many drivers to nonadherence—cost is one important one. Historically, approximately a third of US adults have reported cost-related nonadherence during previous year.

Sources: Chisholm-Burns, M. A., & Spivey, C. A. (2012). The 'cost' of medication nonadherence: consequences we cannot afford to accept. *Journal of the American Pharmacists Association: JAPhA*, 52(6), 823–826. <https://doi.org/10.1331/JAPhA.2012.11088>; Lemstra, M., Nwankwo, C., Bird, Y., & Moraros, J. (2018). Primary nonadherence to chronic disease medications: a meta-analysis. *Patient Preference and Adherence*, 12, 721–731. <https://doi.org/10.2147/PPA.S161151>

There Are Many Ways to Measure Adherence

- ▶ Clinical judgment
- ▶ Self-report
 - ▶ Clinical interview, questionnaire, diary
- ▶ Medication measurement
 - ▶ Pill count, canister weighing
- ▶ Pharmacy refills
- ▶ Electronic monitors
- ▶ Biochemical measures
 - ▶ Assays of drug levels in blood, saliva, urine

Medication Possession Ratio and Other Measures

- ▶ Many pharmacoepidemiology studies use medication possession ratio (MPR) to characterize adherence
- ▶ The MPR is equal to the ratio of the sum of days covered [in a given period] divided by the sum of days (in that same period) × 100
- ▶ Proportion of days covered is similar but does take into account “stockpiling”
- ▶ Typically, windows used are based on continuous use (persistence), requiring gaps that do not exceed certain thresholds, such as 90 days
- ▶ Arbitrary threshold of 80% often used to classify individuals as adherent or not
- ▶ These and other proportionality measures may overstate level of adherence—just consider pills that you have filled but have not taken, sitting in your house

Types of Electronic Adherence Monitors

Types of Electronic Monitors



CPAP



AdhereTech



Propeller Health



i-Neb

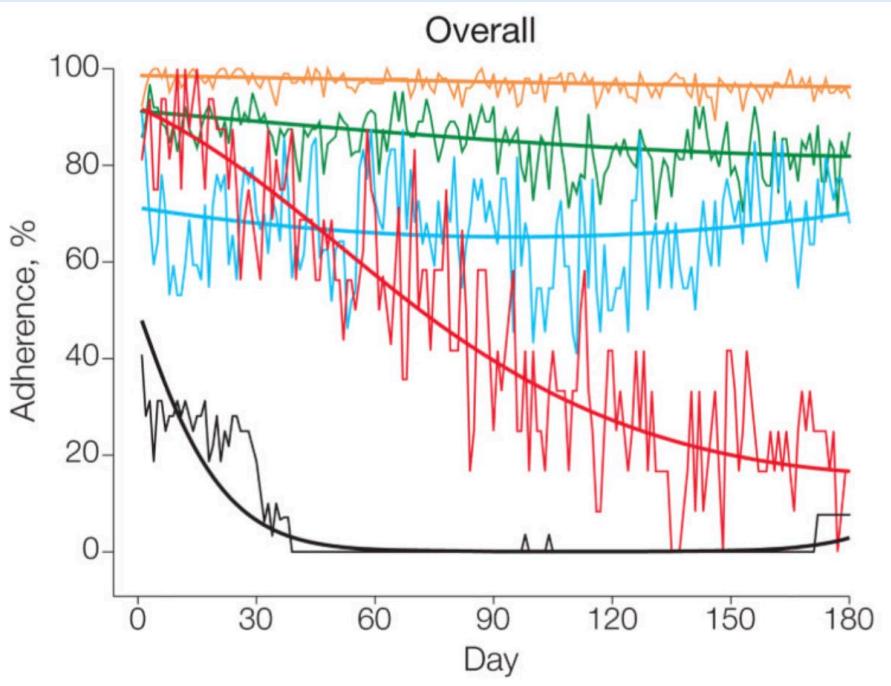


Medminder



Blood Glucose Meters

Adherence Trajectories Reveal Markedly Different Phenotypes



- Near-perfect adherence
- Mild nonadherence
- Moderate nonadherence
- Severe delayed nonadherence
- Severe early nonadherence

Source: Modi, A. C., Rausch, J. R., & Glauser, T. A. (2011). Figure. Six-month adherence trajectories of children with new-onset epilepsy [Graph]. In Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA*, 305(16), 1669–1676. <https://doi.org/10.1001/jama.2011.506>

Many Factors Contribute to Adherence and Persistence

Condition-related factors (n=55)

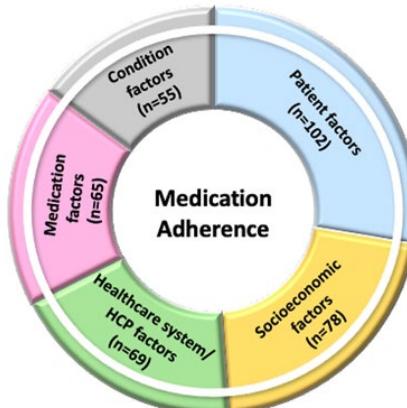
- Disease control (i.e., symptoms, complications, severity, acute events/ deterioration, impact on lifestyle)
- Disease characteristics (i.e., cognitive deficit, symptom bother, consequence)
- Patient specific (i.e., comorbidities, time since diagnosis, declining health)

Medication-related factors (n=65)

- Medication regimen (i.e., complexity, dosage, type, pill burden, interference in routine, clarity of instructions on label, regimen familiarity)
- Medication effects (i.e., side effects, safety, efficacy, benefits, patient experience)
- Medication properties (i.e., cost, physical properties, formulation)

Health care system/Health care provider (HCP)-related factors (n=69)

- HCP characteristics (i.e., relationship, communication, trust in provider, clinical care, ability to relate, provision of training/follow-up, prescription practice, patient education)
- Health care system-related factors (i.e., access, provider continuity, cost, drug supply, regulation processes, quality of health services, information support, insurance coverage)



Patient-related factors (n=102)

- Cognitive and psychological factors (i.e., perceptions, beliefs, concerns, knowledge/health literacy, emotions, motivation/goals)
- Behavioral factors (i.e., organization, planning, lifestyle)
- Priorities (i.e., quality of life, other competitive needs)
- Nonmodifiable characteristics (i.e., demographics, experience, type of user, physical factors)
- Family/caregiver characteristics (i.e., hesitancy, support, relationship)

Socioeconomic factors (n=78)

- Social/environmental factors (i.e., social context, interaction, support, culture, language, stigma, norms, external influences, sociodemographic, promotional prompts, environment)
- Lifestyle factors (i.e., alcohol, drug use)
- Economic factors (i.e., income, education, occupation, living condition, insurance)

No Magic Bullets! Solutions Must Be Fit-for-Purpose

Adherence typologies



Unwitting: patient and provider mistakenly believe that the patient is adherent



Erratic: patient understands and agrees with therapy but has difficulty consistently maintaining regimen



“Intelligent”: patient deliberately alters or discontinues therapy



Off-Label Use

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A Black Box Warning

HALDOL®
brand of
haloperidol injection
(For Immediate Release)

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

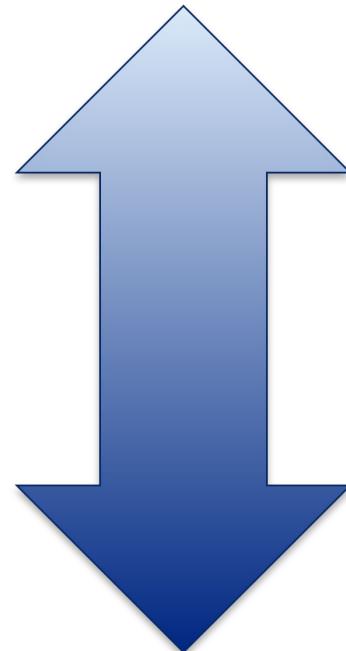
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. HALDOL Injection is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

What Is Off-label Use?

