**Annals of Pharmacy Practice and Pharmacotherapy**
**ISSN: 3062-4436**
2023, Volume 3, Issue 2, Page No: 105-113

Available online at: www.galaxypub.co/page/journals

**Galaxy Publication**

# Clinical Efficacy Can Be Attenuated by Nonpersistence, Monitoring Failure, and Fragmented Care Before It Becomes a Real-World Outcome

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**Received:** 09 August 2023; **Revised:** 05 November 2023; **Accepted:** 08 November 2023

## ABSTRACT

The difference between treatment efficacy demonstrated under trial conditions and effectiveness realized in routine care is often described as an efficacy–effectiveness gap. That shorthand is useful but analytically incomplete. After prescribing, several distinct processes can alter whether an efficacious treatment becomes an effective real-world intervention: treatment may never be initiated; persistence may end early; implementation of the regimen may be irregular; clinically necessary monitoring may not occur or may be uninformative; new information may fail to produce appropriate dose or treatment adaptation; access may be interrupted; care may become fragmented; and outcomes may be incompletely observed or incorrectly attributed. These processes operate at different times, leave different data signatures, and imply different remedies. They also should not be assumed to produce a monotonic loss of benefit. Appropriate treatment switching, risk-responsive monitoring, dose adjustment, restoration of access, or improved coordination can preserve benefit or reduce harm. This Current Opinion argues that economic and outcomes research should represent post-prescribing effectiveness as a sequence of mechanism-specific processes rather than as a single adherence penalty or fixed efficacy multiplier. The practical implication is that models should distinguish changes in treatment exposure from failures of care response and from distortions in outcome ascertainment. Doing so clarifies causal responsibility, improves correspondence between real-world data and decision models, and makes assumptions about preventability and value more transparent.

**Keywords:** Real-world effectiveness, Medication persistence, Medication adherence, Therapeutic monitoring, Dose adaptation, Care fragmentation

**How to Cite This Article:** Bennett S, Asante K, Rossi E. Clinical Efficacy Can Be Attenuated by Nonpersistence, Monitoring Failure, and Fragmented Care Before It Becomes a Real-World Outcome. Ann Pharm Pract Pharmacother. 2023;3(2):105-13. https://doi.org/10.51847/eBbSia1tXp

## Introduction

Efficacy established in a randomized trial is an estimate produced under a defined protocol, eligibility structure, follow-up regime, and treatment environment. Routine practice replaces those conditions with heterogeneous patients, variable access, shifting clinical priorities, and less standardized observation. The resulting efficacy–effectiveness gap may involve survival, symptoms, quality of life, toxicity, resource use, and patient time rather than one outcome alone [1]. For decision makers, the important question is therefore not merely whether trial effects attenuate, but what happens between prescribing and the eventual clinical and economic outcome.

The distinction matters because an efficacy estimate does not automatically describe what a patient or population should expect after treatment enters routine use [2]. Some divergence is created before prescribing through trial selection and baseline case mix. The present argument is narrower: once a clinician has selected and prescribed a

treatment, several subsequent processes can still modify realized exposure, treatment appropriateness, continuity, and the observation of outcomes. Treating those processes as one generic "real-world loss" obscures both mechanism and responsibility.

Real-world evidence can make these processes observable, but observational data do not become decision-ready simply because they arise in routine care. Study design, data provenance, exposure definitions, follow-up, confounding control, and outcome construction remain central to validity [3]. A model that estimates effectiveness from dispensing records, for example, answers a different question from one that also observes dose changes, laboratory monitoring, treatment switching, or outcomes after discontinuation.

The measurement problem is visible in the adherence literature itself. A systematic review of medication-adherence-enhancing interventions found extensive heterogeneity in the outcomes used to judge success, with adherence outcomes much more commonly assessed than economic or patient-reported outcomes [4]. Improving a medication-taking metric cannot therefore be assumed to produce a known clinical or economic gain. The central question for this Current Opinion is which post-prescribing mechanisms attenuate trial efficacy before it becomes population-level effectiveness, and how economic and outcomes research should represent those processes without assuming that every deviation is harmful, monotonic, or patient-caused.

