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Adverse Events After Drug Discontinuation: A Pharmacovigilance Framework for Distinguishing Withdrawal Syndromes, Rebound Effects, Disease Recurrence, and Delayed Treatment-Related Harm

Sofia Marchetti[1]*, Aisha Rahman[2], Elena Rossi[3]

[1]Department of Pharmacovigilance, University of Milan, Milan, Italy.
[2]Department of Pharmacogenomics, Lahore University of Management Sciences, Lahore, Pakistan.
[3]Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy.

***Email:** sofia.marchetti@unimi.it*

ABSTRACT

Drug discontinuation is an exposure transition that can prevent continuing treatment-related harm while generating, revealing, or coinciding with new adverse outcomes. Interpretation is difficult because withdrawal syndromes, rebound effects, recurrence of the treated disorder, delayed treatment-related injury, and unrelated illness can share clinical features and overlapping observation windows. This original, nonempirical analysis extends causal reasoning about medication cessation by specifying when familiar adverse-reaction and dechallenge assumptions become insufficient. Evidence from discontinuation trials, comparative cohorts, biological investigations, guidelines, and pharmacovigilance methodology is used selectively to distinguish mechanisms and their observable signatures. The proposed classification connects five rival explanations to exposure trajectories, pretreatment and on-treatment baselines, mechanism-relevant measurements, longitudinal comparators, and competing causes. It permits concurrent explanations and an unresolved category when evidence is insufficient. Its contribution is a set of conditional attribution rules and discriminating tests, not a validated diagnostic instrument. Post-discontinuation reporting should preserve the difference between temporal occurrence, mechanistic plausibility, and causal attribution; prospective testing is required before the approach is used to assign event-level probabilities.

Key words: *Drug discontinuation, Adverse drug withdrawal events, Rebound effects, Disease recurrence, Pharmacovigilance, Causal attribution*

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INTRODUCTION

Medication discontinuation is routinely represented as removal of a risk-generating exposure. That interpretation becomes incomplete when cessation introduces a distinct exposure contrast: continued treatment against a specified reduction or stop, each followed through a clinically relevant interval. Deprescribing research therefore faces two simultaneous questions—whether stopping prevents adverse drug effects and whether it produces adverse drug withdrawal events. The methodological distinction has consequences for time-zero assignment, outcome ascertainment, and confounding control [1].

Pharmacovigilance systems inherit this ambiguity. Spontaneous reports can provide case detail and initial signals, whereas longitudinal healthcare records add treatment histories and follow-up at the cost of other forms of misclassification. Neither information stream automatically establishes which causal pathway produced the

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reported event [2]. Divergent safety assessments can also arise from differing assumptions about biological plausibility, acceptable uncertainty, and the interpretation of incomplete evidence [3].

This article develops a boundary-condition extension to discontinuation-related causal reasoning. The hidden assumption under examination is that clinical change after drug removal can be interpreted against a stable, untreated counterfactual. That assumption may fail when chronic exposure has altered physiological regulation, when treatment has suppressed an active disorder, or when treatment-induced injury continues to evolve after the final dose. The analytical task is to distinguish a syndrome attributable to loss of adaptation, a physiological overshoot, renewed disease activity, delayed effects of previous exposure, and intercurrent events. These possibilities can coexist. The present contribution specifies observable contrasts and uncertainty conditions; it neither supplies new patient data nor claims validated diagnostic performance.

Drug discontinuation as a distinct pharmacovigilance problem

The discontinuation decision creates a surveillance transition with its own exposure history. Dose reductions, irregular adherence, a planned taper, abrupt cessation, and substitution by another treatment should not be collapsed into a single binary variable. Each may change residual pharmacological action and the amount of time during which an event could reasonably become apparent. A trial of electronic deprescribing support among hospitalized older adults demonstrates that cessation decisions and their outcomes can be evaluated within a defined clinical observation period [4]. The duration and sensitivity of that period still govern which subsequent harms can be detected.

A post-discontinuation adverse event is an observed unfavorable change following a treatment transition; the label itself makes no causal assertion. An adverse drug withdrawal event is a stronger interpretation in which the reduction or cessation contributes causally. For both questions, eligibility at the moment of the treatment decision, baseline symptom state, concurrent therapies, disease severity, and the reason for stopping require documentation. Otherwise, confounding by indication, selective monitoring, and outcome ascertainment may make patients who stop appear systematically different from those who continue [1].

