

## Minireview

# Attenuation of Response to Repeated Drug Administration: A Proposal for Differentiating Tachyphylaxis and Tolerance

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### ABSTRACT

Attenuation of drug response with repeated administration is referred to as tachyphylaxis or tolerance, though the distinction between these two is obscured through both their usage in the literature and imprecise definitions in common pharmacology texts. In this perspective, I propose that these terms be distinguished by the mechanisms underlying the attenuation of drug response. Specifically, tachyphylaxis should be reserved for attenuation that occurs in response to cellular depletion, whereas tolerance should be used to describe attenuation that arises from cellular adaptations. A framework for understanding behavioral tolerance, physiologic tolerance,

and dispositional tolerance as distinct phenomena is also discussed. Using this framework, a classification of drugs exhibiting attenuation of drug response with repeated administration is presented.

### SIGNIFICANCE STATEMENT

Distinction between tachyphylaxis and tolerance is unclear in the literature. Nonetheless, a mechanistic basis for distinguishing these important terms has practical implications for managing or preventing attenuation of drug response with repeated administration.

### Introduction

Are the terms tachyphylaxis and tolerance synonyms, related responses distinguished quantitatively, or distinct phenomena? Examination of standard texts in pharmacology fails to provide a clear answer to this question. For example, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, tachyphylaxis is described as “the rapid development of complete tolerance” (Blumenthal, 2017). The standard pharmacology text in the Lange Medical Books series is likewise imprecise in asserting that “[w]hen responsiveness diminishes rapidly after administration of a drug, the response is said to be subject to tachyphylaxis” (von Zastrow, 2021). Other texts provide similarly ambiguous differentiation between these terms (Neubig, 1990; Alenghat and Golan, 2017). What demarcates *rapid* tolerance from tolerance (seconds, minutes, hours, days?) is nowhere specified. Perhaps not surprisingly, investigators use the term tachyphylaxis to describe attenuation of responses that occur with repeated administration of drugs over minutes (de Moraes and de Carvalho, 1968), hours (du

Vivier and Stoughton, 1975), days (Vaidyanathan et al., 2010), weeks (Foroghian et al., 2009), or even months (Katz, 2011).

Characterization of dose- or time-dependent attenuation of drug response is further obscured by labeling such responses as desensitization or refractory. Collectively, these terms are sometimes used with little to no effort to specify their meaning. It is no wonder that students of pharmacology struggle to define and differentiate these labels for seemingly near-identical phenomena (<https://derangedphysiology.com/main/cicm-primary-exam/required-reading/variability-drug-response/Chapter%2022/1/mechanisms-tolerance-and-tachyphylaxis>). The objective of this perspective is to provide a framework for differentiation between the terms used to describe attenuation of drug response after repeated doses and to categorize drugs known to exhibit such a diminution in response.

### Early Observations on Tolerance and Tachyphylaxis

Barger and Dale (1910), who proposed the term sympathomimetic, appear to have been the first to note an attenuation of response to repeated doses of pharmacologic agents through their studies of a series of basic amines. Subsequent investigations examining the pressor effect of pituitary extracts found

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**ABBREVIATIONS:** AChR, acetylcholine receptor;  $\beta$ -AR,  $\beta$ -adrenergic receptor; bpm, beats per minute;  $E_{\max}$ , the maximal effect achieved as dose or concentration is increased; mAb, monoclonal antibody; NNMBA, nondepolarizing neuromuscular blocking agent; VEGF, vascular endothelial growth factor.

that sequential doses of these extracts exhibited a reduced *in vivo* pressor response in comparison with the first dose, a phenomenon that was both dose and time-interval dependent (Dudley, 1923; Hogben et al., 1924). This diminution in effect was termed *acquired tolerance* and was found to be overcome through an adequate lapse of time between doses. Whether the tolerance was due to physiologic adaptations or the presence of another (contaminating) substance in the preparations used was a matter of debate. Chen and Meek (1926) demonstrated a similar phenomenon with ephedrine and termed the effect *transient tolerance*. A similar diminution in effect was not observed with epinephrine or tyramine (Chen and Meek, 1926; Chen, 1928).

Among the earliest demonstrations of tolerance to drugs in humans was that observed among chronic opiate users who reported the ability to consume doses normally lethal to naive users (Gunn, 1923). Similar observations were made in users of cocaine. Early efforts to reproduce these effects and uncover the mechanism for acquired tolerance yielded conflicting results (Schmidt and Livingston, 1933a,b; Beecher, 1953).

The first retrievable usage of the word 'tachyphylaxis' in the English language scientific literature was by Bernard Fantus in 1918, who asserted that the term was introduced in a French publication in 1911 (Fantus, 1918). As first applied, the word denoted the development of immunity in response to repeated doses of a testicular extract that protected animals against subsequent exposure to larger doses. It was not until 1931 that the term was applied to drug effects, when Hartung et al. (1931) noted in passing that ephedrine and phenylpropanolamine induced tachyphylaxis. Not long thereafter, attenuation in the response to repeated doses of renin was also characterized as tachyphylaxis (Page, 1939). Importantly, tachyphylaxis to renin was ascribed to the depletion of an endogenous substance (renin-activator factor). It was after these observations that investigators first began to characterize the phenomenon of tachyphylaxis. Based upon an analysis of usage of the word in books within the Google repository (Fig. 1A), interest in tachyphylaxis escalated in the 1930s, reaching a peak in 1988 and rapidly declining thereafter, though experiencing a brief renaissance from 2007 to 2014. In contrast, interest in tolerance began to rise significantly around 1920 and has been relatively sustained at a plateau first achieved in the 1980s (Fig. 1B).