*The efficacy–effectiveness gap is a sequence of post-prescribing processes*

The phrase efficacy–effectiveness gap often compresses several phenomena into one contrast between trials and practice. For post-prescribing analysis, that compression is too coarse. A treatment can fail to become an initial exposure, become an exposure that is intermittently implemented, stop earlier than intended, remain prescribed without clinically necessary monitoring, continue despite new information that should have triggered adaptation, become temporarily inaccessible, or move across poorly coordinated providers. Even when exposure and care are unchanged, the observed effectiveness estimate can shift because outcomes are incompletely captured or attributed.

These mechanisms matter because similar endpoints can arise from different underlying processes. A hospitalization after treatment initiation might follow inadequate biological exposure, delayed recognition of toxicity, loss of follow-up, an affordability-related interruption, or progression despite fully appropriate care. Each explanation has a different prevention strategy and a different place in an economic model. The relevant unit of analysis is therefore the process that changes exposure, care, or observation, not the downstream event by itself.

This distinction also prevents the efficacy–effectiveness gap from becoming a residual category for everything that goes wrong outside a trial. Some routine-practice differences are expected consequences of broader eligibility, different comorbidity distributions, or different competing risks. Others are generated after prescribing and are potentially modifiable. Still others arise from how data are collected or analyzed. A useful post-prescribing account should keep these sources separate even when they coexist in the same patient trajectory.

*Initiation, persistence, and adherence quality are different exposure problems*

The first post-prescribing transition is from a treatment decision to actual treatment initiation. Primary nonadherence is commonly identified when a newly prescribed medicine is not obtained through the observed dispensing pathway; this indicates possible noninitiation but does not directly measure ingestion [5-7]. Linked prescribing and dispensing data are especially important here because a prescription record alone can misclassify intended treatment as actual treatment. The clinical meaning of noninitiation also depends on context: failure to fill may reflect cost, uncertainty, preference, an adverse experience with prior therapy, changed clinical advice, or a decision that the original prescription is no longer appropriate. It is therefore an observed dispensing pattern, not a diagnosis of patient behavior.

Persistence begins only after treatment has been initiated. It concerns how long treatment continues before discontinuation and is intrinsically time dependent. Analyses that treat every patient as belonging to one homogeneous discontinuation process can misrepresent persistence when a subgroup remains on therapy for substantially longer periods. Mixture-cure modeling has been proposed as one way to represent such heterogeneity in real-world persistence data [8]. The broader lesson is methodological: persistence should be modeled according to the observed temporal structure rather than converted automatically into a single average continuation probability.

Adherence quality during persistent treatment is another process. A patient can remain classified as persistent while taking doses at irregular intervals, omitting doses, altering timing, or otherwise implementing the regimen differently from the prescribed schedule. Barriers include treatment burden, formulation and delivery characteristics, competing daily demands, adverse effects, beliefs, health-system friction, and regimen complexity; drug-delivery design can reduce some of that burden [9]. Intervention evidence, however, remains heterogeneous, and no single adherence strategy is consistently effective across diseases and contexts [10].

The distinction among initiation, implementation, and persistence is well established in chronic pharmacotherapy [11], but the determinants of each are not reliably reducible to a stable patient profile. Reviews of adherence determinants repeatedly show inconsistent associations and variable evidence quality across social, economic, treatment, condition, patient, and health-system factors [12]. This matters for both ethics and modeling. When nonadherence is represented as a fixed patient characteristic, models risk converting changeable treatment or system constraints into apparently intrinsic patient behavior.

Digital adherence technologies illustrate why measurement should not be mistaken for intervention. In a cluster-randomized tuberculosis trial, electronic medication monitoring was embedded in a care process that included review of dosing histories and differentiated management [13]. The actionable component is therefore the pathway from detected information to a clinical or behavioral response. A technology that improves observation but is disconnected from care can identify an exposure problem without resolving it. That distinction becomes even more consequential when the required response is a laboratory test, dose adjustment, or treatment switch.