- ▶ Drugs are approved with a “label”
 - ▶ Stipulating dose, intended population, duration of use, other specifications
- ▶ Spectrum of off-label use
 - ▶ Guideline-recommended practice (e.g., aspirin in diabetes for prophylaxis against coronary artery disease)
 - ▶ First-line therapy (e.g., gabapentin [Neurontin] for painful diabetic neuropathy)
 - ▶ Last resort therapy (e.g., tacrolimus [Prograf] for autoimmune diseases)

A Continuum of Evidence

- ▶ Strong evidence support and promoted in guidelines
- ▶ Supported by trials, but with less evidence or rigor
- ▶ Promising trial evidence of benefit
- ▶ Anecdotal evidence of benefit
- ▶ Frank experimentation



Pathways to Off-label Use—1

- ▶ Unapproved clinical conditions
 - ▶ Example: antipsychotic agent quetiapine (Seroquel) prescribed for depression
- ▶ Unapproved subpopulations
 - ▶ Example: paroxetine (Paxil) for depression in children
- ▶ Extension to related conditions
 - ▶ Example: antiasthmatic montelukast (Singulair) for chronic obstructive pulmonary disease
- ▶ Expansion to distinct conditions sharing physiological link
 - ▶ Example: antidiabetic drug metformin to treat polycystic ovarian syndrome

Pathways to Off-label Use—2

- ▶ Presumed class effect
 - ▶ Example: ACE inhibitors for diabetic nephropathy
- ▶ Extension to milder forms of an approved indication
 - ▶ Example: paroxetine (Paxil) for dysthymia
- ▶ Extension to conditions whose symptoms overlap with those of an approved indication
 - ▶ Example: antipsychotics for delirium

Advantages and Disadvantages of Off-label Use

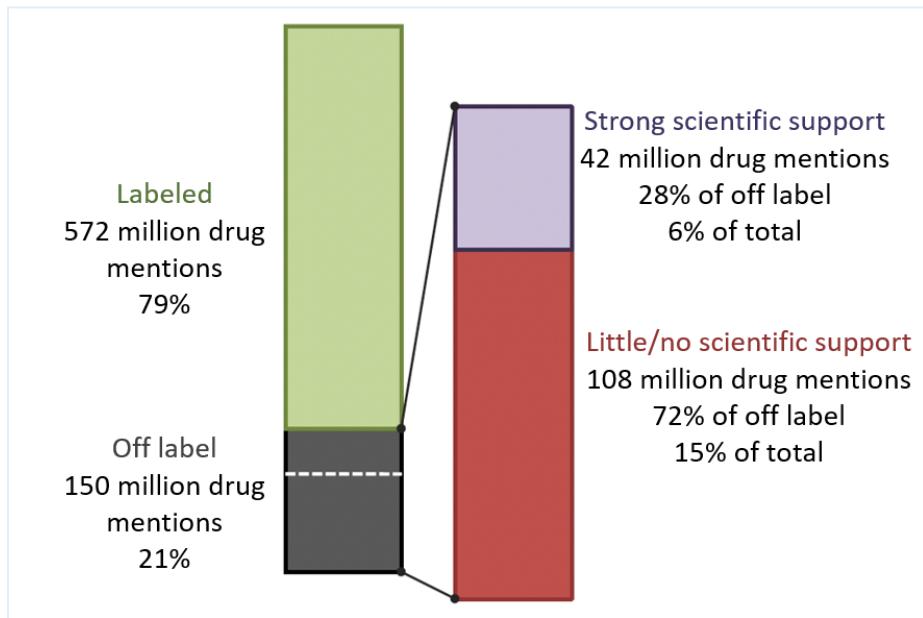


Drugs Commonly Prescribed Off-label

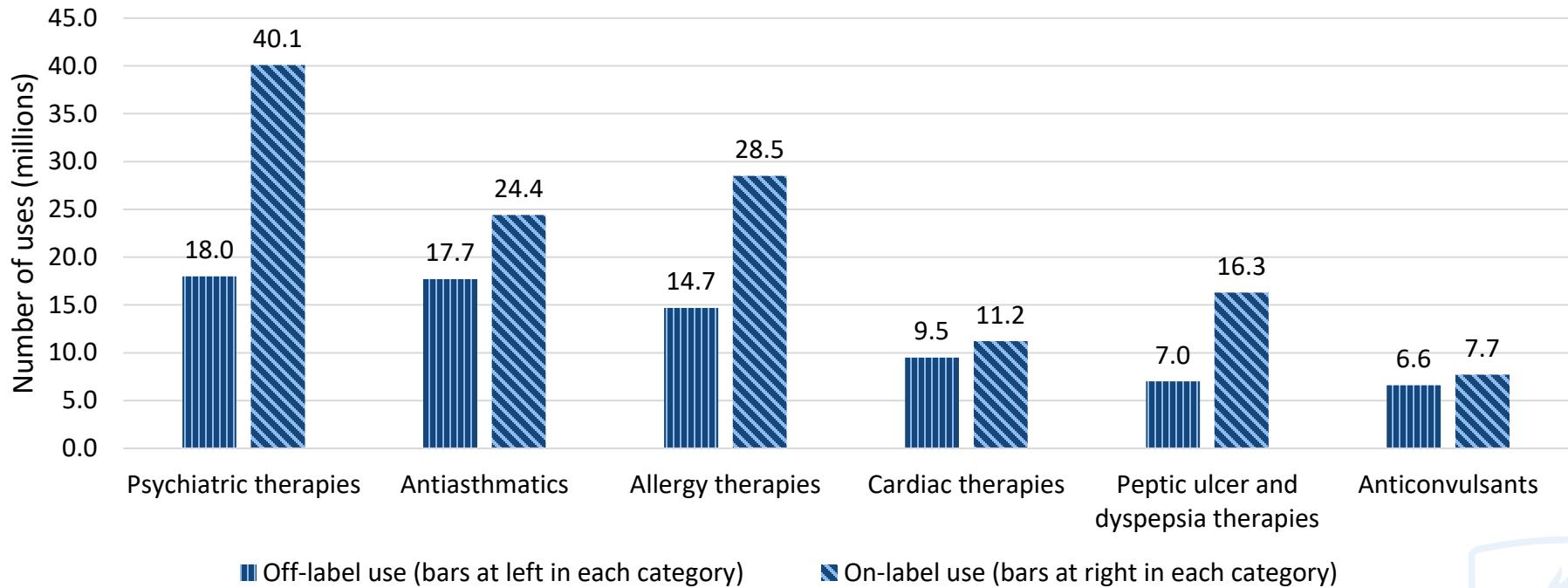
Class of drug	Examples of off-label use
Anti-seizure drugs	Migraines, depression, nerve pain
Antipsychotics (for schizophrenia)	Alzheimer's disease, autism, dementia, ADHD
Antidepressants	Chronic pain, ADHD, bipolar disorder
Antihistamines (for allergies)	Colds, asthma, ear infection symptoms, sleep aid
Antibiotics	Viral infections (i.e., common cold and flu)
Beta-blockers (for hypertension and heart disease)	Migraines, heart rhythm disorders, anxiety
Drugs to treat attention deficit hyperactivity disorder (ADHD)	For people not diagnosed with ADHD, to enhance alertness and concentration
Narcotic pain relievers	For people with only mild, infrequent pain