Seevers and Woods (1953) attempted to differentiate tachyphylaxis and tolerance, wherein the former was specified as a subset of the latter—distinguished by rapid development and short duration. This time-dependent basis for differentiating tachyphylaxis and tolerance has been the most common framework used in textbooks and journal articles. A decade later, Cowan (1963) noted inconsistency in the use of tachyphylaxis by pharmacologists and surmised that mechanistic understanding of the phenomenon might yield greater clarification. Yet, as previously noted, the practical distinction between the two remains opaque in common usage. Thus, there is a need for a more rigorous distinction between these labels that characterize important responses to drugs.

## General Definitions and Conceptual Framework

Attenuation of response to repeated doses of a drug is a reduced pharmacologic effect with either continuous or inter-

mittent dosing over time. This attenuation is quantitatively demonstrated by a rightward shift in the dose- or concentration-response relationship, such that the  $ED_{50}$  or  $EC_{50}$  is increased with or without an accompanied decrease in the maximal effect achieved ( $E_{max}$ ). This movement in the concentration-effect curve may be demonstrated *in vitro* or *in vivo*. Although determination of  $EC_{50}$  and  $E_{max}$  represents the most robust means with which to characterize changes in drug response, investigators have rarely conducted a careful dose- or concentration-response assessment in their investigations into tachyphylaxis/tolerance. Instead, most have simply measured effect after a standard dose administered repeatedly. This approach diminishes the rigor of the characterization of the attenuation in response and limits mechanistic insight, as discussed further below.

The core issue revolves around a simple question: Should tachyphylaxis be viewed as a subset of tolerance, or is it advantageous to view the terms as distinct and nonoverlapping? In either case, how should they be distinguished? Whichever view one takes regarding their relationship, the potential framework for distinction between them would appear to encompass three possibilities:

1. **Chronologically:** differentiation based upon the speed of development of attenuation of drug response
2. **Phenomenologically:** differentiation based upon experimental observations, such as the ability of increased concentrations to overcome the attenuation of drug response
3. **Mechanistically:** differentiation based upon the biologic changes causing the attenuation of drug response

An assessment of the experimental literature demonstrates deficiencies with using a chronological or phenomenological framework, whereas a mechanistic framework enables an objective basis for distinguishing tachyphylaxis and tolerance as distinct responses to drugs without setting arbitrary time boundaries.

**Chronologically.** Most pharmacologists have asserted rapidity of onset as the means of distinction between terms, viewing tachyphylaxis as a subset of tolerance. Hence, it is assumed that differentiation is based on chronology, which is logically rooted in the word itself. Derived from the Greek *ταχυς* (*tachys*), meaning 'rapid,' and *φυλαξις* (*phylaxis*), meaning 'protection,' tachyphylaxis is inherently anchored in time. From an etymological perspective, therefore, it would seem appropriate that speed of onset of attenuation of response might be the logical means to distinguish tachyphylaxis and tolerance. But where on the time scale do tachyphylaxis end and tolerance begin? Selecting a specific time frame would be arbitrary, though it may practically distinguish between the terms. Seevers (1958) asserted that tachyphylaxis was differentiated from other forms of tolerance in that it developed rapidly *and* was short-lived, framing the effect in time for both onset and duration. Nonetheless, this simply compels the establishment of two arbitrary boundaries for distinction for which no consensus appears to exist.

A further complicating factor is that too short of an interval between drug administration is likely to provoke 'pseudo'