*Monitoring and dose adaptation determine whether exposure becomes appropriate*

Continued medication use does not guarantee appropriate treatment over time. Many therapies require laboratory, clinical, pharmacokinetic, or toxicity monitoring because the benefit–risk balance changes with physiology, concomitant treatment, disease activity, or accumulated toxicity. Yet the desirable amount of monitoring is not necessarily maximal. Risk-stratified work in methotrexate-treated patients shows that monitoring intensity can be adapted to the probability of clinically relevant abnormalities rather than assumed to be uniform for every patient [14]. Monitoring failure should therefore mean failure to obtain sufficiently informative information when it is clinically needed, not simply fewer tests.

The informativeness of monitoring also depends on what is measured and how reliably that measurement represents the underlying exposure or response. Quantitative comparisons of therapeutic drug monitoring and pharmacogenetic information show that the value of a concentration measurement changes with interindividual variability, interoccasion variability, residual error, and the pharmacokinetic structure of the drug [15]. A recorded test can therefore be technically complete while still providing weak guidance for the next decision. Economic analyses that count the presence of monitoring without representing its informational value may overstate the effectiveness of a monitoring strategy.

The next transition is from information to action. Therapeutic drug monitoring becomes clinically consequential when observed concentrations are interpreted and connected to a dosing decision, and model-informed precision dosing formalizes that feedback process [16, 17]. Several events can interrupt the chain: the test may not be ordered; the sample may be delayed; the result may be noisy; the model may be poorly validated for the relevant population; the recommendation may not reach the clinician; the clinician may appropriately reject it; or the revised dose may not be implemented. These events have different resource and outcome implications; appropriate rejection of a recommendation is not itself a care failure.

Dose adaptation can preserve benefit or reduce harm during routine care. A dose reduction after emerging toxicity may decrease nominal exposure while improving net effectiveness by avoiding treatment discontinuation or serious harm. A dose increase after inadequate exposure may restore an expected effect. An appropriate switch may be superior to continuing the originally prescribed therapy. Real-world effectiveness is therefore a property of the evolving treatment strategy and care response, not merely of persistence with the initial prescription.

*Access interruptions and fragmented care redistribute responsibility across the system*

Medication-taking behavior is constrained by whether treatment remains obtainable. Cost-related nonadherence among older adults in the United States demonstrates that affordability can directly alter whether medicines are purchased or used as intended [18]. Such interruptions are analytically different from forgetting doses or intentionally stopping because of adverse effects. They arise from benefit design, prices, coverage, information,

and household resources. Treating them as a generic adherence decrement places a system-generated exposure problem inside a patient-level parameter.

The economic consequences of nonadherence are substantial in many disease areas, but estimates vary widely across conditions and costing methods [19]. That heterogeneity is expected if nonadherence is produced by different mechanisms and has different downstream consequences. Missing an inexpensive preventive medicine, interrupting a narrow-therapeutic-index drug, and discontinuing a high-cost treatment after toxicity do not create the same cost pathway. Economic models therefore need to represent the mechanism linking altered exposure to resource use instead of importing a universal monetary penalty for "nonadherence."

Care fragmentation introduces another level of complexity. Fragmentation, continuity, and coordination are related but non-equivalent constructs [20]. Multiple clinicians can be clinically necessary and beneficial; the problem arises when information, responsibility, or follow-up is not coherently transferred. In medication management, that may mean duplicated prescribing, failure to reconcile a discontinuation, missed laboratory surveillance, incompatible dose changes, or uncertainty about which clinician is responsible for acting on a result. The exposure problem is then generated by distributed care rather than by an isolated patient decision.

Observational work in complex Veterans Affairs home-based primary care populations has linked outpatient care fragmentation with acute-care utilization [21]. Such associations should not be interpreted as proof that fragmentation directly attenuates the pharmacological effect of a medicine. They do, however, support treating fragmentation as an observable health-system condition that may alter continuity, recognition of risk, and timely response. The analytic task is to identify which coordination failure changes the treatment pathway rather than using provider count as a proxy for harm.

Across these mechanisms, the same apparent reduction in real-world effectiveness can originate at different points and can therefore require different corrective actions. The comparison below separates the post-prescribing processes by timing, what they change, how they can be observed, and the circumstances under which prevention or correction is plausible.