Prevalence of Off-label Use in the US

- ▶ 722 million total drug uses
- ▶ 572 million labeled (79%)
- ▶ 150 million off-label (21%)
- ▶ Off-label uses:
 - ▶ 42 million with strong scientific support (28%)
 - ▶ 108 million with uncertain or inadequate scientific support (72%)
- ▶ Off-label use exceeded 50% for 10% of medications (16 of 160)



Estimated Number of Prescriptions for On-Label and Off-Label Uses of Medications in Various Functional Classes, 2001



Number of Drug Uses, by Off-Label Status and Level of Supporting Evidence, July 2005 Through June 2007

Rank	Generic Name	DRUG USES IN THOUSANDS		
		On-Label	Total Off-Label	Off Label Inadequate Evidence
1	quetiapine	2120	6507	6507
2	warfarin	13000	5325	5325
3	clonazepam	1297	4235	4235
4	escitalopram	21376	3580	3580
5	gabapentin	446	6334	2827
6	promethazine	208	2732	2732
7	risperidone	2366	4034	2569
8	digoxin	4701	2561	2561
9	lorazepam	3841	2490	2490
10	lisinopril	32140	2601	2374
11	prednisilone	6024	2359	2359
12	trazodone	2858	2166	2166
13	zolpidem	5114	2085	2085
14	sertraline	16617	2071	2071
15	bupropion	12196	1929	1929
16	acet/tramadol	2925	1802	1802
17	dexamethasone	784	2455	1652
18	metronidazole	2644	1648	1648
19	amitriptyline	848	1918	1540
20	albuterol	11749	8373	1492

Source: Walton, S. M., Schumock, G. T., Lee, K. V., Alexander, G. C., Meltzer, D., & Stafford, R. S. (2008). Top 25 drugs by number of uses off-label with inadequate evidence [Table]. In Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy*, 28(12), 1443–1452. <https://doi.org/10.1592/phco.28.12.1443>

Physician Knowledge of Off-Label Use

Drug	Indication	Level of evidence	Field	Percent MDs using drug	Percent reporting drug FDA-approved
Valproic acid (Depakote®) Fluticasone (Flovent®)	Bipolar, mania Asthma	On label	All PCP	64 76	81 95
Escitalopram (Lexapro®) Lisinopril (Zestril®) Donepezil (Aricept®)	Panic disorder Proteinuria MCI	Off-label, strong evidence	All PCP Psych	61 75 38	43 36 51
Gabapentin (Neurontin®) Atorvastatin (Lipitor®) Haloperidol (Haldol®)	DM neuropathy PWD Delirium	Off-label, some evidence	All PCP Psych	53 38 38	52 29 23
Trazodone (Desyrel®) Bupropion (Wellbutrin®)	Insomnia Adult ADHD	Off-label, inconclusive	All Psych	79 61	11 15
Venlafaxine (Effexor®) Quetiapine (Seroquel®) Lorazepam	Adjustment disorder Agitated dementia Chronic anxiety	Off-label, not listed in DrugDex	All All Psych	25 42 72	17 19 33
Budesonide (Pulmicort®) Paroxetine (Paxil®)	COPD Bipolar, depression	Off-label, ineffective	PCP Psych	42 38	51 25

PCP: primary care physician; MD: medical doctor; MCI: mild cognitive impairment; DM: diabetes mellitus; PVD: peripheral arterial disease; ADHD: attention-deficit/hyperactivity disorder;

COPD: chronic obstructive pulmonary disease

Source: Chen, D. T., Wynia, M. K., Moloney, R. M., & Alexander, G. C. (2009). U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidemiology and drug safety*, 18(11), 1094–1100. <https://doi.org/10.1002/pds.1825>

FDA Policy on Off-label Use

- ▶ FDA focuses on market entry for drugs with indication specific approvals
- ▶ Recognizes off-label use may represent standard of care
- ▶ Physicians may legally prescribe off-label according to best knowledge and judgment
- ▶ Yet attempt to limit off-label prescribing
 - ▶ No advertising for off-label purpose
 - ▶ No physician detailing for off-label use
 - ▶ Limited distribution of written materials promoting off-label use
 - ▶ Risk evaluation and mitigation strategies (REMS) and other risk mitigation strategies may target off-label use

Policy Strategies to Improve Off-label Use

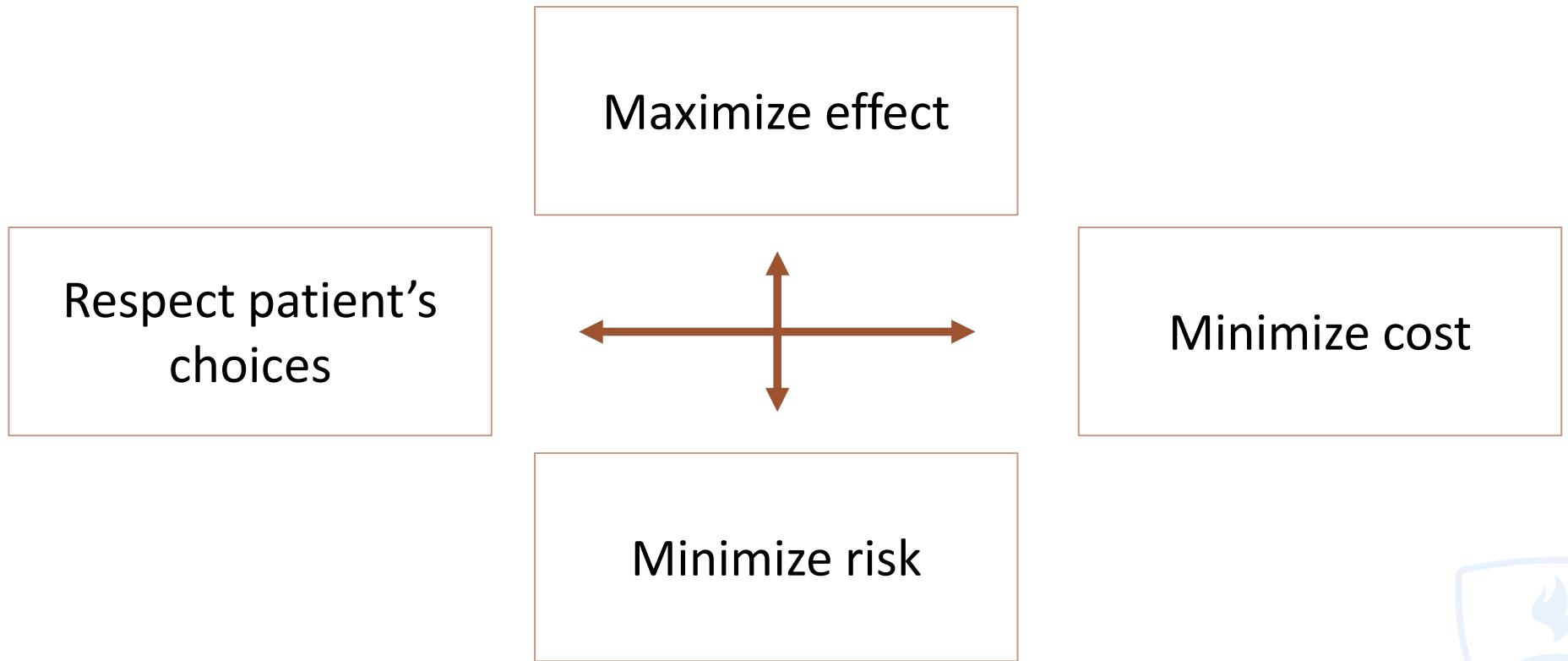
- ▶ Are there systematic policies that could improve off-label use?
- ▶ Need for FDA to play an expanded role in concert with other organizations?
- ▶ For example, could FDA ...
 - ▶ Help payers determine what products are unproven and how they compare?
 - ▶ Bolster physician autonomy through objective synthesis of evolving evidence?
 - ▶ Carefully allow market expansion based on clinical motives, not profitability?
 - ▶ Provide more solid reassurance about drug safety and efficacy while resetting unrealistic public expectations?