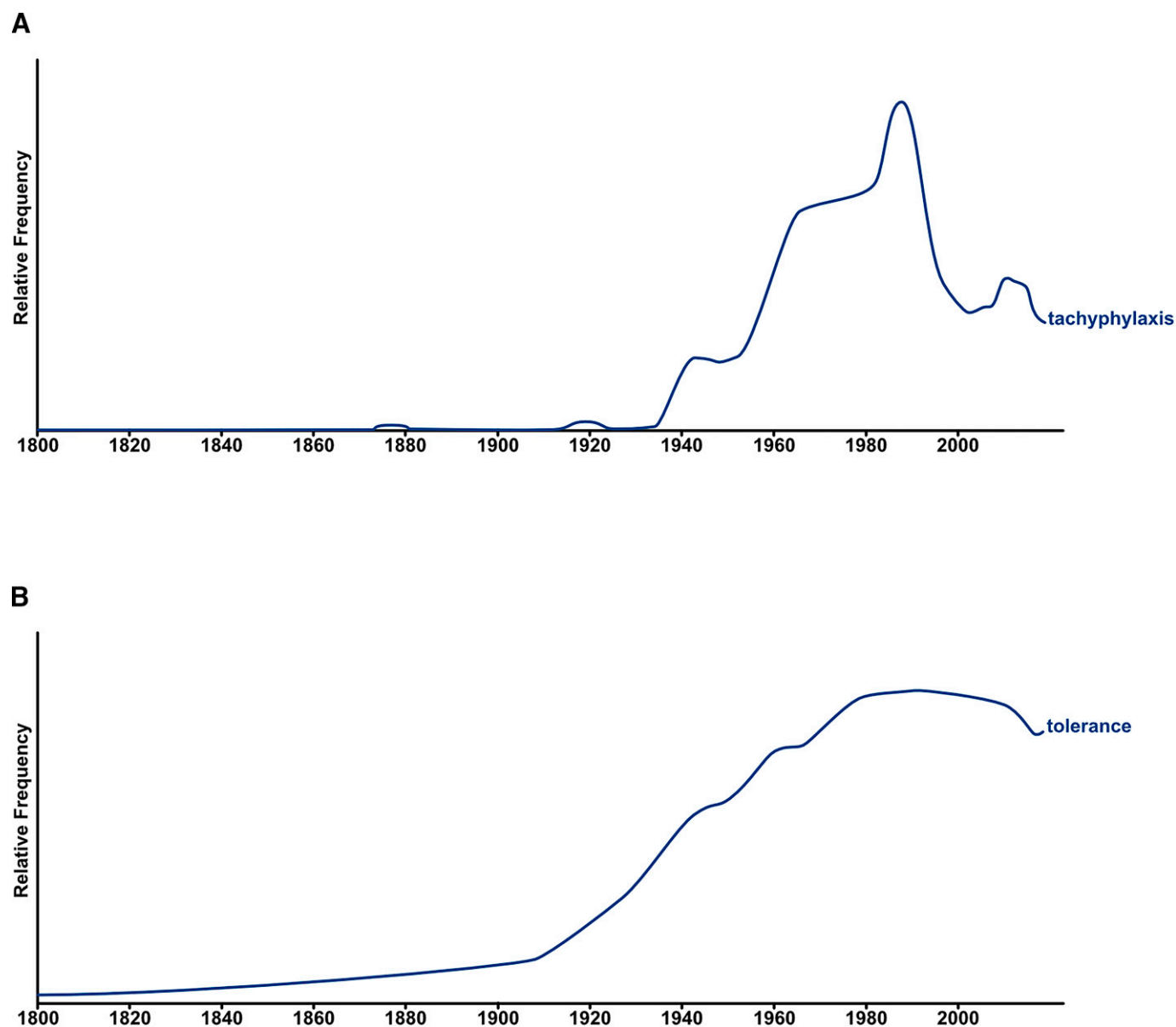
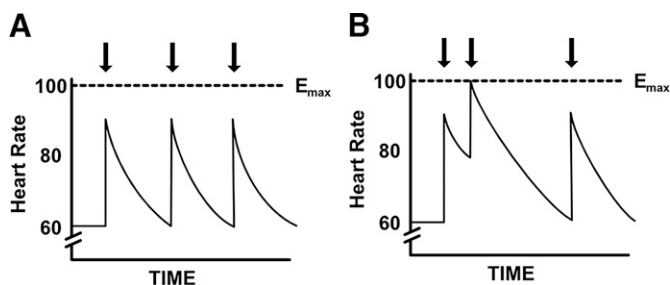


Fig. 1. Google Books Ngram analysis of appearance of (A) tachyphylaxis and (B) tolerance over time.

tachyphylaxis due to achieving the  $E_{\max}$  as a result of residual drug remaining from the previous dose. In particular, administration of the second dose of a drug *before* return to basal conditions (because residual drug continues to have an effect) could result in a *proportionately* smaller increase in effect after the second dose, not because of attenuation of effect but simply because the added effect of residual drug and the second dose produces a concentration beyond that which achieves  $E_{\max}$ . This scenario is illustrated for a hypothetical chronotropic agent in Fig. 2. Assume that the drug does not induce any form of tolerance and is administered to a subject at varying intervals at the same dose. In Fig. 2A, a single dose of drug increases the measured heart rate from 60 to 90 beats per minute (bpm), an increase of 30 bpm (50%) above baseline. If the effect is allowed to return to basal level, the second and third doses will similarly increase the heart rate by 50%. However, if the second dose is administered before drug from the

first dose is eliminated and the heart rate returns to basal levels (Fig. 2B), the second dose will increase the heart rate to the  $E_{\max}$  (100 bpm). Thus, the increase from a second dose in this case is only 20 bpm (20% above the heart rate just prior to giving the second dose). If the heart rate is then allowed to return to basal levels, the response to a third dose will be the same as that seen with the first. Thus, the second dose may mimic tachyphylaxis, but as the subsequent dose demonstrates, it is merely a function of achieving the maximal effect with the second dose due to the residual concentration of drug from the first dose. As described by Johnson and Fleming (1989), a similar problem occurs when seeking to demonstrate tolerance after chronic morphine administration if one does not account for residual drug at the time that a 'test' dose is administered to quantify morphine response.

From this illustration it can be seen that the demonstration of tachyphylaxis would experimentally need to be bounded by



**Fig. 2.** Changes in response as a function of dosing interval. Curves represent a hypothetical chronotropic agent administered at the intervals denoted by arrows and the effect on heart rate. (A) After the initial dose, each subsequent dose is not administered until heart rate returns to basal levels. The identical response with the three doses illustrates the absence of tolerance. (B) The same drug is administered at intervals denoted by arrows. Since the second dose is administered before heart rate returns to the basal rate, the residual concentration of the first dose, combined with the second dose, results in a concentration exceeding that which produces  $E_{max}$ . As a consequence, it appears that the proportional response to the second dose is attenuated. But if the third dose is not administered until heart rate returns to the basal level, the proportional response is restored, showing that tolerance has not developed.

both a minimal and a maximal time between doses. A minimal time is needed for the parameter of interest (e.g., blood pressure) to return to basal conditions, which may vary based on the parameter measured, the pharmacokinetics of the drug, and other factors. Hence, the simple use of ‘rapid’ as the determinant for differentiating tachyphylaxis and tolerance is insufficiently precise.