**Table 1.** Distinct post-prescribing processes through which expected treatment benefit can diverge from realized effectiveness

| Post-prescribing process | Typical point in the care trajectory | Primary quantity changed | Observable evidence in routine data or care | Potential for prevention or correction |
|---|---|---|---|---|
| **Noninitiation** | Immediately after prescribing | Whether pharmacological exposure begins | Prescription–dispensing linkage, patient report, pharmacy claims | Potentially modifiable when driven by affordability, communication, access, or reversible treatment concerns; not every unfilled prescription represents inappropriate behavior |
| **Nonpersistence** | After treatment initiation | Duration of exposure | Refill gaps, discontinuation records, treatment-stop dates, longitudinal dispensing data | Depends on why treatment stops; premature discontinuation may be preventable, whereas stopping for toxicity, lack of benefit, or changed goals may be appropriate |
| **Suboptimal regimen implementation** | During periods classified as persistent | Dose timing, dose completion, or regimen concordance | Electronic monitoring, refill-derived measures, pill counts, self-report, drug concentrations in selected settings | Often modifiable through regimen simplification, delivery design, support, or management of adverse effects, but determinants are heterogeneous |
| **Monitoring failure** | During treatment when safety, exposure, or response information is required | Availability and informativeness of clinical feedback | Laboratory records, concentration measurements, visit records, monitoring schedules | Modifiable when the required information is known and actionable; more monitoring is not automatically better when risk is low or tests are poorly informative |
| **Dose- or treatment-adaptation failure** | After new clinical, laboratory, pharmacokinetic, or toxicity information | Appropriateness of continued dose or treatment strategy | Dose histories, prescribing changes, model recommendations, clinical notes, switch records | Potentially modifiable through validated decision support, timely review, clearer responsibility, and workflow integration |
| **Access interruption** | At dispensing, renewal, insurance transition, or other access points | Continuity of treatment availability | Claims denials, refill interruption, cost-related patient reports, coverage changes | Often system-modifiable through affordability, benefit design, supply continuity, and timely access support |

| | | | | |
|---|---|---|---|---|
| **Care fragmentation** | Across transitions or concurrent providers | Continuity of information, responsibility, monitoring, and coordinated action | Provider dispersion measures, reconciliation records, referral/transition data, duplicated or conflicting orders | Modifiable when fragmentation reflects information or coordination failure; multiple-provider care itself is not necessarily harmful |

*Outcome ascertainment can create or conceal apparent attenuation*

Observed real-world effectiveness is partly a property of how treatment exposure and outcomes are defined. Healthcare-database studies require explicit operational decisions about eligibility, treatment initiation, discontinuation, follow-up, and outcome construction because small differences in those definitions can alter the population and events entering an analysis [22]. A decline in an estimated treatment effect can therefore reflect a genuine post-prescribing process, a change in case mix, or the way routine data encode treatment and follow-up.

Pharmacoepidemiologic bias can further amplify, conceal, or reverse an apparent efficacy–effectiveness difference. Misclassification, selection, immortal-time structures, missing information, and confounding can arise from the population, study design, or data source [23]. These mechanisms should not be treated as additional forms of clinical attenuation. They alter the estimate of effectiveness, whereas noninitiation, interruption, inadequate monitoring, or failed adaptation alter the treatment or care actually received.

Treatment discontinuation illustrates the distinction. Clinically relevant outcomes may continue after the original therapy stops, particularly when subsequent symptoms, quality of life, toxicity, or replacement treatment remain part of the decision question. Guidance on patient-reported outcomes after treatment discontinuation therefore emphasizes aligning continued data collection with a prespecified purpose rather than allowing treatment cessation to determine automatically when observation ends [24]. Exposure discontinuation and outcome discontinuation are analytically separate events.

The same principle applies to censoring. When loss of follow-up is associated with prognosis, treatment response, toxicity, or subsequent therapy, the assumption of noninformative censoring can fail and the estimated treatment effect can be distorted [25]. The direction is not fixed. Better ascertainment may reveal a larger or smaller real-world effect without changing the treatment received by any patient. Economic and outcomes research should therefore distinguish processes that alter realized benefit from processes that alter its measurement.