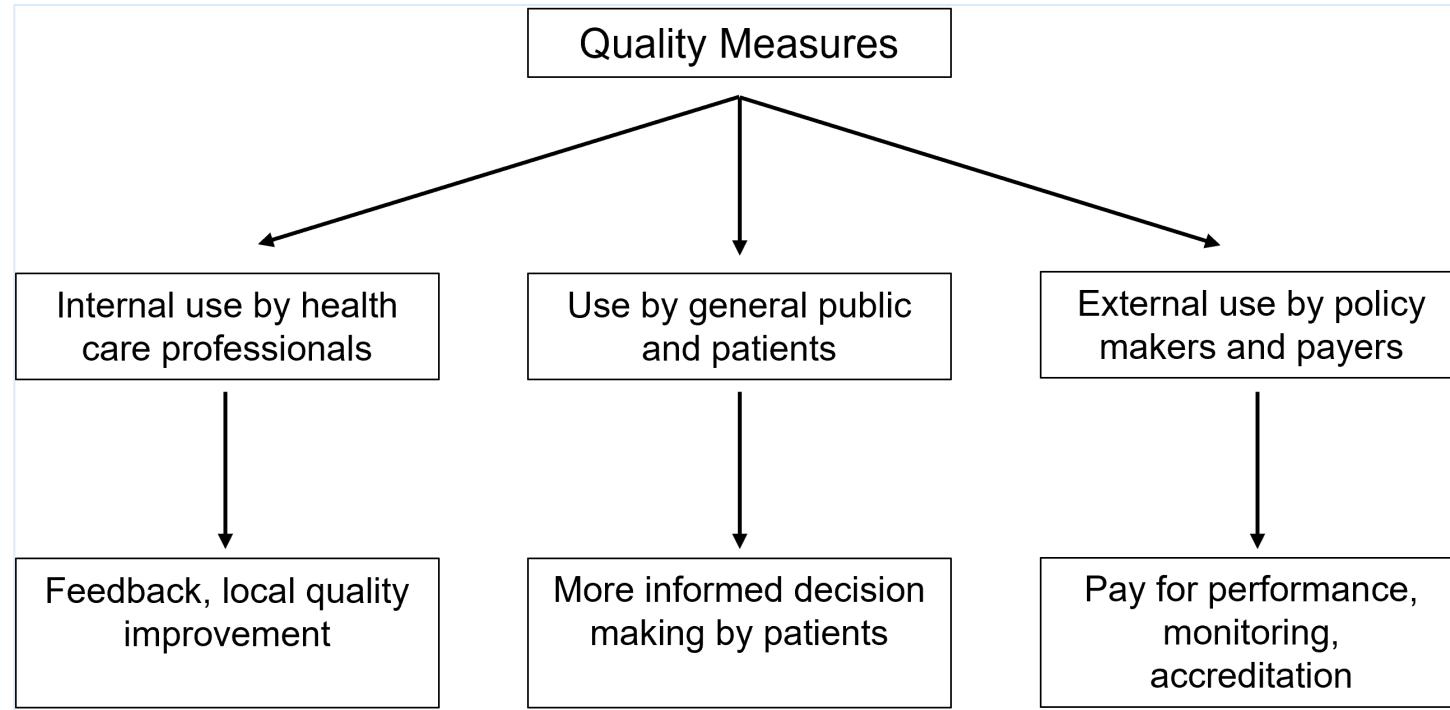
Explicit Quality Indicators

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What Is the Goal of Prescribing?



Who Needs Information About Prescribing Quality?



Quality From Perspective of Risk/Benefit Balance

- ▶ Overuse
 - ▶ Antibiotics for upper respiratory infection
 - ▶ Opioids for chronic pain
- ▶ Underuse
 - ▶ Statins for cardiovascular disease
 - ▶ Bisphosphonates for osteoporosis
- ▶ Misuse, such as suboptimal selection, dosing, duration, monitoring, follow-up
 - ▶ Warfarin for first episode of deep vein thrombosis
 - ▶ Antidepressants for major depressive disorder

What Is Quality of US Pharmacologic Care?

- ▶ Large gaps in quality of US pharmacologic care, affecting diverse populations across health care settings
- ▶ Ambulatory medication errors common, especially prescribing and dosing errors, accompanying as many as 23%–92% of prescribed drugs (Naseralallah et al., 2023)
- ▶ Elderly vulnerable to a variety of medication-related problems, including underuse, overuse, and polypharmacy (Vyas et al., 2019)

TABLE 3. Adherence to Pharmacologic Quality of Care Indicators

Pharmacologic Quality Domain	No. Eligible Patients	Frequency of Eligible Indicators*	Percentage of Recommended Care Received [†]	95% Confidence Interval
Total (aggregate)	3457	10,739	61.9	60.3–63.5
Underuse of appropriate medications	2477	5242	62.6	60.7–64.6
Overuse of inappropriate medication	1292	2004	83.5	81.1–85.9
Medication monitoring	642	983	54.7	49.7–59.7
Education and documentation	1453	2510	46.2	42.9–49.5

*Indicator-patient pairs.

[†]Scores represent percentage of appropriate care received for each category (eg, higher scores always suggest higher quality care in each of the categories presented).