An additional shortcoming in using the chronological approach is that drugs of the same class may exhibit different time frames for tolerance development, which may be a function of how they are administered or their inherent efficacy (Morgan and Christie, 2011). For example, the potent opioid remifentanyl can produce tolerance within the first 2 hours of a 4-hour constant infusion, whereas tolerance to oxycodone is not observed with 5 days of twice-daily oral dosing (Vinik and Kissin, 1998; Cooper et al., 2012). Does this indicate that the attenuation in response to these opioids is fundamentally different? Should the effect of remifentanyl be labeled as tachyphylaxis and that seen with longer-term oxycodone administration as tolerance? And how do we view acute tolerance and chronic tolerance to the same drug, such as morphine? Mechanistically, the tolerance that arises with acute and chronic morphine administration appears to be the same (Fairbanks and Wilcox, 1997). It seems irrational to label this attenuation in response to morphine differently simply because they are induced under different time scales of administration.

It should also be noted that tachyphylaxis is dependent upon dose, not just time (Cowan et al., 1961b). Moreover, tachyphylaxis can be prevented or reversed without changing the variable of time. For example, tachyphylaxis to renin can be prevented or reversed by coadministration of ‘renin-activator’ (Page, 1939). In addition, coadministration of epinephrine prevents or reverses the tachyphylaxis seen in the pressor response to ephedrine (Cowan et al., 1963). Thus, it is clear that time is not the key determinant for the development of tachyphylaxis, which further argues against a chronological basis for distinguishing this phenomenon from tolerance.

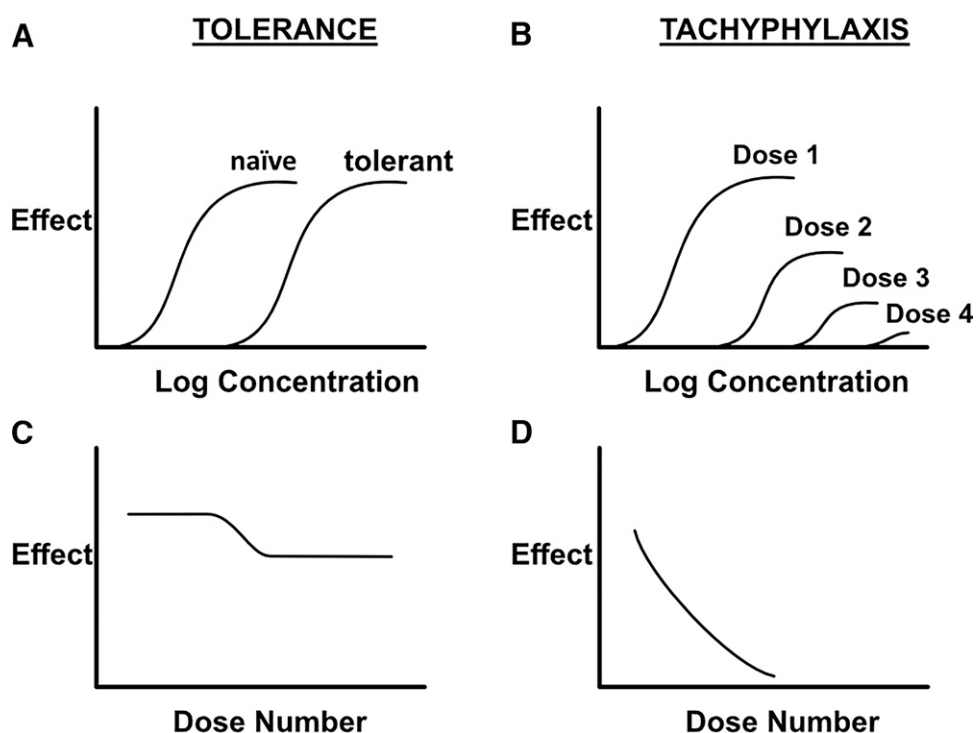
**Phenomenologically.** A second means by which tachyphylaxis and tolerance may be differentiated is how they

appear phenomenologically. In particular, it has been posited that although both exhibit an increase in  $EC_{50}$ , tachyphylaxis is accompanied by a decrease in  $E_{max}$  (Fig. 3, A and B; Kalant et al., 1971). Moreover, although continued administration of a drug producing tolerance will achieve a new and sustained lower level of effect, repeated doses of a drug exhibiting tachyphylaxis will eventually produce a refractory state (Fig. 3, C and D). This phenomenological appearance of response in the setting of tachyphylaxis and tolerance has some experimental support. Morphine is a common example of the shift in dose- or concentration-response exhibited in Fig. 3, A and C (Ingram et al., 2007). Numerous investigations into the response of sympathomimetic amines—agents classically viewed as exhibiting tachyphylaxis—exhibit data consistent with the response characterized in Fig. 3, B and D (Cowan et al., 1961a,b; 1963). Moreover, morphine tolerance has been found to stabilize with chronic administration, as illustrated in Fig. 3C (Xu et al., 2015).

On the surface, this would appear to be a useful means of distinction. Practically, however, this has rarely been demonstrated in the experimental literature, as few investigators perform complete dose- or concentration-response determinations. Thus, whether  $E_{max}$  has declined is unknown. In addition, limited evidence suggests that *chronic* administration of opioids may also reduce  $E_{max}$  to some effects of the drug (Goldstein et al., 1973), thus behaving like tachyphylaxis phenomenologically. Clinically, other drugs demonstrate refractoriness, such that increased doses do not restore effectiveness with long-term administration over weeks or months (e.g., antidepressants) (Katz, 2011). Thus, a phenomenological approach to distinguishing tachyphylaxis and tolerance leaves situations where ambiguity remains in attempts to distinguish the two.