Reporting systems should consequently retain the last administered dose, the actual taper trajectory, antecedent treatment duration, onset relative to dose changes, evolution after the event, and medically plausible competing explanations. This defines the special pharmacovigilance problem: observation begins at a deliberate change in exposure, yet physiological and clinical states may continue to reflect the preceding exposure. The event cannot safely be classified from chronology alone.

Current clinical and pharmacological evidence on post-discontinuation outcomes

Antidepressants provide an informative example because symptom reports and treated-disease symptoms intersect. A systematic review and meta-analysis of antidepressant discontinuation found that symptom frequency requires interpretation against placebo-associated symptoms and study-specific ascertainment [5]. A later synthesis of randomized trials similarly emphasized the importance of controlled contrasts and individual symptom profiles when estimating what follows active-drug cessation [6]. The reviews use different bodies of evidence and operational choices; their aggregate estimates should not be treated as interchangeable measures of a universal withdrawal probability.

Disease activity presents a parallel explanation. In a primary-care randomized trial, antidepressant maintenance and discontinuation yielded different subsequent relapse experiences in patients selected for treatment continuation or cessation [7]. Such comparisons establish the clinical importance of sustained treatment for that population without explaining the cause of every early symptom. A review of published withdrawal data additionally shows sensitivity to definitions, previous exposure, tapering practices, and measurement duration [8]. Withdrawal and relapse are therefore neither mutually exclusive nor reliably distinguished by any single symptom report.

Sedative-hypnotic discontinuation illustrates how the method of stopping can influence observed outcomes. A randomized study combining a masked taper with behavioral support evaluated a specific strategy for discontinuing benzodiazepine receptor agonists [9]. Evidence synthesized across deprescribing interventions also indicates that approaches differ in their ability to facilitate cessation [10]. These findings support recording what patients actually did during the withdrawal process; cessation success must not be mistaken for an event-level estimate of withdrawal causality.

Antipsychotic discontinuation raises a different causal problem. A randomized-trial meta-analysis in chronic schizophrenia related relapse risk to reduction or discontinuation conditions and patient context [11]. The RADAR

randomized study compared reduction or discontinuation strategies with maintenance in recurrent psychotic disorders and assessed longer-term clinical outcomes [12]. A synthesis concentrating on remitted first-episode psychosis examined a population with different illness histories and recovery prospects [13]. Worsening after a dose change may signify recurrence, drug-related adaptation, or an interaction between the two; population-level relapse differences alone do not identify a withdrawal-mediated mechanism for a particular episode.

Denosumab offers a clearer pharmacodynamic basis for a candidate rebound phenomenon. A mechanistic review describes transient bone-turnover overshoot and rapid bone loss following treatment withdrawal [14]. Cross-sectional measurements in treated postmenopausal women found osteoclast precursor differences that could help explain the overshoot hypothesis, although those observations were made during treatment rather than through direct post-cessation causal tracking [15]. A retrospective analysis of patients stopping denosumab documented subsequent fractures, including vertebral events [16]. The chain from target inhibition through cellular adaptation to clinical fracture remains evidence-dependent: biological plausibility and observed fracture risk are separate inferential steps.

Other therapies expose distinct boundaries. Evidence reviewed for proton pump inhibitors supports a potential rebound acid-hypersecretion process, but symptoms overlapping with the original acid-related disorder cannot be assigned automatically to that mechanism [17]. Guidance for systemic glucocorticoid cessation explicitly distinguishes glucocorticoid withdrawal syndrome, adrenal insufficiency, and worsening of the treated condition, each requiring different clinical evaluation [18]. Finally, immune-related complications of checkpoint inhibitors can appear late in the treatment course. A late event counted from treatment initiation must not be relabeled post-discontinuation harm unless exposure and cessation dates establish that chronology [19]. These examples justify a class-sensitive causal assessment instead of a universal onset rule.