Sources: Naseralallah, L., et al. (2023). *International Journal of Clinical Pharmacy*, 45(6), 1359–1377. <https://doi.org/10.1007/s11096-023-01626-5>; Vyas, A., et al. (2019). *Drugs - Real World Outcomes*, 6(4), 173–181. <https://doi.org/10.1007/s40801-019-00162-x>; Shrank, W. H., et al. (2006). Table 3. Adherence to pharmacologic quality of care indicators. In The quality of pharmacologic care for adults in the United States. *Medical Care*, 44(10), 936–945. <https://doi.org/10.1097/01.mlr.0000223460.60033.79>

Example: Quality of Care for Depression

TABLE 4. Quality Performance in Asthma and Depression

Mode	Disease	Indicator	No. Eligible	No. Eligible Events	Mean Score
Underprescribing	Depression	Once diagnosis of major depression has been made, treatment with anti-depressant medication and/or psychotherapy should begin within 2 weeks	261	242	81.41
Underprescribing	Depression	Antidepressants should be prescribed at appropriate dosages.	219	203	81.57
Underprescribing	Depression	Patients with major depression who have medical record documentation of improvement of symptoms within 6 wk of starting antidepressant treatment should be continued on an antidepressant for at least 4 additional months	219	203	41.2
Overprescribing	Depression	Anti-anxiety agents should not be prescribed as a sole agent for the treatment of depression	227	204	96.84
Education and documentation	Depression	If the diagnosis of depression is made, medication use should be documented	261	252	59.03
Education and documentation	Depression	Medication treatment visits or telephone contacts should occur at least once in the 2 weeks after initial diagnosis	218	201	25.77
Monitoring	Depression	At each visit during which depression is discussed, degree of response/remission and side effects of medication should be assessed and documented during the first year of treatment	61	59	54.16

Source: Shrank, W. H., et al. (2006). Table 4. Quality performance in asthma and depression. In The quality of pharmacologic care for adults in the United States. *Medical Care*, 44(10), 936–945.
<https://doi.org/10.1097/01.mlr.0000223460.60033.79>

What Are Prescribing Indicators?

- ▶ A measurable element of prescribing for which there is evidence or consensus that it can be used to assess the quality of care provided (EuroDRUG Quality Indicator Meeting, 2004)
- ▶ Implicit versus explicit indicators
 - ▶ Implicit—subjective criteria requiring application of expert judgment
 - ▶ Explicit—clearly defined and quantifiable measures
- ▶ Types of explicit indicators
 - ▶ Drug-oriented
 - ▶ Disease-oriented
 - ▶ Disease-event oriented (sequential)

Examples of Explicit Prescribing Indicators

- ▶ Prescribing of drugs of limited value or potentially inappropriate drugs (e.g., Beers Criteria, 1991)
- ▶ Range of drugs prescribed, e.g., drug utilization 90%: number of drugs accounting for 90% of the use in defined daily doses (e.g., Bergman, 1998)
- ▶ Generic and/or low-cost prescribing; prescribing of preferred drug within therapeutic class (e.g., Avery, 1998)
- ▶ Polypharmacy as indicator of potential problems

Sources: Bergman, U., Popa, C., Tomson, Y., Wettermark, B., Einarson, T. R., Aberg, H., & Sjöqvist, F. (1998). Drug utilization 90%—a simple method for assessing the quality of drug prescribing. *European Journal of Clinical Pharmacology*, 54(2), 113–118. <https://doi.org/10.1007/s002280050431>; Avery, A. J., Heron, T., Lloyd, D., Harris, C. M., & Roberts, D. (1998). Investigating relationships between a range of potential indicators of general practice prescribing: an observational study. *Journal of Clinical Pharmacy and Therapeutics*, 23(6), 441–450. <https://doi.org/10.1046/j.1365-2710.1998.00187.x>

The Beers Criteria

Drug name or class	Statement
Sedative-hypnotics	
Long-acting benzodiazepines: chlordiazepoxide, diazepam, flurazepam	All use should be avoided; use short-acting benzodiazepines if needed
Meprobamate	All use should be avoided, except in those already addicted
Oxazepam	Any single dose >30 mg should be avoided
Short-acting benzodiazepines: oxazepam, triazolam, alprazolam	Nightly use for >4 weeks should be avoided
Short-duration barbiturates: pentobarbital, secobarbital	All use should be avoided, except in those already addicted; safer sedative-hypnotics are available
Triazolam	Any single dose >0.25 mg should be avoided
Antidepressants	
Amitriptyline	All use should be avoided; use less anticholinergic antidepressant if needed
Combination antidepressants- antipsychotics, e.g., amitriptyline- perphenazine (Triavil)	All use should be avoided; if needed, prescribe individual components at proper geriatric doses; avoid amitriptyline
Antipsychotics	
Haloperidol	Doses >3 mg/d should be avoided; patients with known psychotic disorders may require higher doses
Thioridazine	Doses >30 mg/d should be avoided; patients with known psychotic disorders may require higher doses
Antihypertensives	
Hydrochlorothiazide	Doses >50 mg/d should be avoided
Methyldopa	All use should be avoided; safer antihypertensives are available
Propranolol	All use should be avoided, except if used to control violent behaviors; other beta-blockers offer less central nervous system penetration or more beta selectivity
Reserpine	All use should be avoided; safer antihypertensives are available
Nonsteroidal anti-inflammatory drugs (NSAIDs)	
Indomethacin	All use should be avoided; other NSAIDs cause less central nervous system toxic reaction
Phenylbutazone	All use should be avoided; other NSAIDs are less toxic

Source: Beers, M. H., Ouslander, J. G., Rollingher, I., Reuben, D. B., Brooks, J., & Beck, J. C. (1991). Table 3. Criteria for inappropriate use. In Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Archives of Internal Medicine*, 151(9), 1825–1832.
<https://doi.org/10.1001/archinte.1991.00400090107019>

Statements on Which Panelists Could Not Reach Consensus

- ▶ Antipsychotic medications, such as haloperidol and thioridazine, should be avoided in nonpsychotic persons
- ▶ Diphenhydramine (Benadryl) should generally not be used as a hypnotic agent
- ▶ Cimetidine is less safe than ranitidine
- ▶ All fixed combination drugs should be avoided
- ▶ When thiazide diuretics are prescribed, chlorthalidone should be avoided
- ▶ Disopyramide (Norpace) should be avoided
- ▶ When treating congestive heart failure, a maximum dose of digoxin can be established, above which therapy is inappropriate
- ▶ Ergoloid mesylates (Hydergine) should be avoided

START and STOPP Criteria

- ▶ Explicit criteria for medication review in multi-morbid older people in most clinical settings
 - ▶ Formed in 2010 by a panel of doctors, pharmacists, pharmacologists, and primary care physicians with expertise in geriatric medicine and pharmacotherapy
- ▶ 80 STOPP and 34 START criteria grouped by physiological system (e.g., cardiovascular system, central nervous system)
- ▶ **Screening Tool to Alert to Right Treatment (START)**
 - ▶ Focuses on under-prescription, ensuring necessary medications are prescribed to prevent disease progression and improve quality of life
- ▶ **Screening Tool of Older People's Prescriptions (STOPP)**
 - ▶ Focuses on over-prescription and inappropriate use, aiming to reduce the risks associated with polypharmacy and adverse drug reactions

Drug-Oriented Prescription Quality Indicators

- ▶ Prescription level
 - ▶ Overprescribing, avoidance of inappropriate drugs
 - Percentage of long-acting sulfonylurea-derivatives/all sulfonylurea-derivatives
 - ▶ First-choice drugs
 - Percentage of simvastatin/all statins
 - ▶ Dose or duration
 - Percentage of high-dosed hydrochlorothiazide/all hydrochlorothiazide
 - Percentage of once daily dosing antihypertensive/all antihypertensives
- ▶ Patient level
 - ▶ Comedication use
 - Duplicate: percent of patients with multiple thiazides
 - Safety: percent of ACE + NSAID + diuretic
 - ▶ Stepwise prescribing
 - Percentage of starting on metformin/all oral glucose regulating starts
 - Percentage of all ACE or ARBs that are ACEs