**Mechanistically.** Early investigators posited that tachyphylaxis was secondary to saturation of receptors because of drug remaining at the site of action from the initial dose (Chen, 1928; Seevers and Woods, 1953; Cowan et al., 1961b). Why continued occupancy of receptors by an agonist should result in a diminution of effect over repeated doses was never well explained and subsequent studies have demonstrated that tachyphylaxis occurs with indirect-acting sympathomimetics, which appears to negate the receptor occupancy hypothesis. Nonetheless, these investigators did provide the impetus for seeing tachyphylaxis as mechanistically different from tolerance.

I propose that tachyphylaxis is best understood and differentiated by recognizing that it is a result of cellular *depletion*, whereas tolerance arises from cellular *adaptation* (see definitions in Table 1). By this is meant that the attenuation in the case of the former is driven by the depletion of endogenous signals essential for the pharmacologic effect. Restoration to baseline levels of signal molecules returns cellular responses to their basal levels. Furthermore, prevention of depletion will forestall the attenuation of response. In contrast, tolerance occurs as an adaptive phenomenon, wherein cell signaling by the drug initiates a cascade of molecular events resulting in dynamic changes in cellular responsiveness specifically to return the cell to homeostasis. Seevers and Woods (1953) were the first to posit tolerance as a cellular adaptation. The distinction proposed here differs from the proposition of Johnson and Fleming (1989) that tachyphylaxis can also be viewed as an adaptive change.



**Fig. 3.** Changes in concentration-response relationship with attenuation of drug response after repeated administration. (A) Expected concentration-response relationship when drug is administered to naïve or tolerant subjects (where tolerance has developed as a consequence of multiple dosing). In this scenario,  $EC_{50}$  is greater in tolerant compared with naïve, whereas  $E_{max}$  remains unchanged. (B) Expected concentration-response relationship with repeated doses of a drug producing tachyphylaxis. With each successive dose,  $EC_{50}$  increases and  $E_{max}$  decreases, ultimately reaching a refractory state of nonresponsiveness. (C) Drug response as a function of dose number for a drug producing tolerance. After multiple doses of the same dose, effect decreases, plateauing to a new response level with continued doses. (D) Drug response as a function of dose number for a drug producing tachyphylaxis. Each successive identical dose results in an attenuation in response, reaching a state of nonresponsiveness.

To date, cellular depletion as a means of attenuation of drug effect appears to be uniquely associated with indirect-acting sympathomimetic agents and desmopressin. Evidence that indirect-acting sympathomimetic amines provoke tachyphylaxis via cellular depletion was first provided by Cowan et al. (1961a; 1963), who showed that an infusion of norepinephrine prevented and restored ephedrine-induced tachy-

phylaxis. Similarly, cocaine induces a tachyphylaxis that is reversed by norepinephrine (Maengwyn-Davies and Koppányi, 1966). In addition, tissues rendered unresponsive by cocaine treatment also demonstrated an attenuated response to other indirect-acting sympathomimetics, supporting the depletion of neurotransmitter as the mechanism for the effect.

TABLE 1  
Proposed definitions of terms

Term	Definition
<i>Tachyphylaxis</i>	Attenuation of drug response due to cellular depletion of physiologic stores of signaling chemicals (e.g., neurotransmitters)
<i>Tolerance</i>	Attenuation of drug response due to cellular adaptations (e.g., receptor downregulation)
<i>Behavioral Tolerance</i>	Attenuation of psychoactive drug response due to learned adaptations
<i>Dispositional Tolerance</i>	Attenuation of drug response secondary to reduced access of drug to the active site (e.g., development of neutralizing antibodies)
<i>Physiologic Tolerance</i>	Attenuation of drug response secondary to physiologic counter-regulation (e.g., neurohormonal responses to vasodilation)
<i>Cross-Tolerance</i>	The phenomenon by which one or more doses of a drug reduces response to the first dose of a second drug (compared with the response seen without prior treatment of either drug)
<i>Pseudotolerance</i>	Attenuation of drug response due to worsening disease, secondary pathology, or noncompliance with drug regimen
<i>Refractory State</i>	A state at which an organism displays complete unresponsiveness to a pharmacologic agent after initial response, such that subsequent doses provoke no response
<i>Resistance</i>	A state in which cells have lost initial sensitivity to the lethal effects of a drug during treatment

Administration of desmopressin to patients with hemophilia or von Willebrand disease is associated with an attenuation in response to doses subsequent to the first dose (Mannucci et al., 1992). This arises from cellular depletion of stored factors (von Willebrand factor and Factor VIII) in endothelial cells as a response to the first dose (Takeuchi et al., 1988). The attenuation in effect can be avoided by increasing the interval between doses, allowing restoration of depleted cellular stores (Mannucci et al., 1992).

The mechanism of attenuation of effect to opioids and  $\beta$ -adrenergic receptor ( $\beta$ -AR) agonists has been interrogated more intensely than other drugs, and both occur via multilevel cellular adaptations at their respective G protein-coupled receptors. Development of tolerance to opioids was observed early among addicts who required increasing doses over time to obtain the desired effect and to forestall withdrawal (Gunn, 1923). As described by Williams et al. (2013), the sequential process leading to tolerance of effect mediated through  $\mu$ -opioid receptors includes an initial attenuation arising from receptor phosphorylation (initiated in seconds *in vitro*), leading to arrestin binding and receptor endocytosis. Although the relative role of these respective processes on the clinical phenomenon of tolerance and experiences of withdrawal upon rapid cessation of drug therapy remains a matter of debate, the cellular adaptive responses to continued exposure to opioids is well established.