Conceptual overlap among withdrawal, rebound, recurrence, and delayed harm

The classification problem begins with a shared clinical observation: symptoms or measurable injury appear, intensify, or become recognized after treatment changes. Yet five causal explanations imply different comparisons. Withdrawal refers to consequences of adaptation to ongoing drug action that become clinically expressed as exposure falls. Rebound requires an overshoot relative to an appropriate pretreatment physiological reference, not simply loss of therapeutic suppression. Recurrence concerns renewed activity of the original disease after suppression is removed. Delayed treatment-related harm reflects persisting or evolving consequences of earlier exposure; an intercurrent event has another sufficient or contributory cause.

Clinical contexts alter the defensibility of these claims. Finnish population-based comparisons of antipsychotic treatment strategies offer longitudinal evidence about relapse outcomes while remaining vulnerable to treatment-selection and adherence differences [20]. Pharmacological arguments for hyperbolic antidepressant tapering emphasize that equal milligram changes may not produce equal changes in target occupancy [21]. A review of psychiatric tapering guidance highlights practical formulation and dosage constraints that can prevent an idealized schedule from being implemented [22]. Consequently, the recorded prescribed plan and the actual exposure path can diverge precisely when temporal attribution depends on dose.

The underlying contrasts are condensed in **Table 1**. Each row identifies a candidate explanation and the observation necessary to advance beyond symptom recognition. More than one row may remain plausible for the same event; classification should explicitly preserve mixed or indeterminate accounts.

Table 1. Pharmacological signatures and comparator requirements in post-discontinuation event classification

Candidate causal state	Biological or clinical unit	Relevant post-cessation signature	Essential discriminator	Interpretation boundary
Withdrawal syndrome	Adapted physiological or neurobehavioral system	New symptom cluster during reduced drug action	Exposure/taper trajectory; syndrome phenotype; alternative causes	Rapid onset or response to reinstatement is supportive, not conclusive
Rebound effect	Regulated target system, such as acid secretion or bone turnover	Activity above appropriate pretreatment reference	Baseline marker and serial post-stop change	Loss of treatment benefit without overshoot is insufficient
Disease recurrence	Underlying disease process and patient course	Return of characteristic clinical or objective disease activity	Disease state before treatment change; course and	A recurrence endpoint may contain symptoms also seen in withdrawal

			maintenance comparator	
Delayed treatment-related harm	Persisting tissue injury or immune response	Injury emerges or progresses after earlier exposure	Verified exposure latency and mechanism-relevant follow-up	Time since initiation cannot replace time since cessation
Intercurrent event	Independent disease, new treatment, or external exposure	Compatible event unrelated or only partly related to stopping	Alternative diagnosis, competing drug, background-risk assessment	An unrelated cause may coexist with a drug-related contribution

Note: Analytical distinctions are proposed for case interpretation; no row represents a validated diagnostic rule. Source provenance is maintained in the accompanying evidence matrices.

Challenges in temporal interpretation and causal attribution

Time zero must refer to the clinical question actually being asked. The first dose reduction, last dose, end of pharmacological activity, emergence of a syndrome, and recognition of injury can occur at different times. Studies starting follow-up only at the documented final dose may miss effects arising during tapering; studies beginning at an initial reduction may incorrectly describe events that happened while substantial drug action persisted. Treatment changes prompted by early symptoms can also create reverse causation.

A target-trial perspective makes these problems explicit by requiring defined eligibility, strategy assignment, follow-up start, outcomes, and a clinically meaningful comparator. Methodological work on emulating medication-treatment trials supports that design discipline, although it does not itself validate classification of discontinuation events [23]. Selection into stopping, death or competing events, drug substitution, and informative follow-up can distort apparent risk. In spontaneous reporting, missing treatment dates and inconsistent narratives add a different layer of uncertainty.

Patient-level taper reports reinforce the problem of variable actual exposure. Observational accounts of hyperbolic antidepressant tapering describe individualized paths and symptom experiences, but selection into a particular taper program limits causal comparisons [24]. A symptom improvement after reinstatement may strengthen a hypothesis; it also can reflect expectancy, nonspecific treatment effects, spontaneous resolution, or renewed disease control. Likewise, a delay before symptom emergence may arise from pharmacokinetics, physiological adaptation, gradually returning disease activity, or long-latency injury.

A defensible attribution therefore compares multiple clocks and multiple baselines: treatment initiation, the exposure-reduction sequence, the final effective dose, the pretreatment disease state, and relevant biological observations. The absence of a plausible comparator should reduce confidence without silently converting uncertainty into a preferred diagnosis. In drug classes with no credible overshoot marker, a rebound label is especially fragile.