*Economic evaluation must model process-specific real-world effectiveness*

Economic models commonly require a bridge between efficacy observed in trials and outcomes expected under routine implementation. That bridge should be mechanistic enough to represent how the treatment pathway changes. Reviews of adherence-focused decision models show substantial variation in how adherence is linked to downstream clinical events, costs, and health outcomes [26]. A single proportional reduction in efficacy is convenient, but it can obscure whether the relevant mechanism is noninitiation, discontinuation, intermittent use, delayed monitoring, or a change in treatment strategy.

Implementation assumptions can also alter the preferred decision rather than merely shrinking its expected benefit. Modeling of imperfect adherence in cervical screening demonstrated that different adherence patterns changed the optimal strategy and could expose consistently adherent individuals to additional procedures [27]. Although screening differs from pharmacotherapy, the structural lesson is transferable: the pattern and location of imperfect implementation can matter more than its average magnitude.

Treatment switching creates a related problem. In trial-based economic analysis, adjustment for switching can materially change estimated utility and quality-adjusted life-year differences [28]. Switching should therefore not be coded automatically as treatment failure. It may follow toxicity, progression, insufficient response, changed preferences, or an opportunity to improve treatment. The model must specify whether switching represents loss of the original treatment effect, clinically appropriate adaptation, subsequent-line benefit, or an estimand problem. The modeling implications of these distinctions are summarized below.

**Table 2.** Representing post-prescribing processes in economic evaluations of real-world treatment effectiveness

| Process represented in the model | Structural question | Parameter or data requirement | Consequence of oversimplification |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Treatment initiation** | Does the modeled cohort begin therapy when prescribed, or only when treatment is actually obtained? | Prescription-to-dispensing or initiation probability linked to relevant context | Treats intended treatment as delivered treatment |
| **Persistence** | Is discontinuation a constant risk, time-varying process, or heterogeneous trajectory? | Longitudinal treatment-duration data and explicit permissible-gap rules | Misstates exposure duration and downstream event risk |
| **Adherence quality during persistence** | Does imperfect implementation change exposure continuously, episodically, or only beyond clinically relevant thresholds? | Regimen-specific implementation data connected to outcomes | Converts heterogeneous implementation into an arbitrary efficacy multiplier |
| **Monitoring** | Which tests or clinical observations influence safety or treatment effectiveness, and when? | Monitoring frequency, informativeness, costs, and consequences of missed or delayed assessment | Counts monitoring without representing whether it changes decisions |
| **Dose adaptation** | How does new information alter dose, treatment continuation, or risk? | Decision rules, dose histories, exposure-response relationships, implementation fidelity | Assumes that obtaining information guarantees an effective response |
| **Access interruption** | Are treatment gaps driven by affordability, coverage, supply, or other constraints? | Context-specific interruption and restoration probabilities | Misclassifies system-generated treatment loss as patient behavior |
| **Care fragmentation** | Does disrupted information or responsibility change monitoring, reconciliation, or treatment decisions? | Coordination-sensitive process data where available | Treats provider contact as equivalent to coordinated care |
| **Switching/discontinuation** | Does treatment change represent failure, toxicity management, rescue, or beneficial adaptation? | Reason- and timing-specific switching data plus subsequent outcomes | Forces all treatment changes into the same negative state |
| **Outcome ascertainment** | Are outcomes observed after discontinuation and are censoring mechanisms represented? | Follow-up patterns, missingness mechanisms, sensitivity analyses | Confuses changes in observed effects with changes in treatment effectiveness |

Real-world parameters used in such models should also correspond to an explicit causal question. Target-trial emulation provides one way to make eligibility, treatment strategies, time zero, follow-up, and outcomes more transparent when routine data are used for health technology assessment [29]. It cannot remove unmeasured confounding or repair absent data, but it reduces ambiguity about which treatment contrast an effectiveness estimate is intended to represent.

*Boundary conditions: attenuation can reverse, improve safety, or reflect selection*

Attenuation is a possible trajectory, not a universal law of continuous decline. Monitoring can be intensified for high-risk patients and reduced where risk is low; dose modification can restore appropriate exposure; and discontinuation can prevent avoidable toxicity. Consequently, an observed treatment trajectory may contain loss, stabilization, recovery, or purposeful redirection rather than a one-way erosion of efficacy.