Multiple lines of evidence support the conclusion that chronic use of  $\beta_2$ -agonists results in an attenuation of response that is associated with significant morbidity and mortality in patients with asthma (Yim and Koumbourlis, 2013). Rapid attenuation of response of  $\beta$ -AR has also been readily demonstrated in cultured cells (Harden, 1983). Similar to opioid agonists,  $\beta_2$ -agonists initiate a cascade of events that include receptor phosphorylation via  $\beta$ -AR kinases, binding to arrestin, and receptor translocation (Benovic, 2021; Sun and Kim, 2021). The demonstrated homologous and heterologous attenuation that may occur with G protein-coupled receptors (wherein an agonist of one receptor type downregulates another receptor type) due to common downstream pathways further differentiates tolerance from tachyphylaxis mechanistically.

Differentiating tachyphylaxis and tolerance mechanistically illuminates the basis for both common and differentiating features of the two phenomena (Table 2). Although both are only demonstrated with repeated (or continuous) administration of the drug, cellular depletion is especially sensitive to the dosing interval, as normal homeostasis will rapidly restore the depleted chemical(s). This mechanistic differentiation focused on cellular depletion also preserves the inherent rapidity implied by the term tachyphylaxis, as cellular depletion is tightly linked to the mechanism of action of the drug and in

all known cases occurs within a single dose. Understanding cellular depletion as the mechanism of tachyphylaxis also explains why attenuation of response is not overcome by increasing the dose.

In contrast, cellular adaptation (e.g., receptor downregulation) seen with tolerance may logically be overcome by increasing the dose, yet it is also understandable that some adaptive mechanisms would not be thwarted through larger doses. In addition, cellular adaptation may be quite rapid, as is the case with receptor modulation upon exposure to nicotine (Robinson et al., 2006). A further example, as described previously, is the sequential process leading to tolerance of effect mediated through G protein-coupled receptors that is initiated very rapidly. These observations provide further evidence that speed of onset is not a feasible basis by which to distinguish tachyphylaxis and tolerance.

Nondepolarizing neuromuscular blocking agents (NNMBAs) illustrate how a mechanistic approach can clarify the appropriate terminology to describe attenuation of drug response. Numerous NNMBAs have been found to exhibit a reduced response during repeated dosing or during a constant infusion (Tschida et al., 1996), a phenomenon variously called tachyphylaxis, resistance, hyposensitivity, or tolerance. As this attenuation can occur within hours of dosing, it is unsurprising that it has been referred to as tachyphylaxis. However, the phenomenon appears to occur due to an upregulation of extrajunctional acetylcholine receptors (AChRs) (Berg and Hall, 1975; Martyn et al., 1992). As 95% AChR occupancy is required for complete muscle twitch suppression (Martyn et al., 1992), the increased expression of AChRs in extrajunctional space with repeated or continuous dosing will decrease the fractional receptor occupancy, thereby decreasing the effect of the agent. Hence, the phenomenon of attenuation in response to NNMBAs is appropriately labeled as tolerance, despite the relatively rapid onset.

In contrast, the mechanism by which depolarizing neuromuscular blocking agents (suxamethonium and decamethonium), which act as agonists of the AChR, exhibit a rapid attenuation of effect is less clear (Lee et al., 1978; Hughes et al., 1982). This attenuation has been variously ascribed to self-antagonism (Lee, 1976), slow dissociation of the agents from the cholinergic receptor (Calvey and Williams, 2008), and AChR downregulation (Martyn et al., 1992). Although the latter provides a sound theoretical framework for the phenomenon, definitive experimental observations are lacking. Thus, at present, this is best classified as an attenuation of response by unclear mechanism(s).

A mechanistic framework also provides a basis to understand how a drug could provoke both tachyphylaxis and tolerance, depending on the schedule of administration. For

TABLE 2

Common and differentiating features of tachyphylaxis and tolerance

Tachyphylaxis	Tolerance
Observed with repeated doses	Observed with repeated doses
Highly sensitive to dosing interval	Less sensitive to dosing interval
Not overcome by increasing dose	Usually overcome by increasing dose
Increase in EC <sub>50</sub>	Increase in EC <sub>50</sub>
Progressive decline in E <sub>max</sub>	Usually no change in E <sub>max</sub>
Modest extension of the dosing will prevent occurrence	Modest extension of the dosing interval will not prevent occurrence
Prevented by coadministration of substance otherwise depleted	May exhibit heterologous attenuation via common downstream pathways for different receptors

example, recent evidence would suggest that ephedrine is both an indirect- and direct-acting sympathomimetic (Liles et al., 2006; 2007). Depending upon the interval between doses, cellular depletion leading to tachyphylaxis or cellular adaptation leading to tolerance may be observed. Dosing schedules may avoid the former but not the latter. To date, the ability of ephedrine to induce tolerance has not been investigated. Interestingly, however, there is anecdotal evidence of hockey players developing significant tolerance to another mixed-acting sympathomimetic: pseudoephedrine (<https://vault.si.com/vault/1998/02/02/hockeys-little-helpers-the-legal-drug-of-choice-in-the-nhl-is-sudafed-not-for-cold-relief-but-for-the-once-boost-it-offers>).