Development of the proposed post-discontinuation classification framework

The central extension concerns the scope of the familiar dechallenge assumption. Improvement after withdrawal is informative when exposure is the dominant continuing cause of injury and relevant background conditions remain sufficiently stable. Once persistent adaptation, disease suppression, or delayed injury violates those conditions, the same treatment transition can alter several causal processes. A single event may thus be consistent with more than one pathway. Longitudinal neuroimaging and relapse analyses following antidepressant discontinuation illustrate the promise of mechanism-relevant markers while also showing that a neural association cannot serve as a decisive diagnostic separator [25].

The classification unit proposed here is an *event–exposure transition*: one clinically specified event paired with the actual dose trajectory, antecedent indication, and follow-up interval. The first appraisal establishes whether the event began after a documented change and whether pharmacological activity plausibly changed. The second considers mechanisms independently: adaptation-related syndrome; physiological overshoot against baseline; disease activity against a documented clinical course; persisting exposure-related injury; and other causes. The third asks what observation could discriminate each favored explanation from its nearest rival. Lack of suitable measurements is recorded as indeterminacy, and coexisting explanations remain admissible.

These decisions are conditional rather than an ordinal score. For example, rapid symptoms after antidepressant reduction may support a withdrawal hypothesis, yet recurrence remains live until phenotype, previous disease status, and longitudinal development are examined. A bone-turnover increase after denosumab can support

rebound physiology, while a subsequent fracture requires a further clinical causal assessment. A new endocrinological syndrome after glucocorticoid taper must be examined for adrenal insufficiency and underlying-disease flare before being assigned a withdrawal label. **Table 2** operationalizes the competing tests, and **Figure 1** represents the branching attribution process with cross-links for nonexclusive mechanisms and an explicit unresolved outcome.

Table 2. Discriminating evidence contrasts for rival explanations following a drug-exposure transition

Case-level evidence test	Candidate interpretation strengthened	Rival explanation retained	Consequence for attribution
Document actual dose steps and last effective exposure	Cessation-linked adaptation when symptoms track dose decline	New disease, substitution effects	Preserve dose-path uncertainty if adherence is unknown
Compare physiology with pretreatment reference	Rebound if activity exceeds valid reference	Return to untreated disease state	Do not call loss of suppression an overshoot
Compare symptoms with established disease phenotype	Recurrence if characteristic activity returns	Withdrawal with overlapping manifestations	Require serial clinical assessment where possible
Examine latency and persisting biological injury	Delayed effect of previous treatment	New exposure or intercurrent illness	Check both initiation-to-event and stop-to-event intervals
Evaluate an appropriate continuation/taper comparator	Difference associated with a stopping strategy	Confounding, expectancy, surveillance differences	Population contrast cannot settle individual mechanism
Seek competing causes and convergence of independent indicators	Support for one or multiple causal pathways	Residual unmeasured causes	Assign supported, mixed, or unresolved status provisionally

Note: Evidence tests constitute a proposed causal-reasoning procedure, not a validated scoring system; findings may favor more than one explanation.