Disease-Oriented Prescription Quality Indicators

- ▶ Under-prescribing
 - ▶ Percentage of patients with diabetes prescribed statins
 - ▶ Percentage of patients with diabetes and albuminuria prescribed ACE-inhibitors
- ▶ First-choice treatments
 - ▶ Percentage of patients with diabetes and who are overweight prescribed metformin as first step
- ▶ Safety
 - ▶ Percentage of patients with diabetes and heart failure prescribed thiazolidinediones

Classification of Indicators Linked to Measurement Level

- ▶ Drug-oriented indicators (cross-sectional)
 - ▶ Medication irrespective of the indication, e.g., first-choice drugs, costs, dosing
- ▶ Disease-oriented indicators (cross-sectional)
 - ▶ Medication in relation to disease, e.g., over/undertreatment
- ▶ Disease- and patient-oriented indicators (cross-sectional)
 - ▶ Medication (not) prescribed for specific subpopulations, e.g., elderly, using comedication, having contraindications
- ▶ Disease- and event-oriented indicators (sequential)
 - ▶ Timely action: medication modified after indication, e.g., after specific event or uncontrolled risk factor level

Criteria for Quality Indicators

- ▶ The validity of indicators also must be assessed
 - ▶ Face validity
 - ▶ Content validity
 - ▶ Concurrent validity
 - ▶ Predictive validity
- ▶ Operational feasibility, reliability, and fairness also have to be considered
- ▶ Other factors also important to assess
 - Risk of spotlight effects or other unintended consequences (e.g., overuse, gaming)



Implicit Quality Indicators

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Criteria for Quality Indicators

- ▶ Implicit detailed assessment (record review)
 - ▶ Medication appropriateness index (MAI) per drug focused on pharmacologic aspects (Hanlon, 1992)
 - ▶ Prescribing appropriateness indicator (PAI) on documented agreement with formulary recommendations such as indication and dose (Cantrill, 1998)

The Medication Appropriateness Index

Table 1. Medication Appropriateness Index*

To assess the appropriateness of the drug, please answer the following questions and circle the applicable score:				
1. Is there an indication for the drug? Comments:	1 Indicated	2	3	9 DK†
2. Is the medication effective for the condition? Comments:	1 Effective	2	3	9 DK
3. Is the dosage correct? Comments:	1 Correct	2	3	9 DK
4. Are the directions correct? Comments:	1 Correct	2	3	9 DK
5. Are the directions practical? Comments:	1 Practical	2	3	9 DK
6. Are there clinically significant drug-drug interactions? Comments:	1 Insignificant	2	3	9 DK
7. Are there clinically significant drug-disease/condition interactions? Comments:	1 Insignificant	2	3	9 DK
8. Is there unnecessary duplication with other drug(s)? Comments:	1 Necessary	2	3	9 DK
9. Is the duration of therapy acceptable? Comments:	1 Acceptable	2	3	9 DK
10. Is this drug the least expensive alternative compared to others of equal utility? Comments:	1 Least expensive	2	3	9 DK
Most expensive				

*Complete instructions in the use of the scale are available upon request.

†Don't know.

Source: Hanlon, J. T., Schmader, K. E., Samsa, G. P., Weinberger, M., Uttech, K. M., Lewis, I. K., Cohen, H. J., & Feussner, J. R. (1992). A method for assessing drug therapy appropriateness. *Journal of Clinical Epidemiology*, 45(10), 1045–1051. [https://doi.org/10.1016/0895-4356\(92\)90144-c](https://doi.org/10.1016/0895-4356(92)90144-c)

The Medication Appropriateness Index (MAI): Thirty Years Later

- ▶ While there are multiple explicit measures of quality, we have few implicit measures other than the MAI and PAI—explicit measures don't address effectiveness, directions, therapeutic duplication, or cost
- ▶ MAI has good inter- and intra-rater reliability—typically 0.8 to 0.9
- ▶ Content and predictive validity have also been assessed
 - ▶ “One study determined the prevalence of PIPs according to Beers, STOPP, FORTA (Fit fOR The Aged), and MAI criteria ... PIPs were present in 53.1%, 55.7%, 44.3%, and 74% of patients according to Beers, STOPP, FORTA, and MAI criteria, respectively.”
- ▶ Responsiveness to change in clinical trials has also been demonstrated—most trials have focused on pharmacist-led interventions among older adults in ambulatory practice

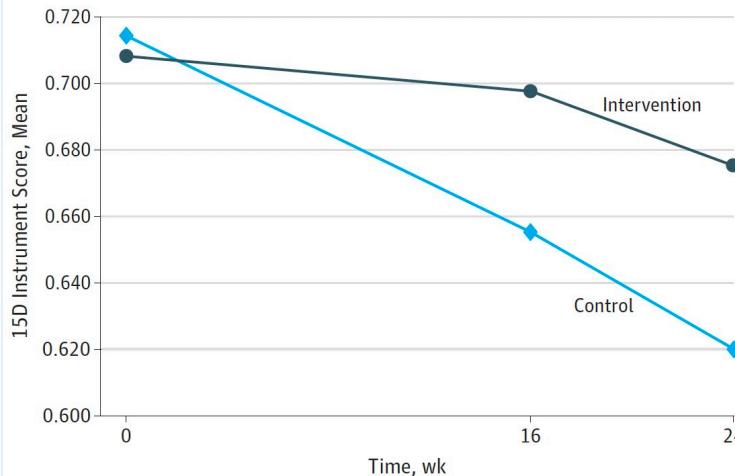
The Prescribing Appropriateness Indicator (PAI)

1. The indication for the drug is recorded and upheld in the British National Formulary (BNF)
2. The reason for prescribing a drug of limited value is recorded and valid
3. Compared with alternative treatments in the same therapeutic class, which are just as safe and effective, the drug prescribed is either one of the cheapest or a valid reason is given for using an alternative
4. A generic product is prescribed if one is available
5. If a potentially hazardous drug-drug combination is prescribed, the prescriber shows knowledge of the hazard
6. If the total daily dose is outside the range stated in the BNF, the prescriber gives a valid reason
7. If the dosing frequency is outside the range stated in the BNF, the prescriber gives a valid reason
8. If the duration of treatment is outside the ranges stated in the BNF, the prescriber gives a valid reason
9. Prescribing for hypertension adheres to the evidence-based guidelines in the BNF

The Impact of Clinical Geriatric Assessments

JAMA Internal Medicine | Original Investigation
Effect of Clinical Geriatric Assessments and Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Home-Dwelling Older Patients Receiving Polypharmacy A Cluster Randomized Clinical Trial

Figure 2. Primary Outcome of Health-Related Quality of Life as Measured by the 15D Instrument



Shown are mean (SD) 15D instrument scores at baseline, week 16, and week 24. The score range is 0 to 1, with higher scores indicating better quality of life.

Source: Romskaug, R., Skovlund, E., Straand, J., Molden, E., Kersten, H., Pitkala, K. H., Lundqvist, C., & Wyller, T. B. (2020). Effect of clinical geriatric assessments and collaborative medication reviews by geriatrician and family physician for improving health-related quality of life in home-dwelling older patients receiving polypharmacy: A cluster randomized clinical trial. *JAMA Internal Medicine*, 180(2), 181–189. <https://doi.org/10.1001/jamainternmed.2019.5096>

Conclusions and relevance:
This study's findings indicate that, among older patients exposed to polypharmacy, clinical geriatric assessments, and collaborative medication reviews carried out by a geriatrician in cooperation with the patient's family physician can result in positive effects on health-related quality of life.