Even sympathomimetics that act solely via an indirect mechanism can induce both tachyphylaxis and tolerance, as exemplified by amphetamine. Early evidence was provided that chronic administration of amphetamine could produce tolerance to the lethal effects of the drug in monkeys (Seevers, 1958). Bingeing, or runs of high-dose consumption, among stimulant abusers is a well known phenomenon. Experimental evidence supports the ability of this mode of administration to modulate dopamine autoreceptor function (Kuczenski and Segal, 1997), reflecting an induction of tolerance. Thus, acute administration of this indirect-acting sympathomimetic produces tachyphylaxis, but with an appropriate chronic dosing regimen, it may also induce tolerance. These two forms of repeated dose attenuation of biologic response are mediated differently and best distinguished using differentiating terminology.

In addition to differentiating tachyphylaxis and tolerance, it is important to categorize forms of apparent tolerance that do not arise from cellular adaptation but rather from events distant to the target cell. In particular, distinguishing between tolerance, behavioral tolerance, physiologic tolerance, and dispositional tolerance provides further mechanistic-based clarification of these diverse phenomena (Table 1). Indeed, this distinction enables the classification of drugs that exhibit biologic response attenuation after repeated drug administration based upon the mechanism underlying this change (Table 3).

### Behavioral Tolerance

A belief among consumers in the ability of an individual's self-determination to modulate the behavioral impact of psychoactive agents, such as alcohol and cannabis, appears to be widely held (Vogel-Sprott, 1997). Experimental confirmation of this, which is often termed *behavioral tolerance*, is both difficult and sparse. The experimental paradigms to tease out the effects of subject-controlled (or intentional) adaptations from drug-induced phenomena, especially in humans, are both complex and controversial. Nonetheless, the concept of behavioral tolerance to psychoactive agents has been widely studied by psychopharmacologists. It is clear that some responses commonly labeled as behavioral tolerance may be mediated by receptor adaptations, as appears to be the case with lysergic acid diethylamide (LSD) (Gresch et al., 2005). These attenuations in response would, therefore, be appropriately classified as true tolerance. On the other hand, it appears that tolerance to some effects of alcohol is learned adaptation for specific tasks under an intoxicated state and is best classified as behavioral tolerance (Vogel-Sprott, 1997; Grattan and Vogel-Sprott, 2001). Advances in brain imaging and experimental paradigms may eventually provide a clearer differentiation

between biologic tolerance and behavioral tolerance, but at present, differentiation between the two should be viewed as tentative.

### Physiologic Tolerance

Physiologic tolerance arises when responses outside the site of action occur to restore physiologic homeostasis. This mechanism of attenuated drug response can be seen with vasodilator drugs (e.g., nitroprusside) and diuretics (e.g., furosemide). In the former, vascular resistance or cardiac output changes blunt the hypotensive effects initially seen with the vasodilator (Colucci et al., 1981). Similarly, autoregulatory mechanisms counter the fluid loss provoked by furosemide, blunting its diuresis effect in vivo (Wakelkamp et al., 1996). Another example is seen with H<sub>2</sub>-receptor antagonists, which demonstrate a rapid onset of tolerance (within the first 3 days of dosing) to the gastric acid reduction induced by these drugs—an attenuation of effect not seen with proton pump inhibitors (McRorie et al., 2014). Although sometimes referred to as tachyphylaxis, this is another example of an agent best classified as physiologic tolerance, as the attenuation arises from hormonal counter-regulation through a rise in serum gastrin (Qvigstad and Waldum, 2004).

The attenuation in response to opioids is best seen as dual in nature. Initial tolerance is mediated by receptor adaptation (tolerance), whereas growing evidence suggests that an upregulation of pronociceptive pathways (physiologic tolerance) occurs in some patients during long-term treatment (Martyn et al., 2019). The tolerance to opioids can be managed by increasing the dose. In contrast, escalation of dose in the event of physiologic tolerance may worsen patient pain and is better managed with adjunctive or alternative analgesics. This example demonstrates the practical impact of providing clarity to attenuation in drug response based upon underlying mechanism(s).

### Dispositional Tolerance

Early investigators considered the potential that changes in the disposition of a compound (e.g., induction of metabolism) might be a mechanism underlying attenuated responses to drugs (Seevers and Woods, 1953). In this case, the change of response is rooted in a reduction in the amount/concentration of drug that reaches or accumulates in the site of action, rather than a form of cellular adaptation. This is best termed *dispositional tolerance*, and the phenomenon is well illustrated by the nature of attenuation of response that develops to monoclonal antibodies (mAbs). For example, use of the mouse-derived humanized antivascular endothelial growth factor (anti-VEGF) mAbs (ranibizumab and bevacizumab) in the treatment of macular degeneration exhibits an attenuation of response in about 10% of patients (Forooghian et al., 2009). This arises as the result of neutralizing antibodies with chronic administration (Brown et al., 2009). Switching from one anti-VEGF mAb to the other restores responsiveness in over 80% of patients (Gasperini et al., 2012). Since these mAbs have identical mechanisms of action, true tolerance would not be overcome by switching products. On the other hand, limited cross-immunoreactivity of neutralizing antibodies

TABLE 3  
Proposed classification of drugs exhibiting repeated dose attenuation of response