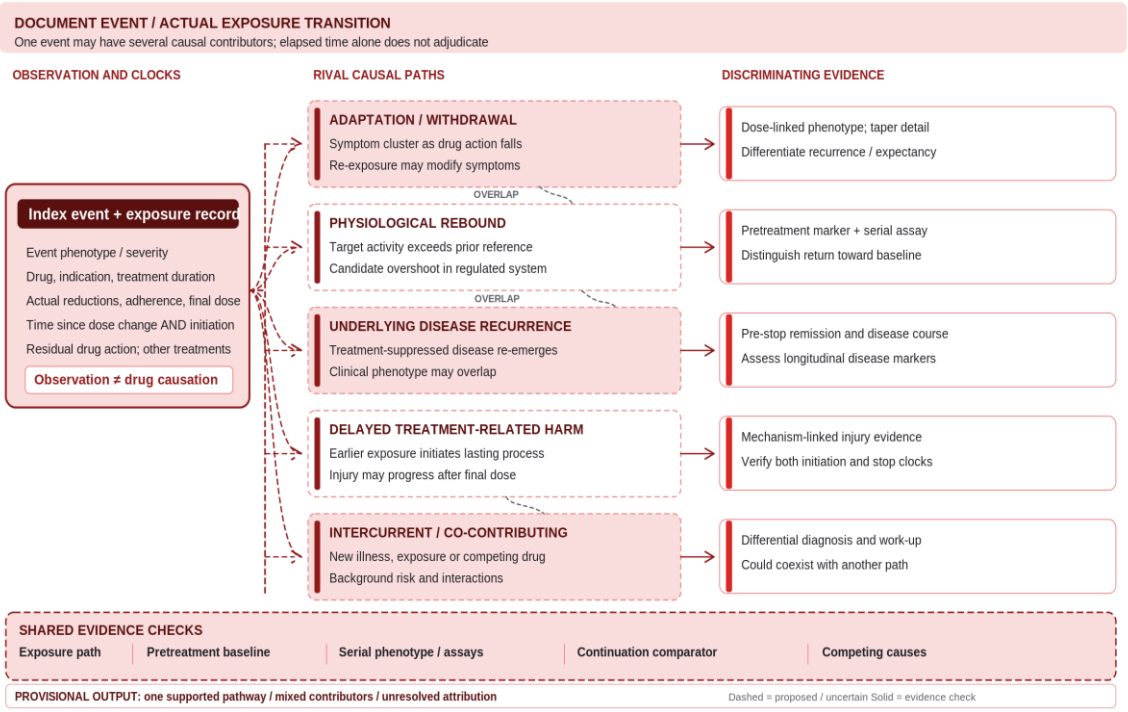


Figure 1. Differential causal attribution after a documented drug-exposure transition

Figure legend. The branching tree begins with a documented post-discontinuation event and places actual exposure change, drug effect persistence, the antecedent disorder, and outcome onset on separate observational clocks. Five candidate paths identify adaptation-related withdrawal, physiological rebound, disease recurrence, delayed treatment-related harm, and an intercurrent explanation. Each path connects a plausible mechanism to a

discriminating observation and a live alternative; dashed cross-links denote unresolved overlap or co-occurrence. A lower evidence band lists the independent records needed to strengthen attribution. Solid borders indicate empirical or clinical distinctions discussed in the cited literature; dashed borders and connectors signify the manuscript's proposed case-level classification procedure, not validated causal dependencies. Terminal outputs are provisional support for one explanation, mixed explanations, or unresolved attribution. The diagram contains no rates, thresholds, or performance estimates.

Figure 1 alt text. Landscape differential-attribution tree. An event and actual drug-dose transition are anchored at left. The tree fans into five staggered branches: withdrawal adaptation, rebound beyond baseline, recurrence of underlying disease, delayed effects of preceding exposure, and an intercurrent cause. Mechanism boxes lead to short discrimination tests, with diagonal dashed links between clinically overlapping pathways. A cross-cutting band beneath the branches shows exposure trajectory, pretreatment baseline, serial phenotype or biomarkers, comparator, and competing-cause checks; a final uncertainty box permits provisional single, mixed, or unresolved attribution.

Implications for pharmacovigilance assessment and safety reporting

When an event occurs during dose reduction or after a final dose, the initial report should distinguish the event from the reporter's causal interpretation. The minimum useful narrative is anchored in a dated exposure trajectory, the condition for which treatment was given, the clinical state immediately before reduction, and the onset and course of the suspected event. Follow-up can recover missing exposure and outcome details, although a scoping review documents substantial variation in how such follow-up is defined, conducted, and evaluated [26]. Requests for further information should therefore be tailored to the nearest plausible rival explanation, with uncertainty retained when patients or reporters cannot reconstruct events reliably.

The distinction also affects safety-signal evaluation. A spontaneous report of dizziness after antidepressant cessation might identify a previously insufficiently recognized post-stop pattern; an electronic record may clarify the sequence of dispensing, symptoms, diagnostic assessments, and subsequent treatment. Each source offers incomplete access to actual ingestion and clinical context. Linking reports and longitudinal data can strengthen temporal description while introducing risks of differential surveillance and missing undocumented taper steps [2]. A signal concerning all events after stopping answers a different question from a signal concerning adaptation-related withdrawal specifically.