Methods to Improve Pharmacotherapy

Produced by the Center for Teaching and Learning at the Johns Hopkins Bloomberg School of Public Health.

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Examples of Methods to Improve Pharmacotherapy

- ▶ Value-based insurance designs
- ▶ Audit and feedback
- ▶ Patient education
- ▶ Medication therapy management

Value-Based Insurance Designs

- ▶ Standard economic theory uses cost sharing to allocate medical services, contain costs
- ▶ Presumes consumers will use only services whose benefit exceeds cost to them
- ▶ Increasing costs at point of service—moral hazard can be reduced, value increased
- ▶ Optimal cost sharing reflects balance between risks of noninsurance against moral hazard costs—want to dissuade overuse while ensuring adequate access
- ▶ Prescription drugs, like other goods and services, have an elasticity of demand—basic concept describing how demand changes as a function of price
 - ▶ $PEoD = (\% \text{ change in quantity demanded}) / (\% \text{ change in price})$
 - ▶ What types of factors determine price elasticity?
 - ▶ What is price elasticity of demand for prescription drugs?



This Isn't Just Theory!

- ▶ Many investigations have examined effect of changes in coverage and reimbursement on changes in use
- ▶ Even modest copayments changes may lead to large changes in utilization
- ▶ Stronger studies: large samples, variation in benefit designs over people and time, strong controls for other potential explanatory factors
- ▶ Mixed evidence regarding whether elasticities greater for nonessential therapies

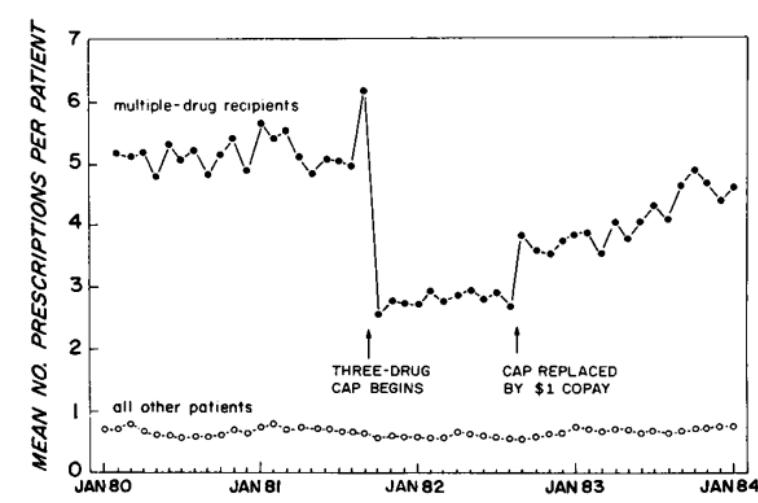


Figure 1. Time Series of Average Number of Constant-Size Prescriptions per Continuously Eligible Patient per Month among Noninstitutionalized Patients Receiving Multiple Drugs ($N = 860$) and Other Outpatients ($N = 8002$).
Patients with no prescriptions throughout the four-year period ($n = 1872$) were excluded from the denominator.

Sources: Goldman, D. P., Joyce, G. F., & Zheng, Y. (2007). Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA*, 298(1), 61–69. <https://doi.org/10.1001/jama.298.1.61>; Soumerai, S. B., Avorn, J., Ross-Degnan, D., & Gortmaker, S. (1987). Figure 1 [Graph]. In Payment restrictions for prescription drugs under Medicaid. Effects on therapy, cost, and equity. *The New England Journal Of Medicine*, 317(9), 550–556. <https://doi.org/10.1056/NEJM198708273170906>

Approaches to Value-Based Insurance Design

- ▶ Reduced or waived copayments
 - ▶ Reducing copays for high-value drugs (e.g., drugs for hypertension, diabetes, depression, high cholesterol) while maintaining tier
 - ▶ Agnostic to individuals—make safer/more effective drugs relatively cheaper
- ▶ Targeted incentives
 - ▶ Directed to specific **individuals** based on their diagnoses
 - ▶ Free statins for diabetics, free thiazides for those with hypertension, free beta-blockers for those with myocardial infarction
- ▶ Targeted health promotion and disease management
 - ▶ Includes a broad range of programs and interventions, such as evidence-based management of chronic conditions
 - ▶ These interventions seek to encourage participation of high-risk patients in health promotion to reduce health care costs

Challenges to Realizing Value-Based Insurance

- ▶ Need for sophisticated data systems
- ▶ Short-term increase in utilization and cost, difficulty of measuring outcomes and determining clinical and economic return on investment
- ▶ Dissatisfaction with differential copayments for same services, privacy issues
- ▶ Unintended incentives, adverse selection, potential for fraud

Full coverage for preventive medications after myocardial infarction

Table 2. Medication Adherence during Follow-up.*

Variable	Absolute Adherence†				P Value	Full Adherence‡			
	Full Prescription Coverage	Usual Prescription Coverage	Absolute Difference (95% CI)	percentage points		Full Prescription Coverage	Usual Prescription Coverage	Odds Ratio (95% CI)	P Value
All patients§									
ACE inhibitor or ARB	41.1±39.8	35.9±38.1	5.6 (3.4–7.7)	<0.001	789/2845 (27.7)	689/3010 (22.9)	1.31 (1.14–1.49)	<0.001	
Beta-blocker	49.3±37.5	45.0±36.6	4.4 (2.3–6.5)	<0.001	873/2845 (30.7)	758/3010 (25.2)	1.32 (1.16–1.49)	<0.001	
Statin	55.1±37.7	49.0±37.3	6.2 (3.9–8.5)	<0.001	1097/2845 (38.6)	950/3010 (31.6)	1.37 (1.20–1.56)	<0.001	
All three medication classes	43.9±33.7	38.9±32.7	5.4 (3.6–7.2)	<0.001	344/2845 (12.1)	268/3010 (8.9)	1.41 (1.18–1.67)	<0.001	
Patients who filled at least one prescription									
ACE inhibitor or ARB	66.5±29.6	60.8±30.7	5.8 (3.6–8.1)	<0.001	789/1759 (44.9)	689/1775 (38.8)	1.28 (1.10–1.49)	0.002	
Beta-blocker	65.0±28.9	61.0±28.9	4.0 (2.1–5.9)	<0.001	873/2159 (40.4)	758/2224 (34.1)	1.31 (1.14–1.50)	<0.001	
Statin	70.5±27.0	65.0±28.4	5.5 (3.6–7.5)	<0.001	1097/2223 (49.3)	950/2267 (41.9)	1.36 (1.18–1.56)	<0.001	
All three medication classes	67.4±15.5	62.9±26.3	4.5 (2.5–6.4)	<0.001	344/1385 (24.8)	268/1389 (19.3)	1.36 (1.12–1.65)	0.002	

* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† Absolute adherence was calculated with the use of a medication possession ratio (i.e., the number of days for which patients had a supply of each medication class available divided by the number of days they were eligible for that medication). Ratios were multiplied by 100 to generate absolute adherence percentages. Values are for mean medication possession.