These trajectories are summarized in **Figure 1**, which separates exposure loss, care-response failure, and observation distortion while allowing clinically appropriate adaptation to restore or preserve realized benefit.

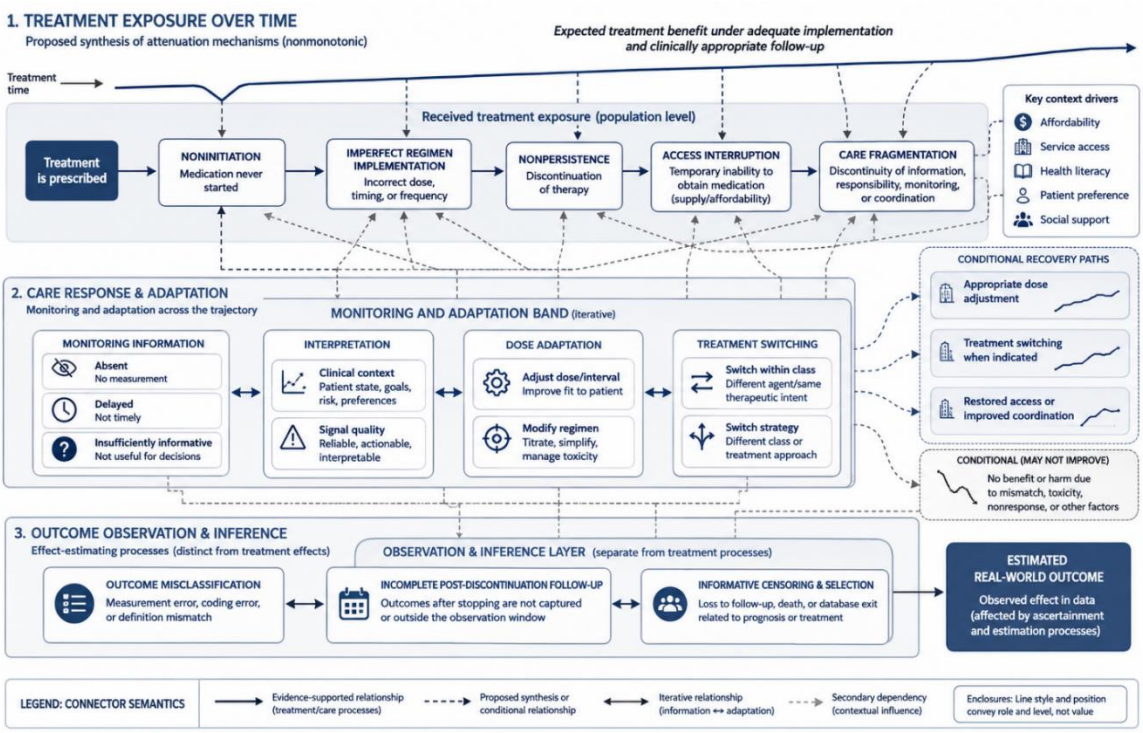


**Figure 1.** Real-world treatment benefit across care time: attenuation, corrective adaptation, and observation

## Conclusion

Clinical efficacy does not pass unchanged from a trial protocol into routine outcomes, but neither does it simply decay at a fixed rate after prescribing. Real-world effectiveness emerges from several separable processes: whether treatment begins, how it is implemented and continued, whether appropriate monitoring occurs, whether new information produces timely adaptation, whether access and coordination are sustained, and whether subsequent outcomes are observed and attributed correctly.

For economic and outcomes research, the practical consequence is to replace generic implementation penalties with mechanism-sensitive assumptions whenever those mechanisms can materially change decisions. Noninitiation should not be represented as imperfect persistence; monitoring should not be equated with action; switching should not automatically be classified as failure; and incomplete ascertainment should not be mistaken for biological loss of treatment effect. The most useful models will therefore allow both attenuation and recovery, assign responsibility across patients, treatments, clinicians, and systems, and make explicit where uncertainty lies in care delivery versus outcome estimation. Under those conditions, the efficacy–effectiveness gap becomes a set of testable and potentially modifiable processes rather than an unexplained residual between trials and practice.

**Acknowledgments:** None

**Conflict of Interest:** None

**Financial Support:** None

**Ethics Statement:** None

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