A pharmacovigilance assessment should preserve three separate statements: what was observed, which explanations remain biologically or clinically credible, and how confidently each explanation is attributable to the treatment transition. Confidence may be limited by incomplete baseline measurements, overlapping syndromes, treatment substitution, or selective follow-up. Safety judgments can differ because analysts weight such evidence differently [3]. Reporter terminology should allow *suspected withdrawal*, *suspected rebound*, *possible recurrence*, *possible delayed exposure-related harm*, mixed explanations, and insufficiently characterized events without implying validated categories. Structured follow-up is useful when it clarifies these distinctions, not simply because it increases the volume of collected fields.

Illustrative classification problems and evidence requirements

Consider a patient reporting insomnia, dizziness, and low mood shortly after a reduction in antidepressant dose. The exposure chronology supports investigating withdrawal, but individual symptoms may be nonspecific. Controlled discontinuation studies show why a comparison with symptoms reported under placebo-related or other conditions matters [5]. The treated depressive disorder could also become active following cessation, as maintenance-versus-discontinuation evidence establishes for selected populations [7]. Classification would therefore require dose-step dates, pretreatment symptom history, the pattern of new versus familiar manifestations, serial assessment, and competing medical causes. A rapid response to reinstatement would be informative but could reflect renewed antidepressant action or other influences; neither pathway is conclusively identified by that observation.

For a patient who develops vertebral fractures after denosumab cessation, a mechanistic hypothesis of bone-turnover rebound is supported at the class level [14]. Documented post-cessation fracture outcomes require attention to baseline skeletal risk and intervening treatment [16]. A new dyspeptic symptom following proton pump inhibitor withdrawal demands a different test: acid-secretion measures relative to an appropriate untreated reference might support physiological overshoot, whereas symptoms alone could reflect the original disorder [17]. After systemic glucocorticoid tapering, deterioration could represent withdrawal syndrome, adrenal insufficiency,

or worsening of the treated illness, and the required endocrine and disease-specific assessments differ [18]. These cases cannot be handled by a uniform onset-time threshold.

An immune-related event recognized long after checkpoint-inhibitor initiation illustrates the importance of the exposure clock. Published late-onset events do not all necessarily start after the last administration; initiation-based and cessation-based intervals must be separately recorded [19]. If onset was definitively after treatment ended, continuing immune injury may be plausible, but competing illness and subsequent therapies still require assessment. The resulting reporting criteria are expressed in **Table 3**. They preserve the clinical signal even where no individual-level causal classification can yet be defended.

Table 3. Post-discontinuation safety-report fields tied to discriminating causal questions

Reportable information unit	Observation to preserve	Rival question that becomes assessable	Attribution safeguard when unavailable
Actual dose-transition record	Dose steps, adherence, last administered dose, replacement treatment	Did the event track loss of drug action or another exposure change?	Retain uncertain effective cessation date
Pretreatment disease course	Indication, prior episodes, functional or objective baseline	Is this a return of the treated condition?	Avoid presuming withdrawal from chronology
Phenotype change	New symptoms, characteristic clusters, severity and serial course	Is the syndrome distinct from the established disease pattern?	Record overlapping or nonspecific phenotype
Physiological reference	Relevant pretreatment biomarker and post-stop trajectory	Is there an overshoot beyond a valid baseline?	Do not label mere loss of suppression as rebound
Prior injury and latency	Exposure duration, injury indicators, dates of first detection	Could injury from previous treatment persist or appear late?	Separate time since initiation from time since cessation
Competing exposures and illness	New medicines, comorbid events, alternative diagnoses	Is an intercurrent cause sufficient or contributory?	Keep competing causes explicitly open
Outcome evolution and follow-up	Reassessment, course with further treatment changes, test results	Which candidate explanation survives longitudinal scrutiny?	Leave classification provisional or unresolved

Note: These are proposed report-level interpretation safeguards. No row is a validated causal rule; unavailable evidence should be stated as missing rather than imputed.