‡ Full adherence was defined as having a supply of medications available on at least 80% of days during follow-up. Patients who did not fill a particular prescription after randomization were considered to be nonadherent.

§ Patients who lost eligibility before randomization or who did not fill a prescription after randomization were considered to be nonadherent.

Sources: Chernew, M. E., et al. (2008). Impact of decreasing copayments on medication adherence within a disease management environment. *Health Affairs (Project Hope)*, 27(1), 103–112.

<https://doi.org/10.1377/hlthaff.27.1.103>; Choudhry, N. K., et al. (2011). Table 2. Medication adherence during follow-up. In Full coverage for preventive medications after myocardial infarction. *The New England Journal of Medicine*, 365(22), 2088–2097. <https://doi.org/10.1056/NEJMsa1107913>

Audit and Feedback

- ▶ Strategy that compares providers' performance to explicit benchmarks or standards in an effort to prompt behavior change
 - ▶ Sequential, cyclical process (e.g., plan-do-study-act cycles)
- ▶ May focus on structure, process or outcomes of care
 - ▶ What types of drug-related measures might be used?
- ▶ Underlying assumption: providers care and will be motivated to improve
- ▶ Cochrane review: "Audit and feedback generally leads to small but potentially important improvements in professional practice. The effectiveness of audit and feedback seems to depend on baseline performance and how the feedback is provided. Future studies of audit and feedback should directly compare different ways of providing feedback."

Patient Education

- ▶ Enormous gaps in health literacy among many individuals
- ▶ What is this medicine for? How is it to be taken? How effective is it? What are the most common or potentially serious effects?
- ▶ Poor quality medication information is a common cause of preventable medication errors
- ▶ Many initiatives to improve health literacy (by regulators, insurers, manufacturers, health systems, advocates, federal government, clinicians, others)
- ▶ Difficult to isolate impact of patient education (but no one argues it's unimportant)

Patient Education (Examples)

Drug facts box (Abilify)

DRUG FACTS

ABILIFY (aripiprazole) for adults with major depression that persists on antidepressants

What is this drug for? To reduce symptoms of major depression—nearly everyday feelings of extreme sadness, or hopelessness.

Who might consider taking it? Adults with major depression that persists after one or more 8-week courses of an anti-depressant.

How long has the drug been used? First approved in 2002 for schizophrenia, in 2007 for persistent depression (based on studies of about 1,000 people). As with all drugs, rare but serious side effects may emerge when new people use it for a new purpose.

What precautions should I take? Use caution driving or operating machinery because ABILIFY may impair judgment, thinking or motor skills. Do not drink alcohol or medications. Check blood tests if you've had low white blood cell counts or high sugar levels.

What other choices are there? Cognitive behavioral psychotherapy, exercise, switch to a different anti-depressant, add another anti-depressant, or electroconvulsive therapy.

Bottom line

Adding ABILIFY to an anti-depressant for persistent depression is a tradeoff: some people's depression will improve but more will experience a somatic side effect—akathisia. And some will gain an substantial amount of weight.

The 2 anti-depressants in the table below show how well each drug helped over 6 weeks. This makes the numbers in the table more believable. Benefits and side effects over a longer time are more uncertain.

Like all anti-psychotic drugs, Abilify can cause a number of uncommon serious or life-threatening side effects including Tardive Dyskinesia, a potentially irreversible movement disorder with uncontrollable, jerky movements of the face or body.

The FDA reviewer was concerned that side effects like weight gain, sedation and serious movement disorders may be worse or more common when Abilify is combined with anti-depressants.

STUDY FINDINGS (combined results of 2 identical trials)

741 people – ages 19 to 67 years – with major depression that persisted after 8 weeks of an anti-depressant were randomized to have either ABILIFY or PLACEBO added for 6 weeks. Here's what happened:

	Anti-depressant + ABILIFY (10 mg each day)	Anti-depressant + PLACEBO (No drug)
What difference did ABILIFY make?		
How did ABILIFY help?		
Depression scores improved by 3 points more than placebo (on a scale from 0 to 60).	9 points better	vs. 6 points better
11% more people had an important response and were no longer considered to have major depression	26%	vs. 15%
Functioning scores improved by 0.5 points more than placebo (on a scale from 0 to 10).	1.2 points better	vs. 0.7 points better
What were ABILIFY's side effects?		
Serious side effects		
21% more people developed akathisia - severe restlessness that makes it hard to keep still	25%	vs. 4%
3% more people developed movement disorders -like Parkinson's disease	8%	vs. 5%
Symptom side effects		
6% more people had insomnia	8%	vs. 2%
5% more had blurred vision	6%	vs. 1%
4% more had substantial weight gain	5%	vs. 1%
4% more had fatigue	8%	vs. 4%
3% more had constipation	5%	vs. 2%
WARNINGS ABOUT UNCOMMON LIFE-THREATENING AND VERY SERIOUS SIDE EFFECTS		
Young adults using anti-depressants for major depression have a higher risk of suicidal thinking and behavior. Elderly patients with dementia-related psychosis should not use antipsychotic drugs – like ABILIFY—because they increase death. Antipsychotic drugs cause: Neuroleptic Malignant Syndrome (very high fever and blood pressure, delirium), Tardive Dyskinesia (uncontrollable facial / body movements), Dangerous Heart Rhythms, Seizures, Low White Blood Cells, Trouble Swallowing, Aspiration Pneumonia, Diabetes, Low Blood Pressure, Trouble Regulating Body Temperature		

Fig. 1. Drug Facts Box for Abilify for adults with major depression that persists on antidepressants.

Source: Schwartz, L. M., & Woloshin, S. (2013). *Proceedings of the National Academy of Sciences of the United States of America*, 110 Suppl 3(Suppl 3), 14069–14074. <https://doi.org/10.1073/pnas.1214646110>

Medication guide (Abilify)

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

MEDICATION GUIDE

ABILIFY® (a BILOFI)

Generic name: aripiprazole

Read this Medication Guide before you start taking ABILIFY and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ABILIFY?

(For other side effects, also see "What are the possible side effects of ABILIFY?").

Serious side effects may happen when you take ABILIFY, including:

- Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ABILIFY can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- Risk of suicidal thoughts or actions:** Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:

 - Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
 - Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions.** Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

- How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
 - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
 - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

Reference ID: 2906732

77

Source: FDA. (2011). ABILIFY® [Medication guide].
Retrieved November 19, 2024.

Medication Therapy Management (MTM)

- ▶ Sometimes referred to as “clinical pharmacy services,” goal is to identify and address, or preempt, drug therapy problems
- ▶ Professional service(s) with variable structure and components
- ▶ Systematic review funded by Agency for Healthcare Research and Quality (AHRQ)
 - ▶ Insufficient evidence to evaluate most associations of interest
 - ▶ Large study of Medicare beneficiaries: improvements in medication utilization, but no clear cost or quality offsets

Summary

- ▶ Recall that drug utilization is complex, with large gaps in care
- ▶ Adherence and persistence have complex determinants and are perennial challenges to optimizing pharmacotherapy
- ▶ Both explicit and implicit indicators offer means of quantifying—and incenting—quality as well as assessing intervention impact
- ▶ There are several commonly used methods to improve pharmacotherapy, including the use of economic incentives such as value-based insurance designs, audit and feedback, patient education, and medication therapy management