Discussion, causal uncertainty, and future research

The classification extends a familiar causal expectation beyond the circumstances in which it is dependable. Drug removal may reduce harm from current exposure, yet previously induced adaptation, suppressed pathology, and persisting tissue or immune effects can follow different trajectories. The implicit assumption of a stable untreated counterfactual consequently breaks down. A post-stop event belongs initially to an exposure-transition observation set, within which withdrawal, rebound, recurrence, delayed toxicity, and unrelated causes remain distinguishable hypotheses. This distinction is especially important when pharmacovigilance signals are discussed publicly. A meta-epidemiological study identified exaggeration of causal statements in later citations of disproportionality analyses, demonstrating the broader danger of allowing an association to acquire unwarranted causal authority [27].

The conceptual extension has testable consequences. First, the informativeness of temporal proximity should depend on whether a mechanism-specific signature exists. If two explanations predict indistinguishable early symptoms and no additional measurement is collected, a mechanistic label is not identifiable from that presentation alone. Second, rebound requires a defensible reference state: a return from suppressed bone turnover or acid secretion to a historical untreated level has a different meaning from an overshoot above that level. Third, late injury cannot be inferred merely from long time since therapy began; documented cessation, a plausible persistence mechanism, and competing-exposure assessment change the interpretation. Each proposition can be weakened by repeated observations that fit the rival mechanism better.

Prospective work should recruit at the discontinuation decision, record actual reduction strategies, and measure outcomes through periods appropriate to the drug and disease. Target-trial thinking helps specify eligibility, competing continuation or taper strategies, aligned time zero, and outcome assessment before examining causal

contrasts [23]. Negative-control outcomes or exposures may expose residual confounding where defensible; they cannot restore measurements that were never made. For rebound hypotheses, serial physiological observations and pretreatment reference values are more informative than symptom inventories alone. For recurrence, validated measures of the underlying illness should be collected independently of withdrawal symptom checklists. For delayed harm, active ascertainment and exposure verification should extend beyond routine treatment records where justified.

Validation must also test the limits of classification. Independent assessors could compare interpretations given event timing alone with interpretations after exposure histories, disease baselines, and mechanism-relevant tests are available. The principal question would be whether additional information improves defensible discrimination, including the appropriate use of a mixed or unresolved designation. It would be inappropriate to announce sensitivity, specificity, or agreement levels before such research is done. Observational taper cohorts reflect real variations in exposure paths but may attract self-selected patients and cannot, on their own, isolate strategy effects [24]. Neural markers associated with relapse following antidepressant discontinuation offer a potential research direction without becoming a diagnostic discriminator of withdrawal at the bedside [25]. The most informative future result may be a demonstration that some clinical presentations cannot be reliably separated under practical measurement conditions.

Limitations and classification boundaries

The reasoning is derived from heterogeneous clinical trials, observational studies, biological work, reviews, and pharmacovigilance methods; it is not based on a formal comparative accuracy study. Drug classes differ in receptor adaptation, tissue persistence, disease course, and availability of untreated reference measurements. Antidepressant symptom estimates are sensitive to symptom definitions and study design [8]. Cellular observations related to denosumab may support an overshoot hypothesis without assigning the cause of an individual fracture [15]. Likewise, late immune events defined from treatment initiation cannot automatically support a cessation-specific causal category [19].

The approach cannot establish universal latency thresholds or convert spontaneous reports into individual causal probabilities. Its categories can overlap, and uncertainty may remain even after careful follow-up. Retrospective fracture associations and other population-level findings do not eliminate patient-specific competing risks [16]. Evaluation of safety signals also varies with the evidence considered and the language used to communicate it [3]. Causal overstatement identified in pharmacovigilance citation practices illustrates why provisional labels must remain provisional [27]. The classification is therefore most defensible as an aid to evidence collection and transparent causal argument, with practical performance, inter-assessor reliability, and applicability across treatment settings left for empirical investigation.

CONCLUSION

An adverse event observed after medication discontinuation is best understood first as a change following an exposure transition, not as proof of a particular drug-related mechanism. Distinguishing withdrawal syndrome, rebound physiology, disease recurrence, delayed treatment-related harm, and intercurrent illness requires the actual dose history, an appropriate disease or physiological reference, mechanism-relevant observations, and serious consideration of rival explanations. The central theoretical boundary arises when stopping a drug changes multiple causal processes at once, defeating an assumption that drug removal reveals a stable untreated state. Provisional, mixed, and unresolved attributions can preserve useful safety information without overstating it. Prospective evaluation is needed to determine whether these distinctions improve pharmacovigilance decisions.

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