Drug(s)	Classification	Mechanism
Acetazolamide	Tolerance	Upregulation of enzyme (Anderson et al., 1989)
Alcohol	Behavioral Tolerance	Learned compensatory responses (Vogel-Sprott, 1997)
Amphetamine	Tachyphylaxis and Tolerance	Neurotransmitter depletion acutely, receptor adaptation chronically (Cowan et al., 1961a; Kuczenski and Segal, 1997)
Antidepressants	Pseudotolerance <sup>a</sup>	Emergence of latent/undiagnosed bipolar disorder, noncompliance, and worsening of disease (Fornaro et al., 2019)
$\beta$ -Adrenergic Agonists	Tolerance	Receptor downregulation (Yim and Koumbourlis, 2013)
Barbiturates	Tolerance	Alterations in receptor dynamics (Ito et al., 1996)
Benzodiazepines	Tolerance	Alterations in receptor dynamics (Gravielle, 2016)
Caffeine	Tolerance	Receptor upregulation (Ramkumar et al., 1988)
Cocaine	Tachyphylaxis	Neurotransmitter depletion (Maengwyn-Davies and Koppanyi, 1966)
$\Delta^9$ -THC	Tolerance and Behavioral Tolerance	Receptor downregulation; some evidence for learned compensatory responses (Ramaekers et al., 2020)
Desmopressin	Tachyphylaxis	Cellular depletion of clotting factors (Takeuchi et al., 1988)
Ephedrine	Tachyphylaxis <sup>b</sup>	Neurotransmitter depletion (Cowan et al., 1963)
Furosemide	Physiologic Tolerance	Neuroendocrine counter-regulation (Wakelkamp et al., 1996)
H <sub>2</sub> -Receptor Antagonists	Physiologic Tolerance	Hormonal counter-regulation; increased serum gastrin secretion (Qvigstad and Waldum, 2004)
LSD	Tolerance	Receptor downregulation (Gresch et al., 2005)
Opiates/Opioids	Tolerance and Physiologic Tolerance	Receptor downregulation acutely, followed by long-term upregulation of pronociceptive pathways (Martyn et al., 2019)
Nicotine	Tolerance	Adaptive changes in nicotinic cholinergic receptor functional state (Robinson et al., 2006)
Nitroglycerin/Nitroprusside	Physiologic Tolerance and Tolerance	Early tolerance due to neurohormonal counter-regulation; later tolerance due to cellular adaptations (Colucci et al., 1981; Munzel et al., 2005)
NNMBAs	Tolerance	Receptor upregulation (Martyn et al., 1992)
Oxymetazoline	Tolerance	Receptor downregulation (Vaidyanathan et al., 2010)
Therapeutic Proteins	Dispositional Tolerance	Neutralizing antibody generation (Baker et al., 2010)

LSD, lysergic acid diethylamide; THC, tetrahydrocannabinol.

<sup>a</sup>Although numerous mechanisms for true tolerance have been hypothesized for antidepressants, conclusive evidence for such changes is currently lacking.

<sup>b</sup>Although ephedrine is a mixed (direct- and indirect-acting) sympathomimetic, tachyphylaxis has been experimentally demonstrated whereas tolerance has not.

(bevacizumab is a full-length mAb, whereas ranibizumab is an antigen-binding fragment) would make product switching a successful approach in the face of dispositional tolerance. The common references in the ophthalmology literature to the attenuation in response to these mAbs as tachyphylaxis (over a hundred such references were identified through a search of Google Scholar) are irrational from both a mechanistic and speed-of-onset perspective (Binder, 2012), and the phenomenon is better labeled as dispositional tolerance. Moreover, this example illustrates that understanding when tolerance is dispositional in nature can provide insight into options to restore pharmacologic response (Baker et al., 2010).

## Restricting the Use of Desensitization as a Pharmacologic Term

*Desensitization* has been used in the experimental literature and pharmacology textbooks to describe the general phenomenon of reduced responsiveness to pharmacologic agents, especially in the context of drugs whose actions are receptor mediated. The prefix *de-* means to stop something. Hence, desensitization to a xenobiotic would refer to a process by which previous exposure has led to sensitization but then repeated exposure causes this responsiveness to be lost. This makes perfect sense in its immunologic use. Prior to mounting an allergic reaction to a drug, a patient must first be exposed,



initiating the sensitization process (Svensson, 2008). Subsequent or continued exposure of a patient who has become sensitized will now elicit an immunologic response, resulting in a potential array of adverse phenomena (e.g., skin rash, bronchospasm, etc.). Desensitization to the drug (such as is done with penicillin) can be undertaken by exposing the patient to escalating doses of the drug (starting at very low doses), which shifts the immune response and creates a state of immunologic tolerance (Castells et al., 2019). In this scenario, the patient has truly become desensitized.

In contrast, first-dose exposure to a drug such as ephedrine, morphine, or nicotine does not sensitize the organism to pharmacologic effects (e.g., blood pressure, heart rate, etc.). The cellular machinery possesses a basal capacity to respond to the drug and will do so upon first-dose exposure. Attenuation of response on repeated dose administration is not, therefore, truly a desensitization process. Hence, I would argue that this term should be abandoned as a means to describe the loss of pharmacologic effect upon repeated doses. Its use is best restricted to the production of immunologic tolerance in a patient previously immunologically sensitized. In circumstances in which decreased response is occurring by an unknown mechanism, it would be preferable to refer to the observation as an attenuation in responsiveness.

### Cross-Tolerance

The ability of repeated doses of one drug to attenuate the first response of a second drug (commonly called cross-tolerance) has been observed with drugs whose mechanisms of action are identical, similar, and distinct. For example, chronic methadone attenuates the response to morphine, and the reverse is also true (though the relative potency of cross-tolerance differs) (Neil, 1982). Cross-tolerance may also be observed with agents acting at different sites in the same signaling system. This is exemplified by the cross-tolerance observed between  $\beta$ -adrenergic receptor agonists and phosphodiesterase inhibitors (Benoy et al., 1975).

There are also examples of cross-tolerance to effects of drugs with distinct and nonoverlapping mechanisms of action. For example, multiple doses of alcohol reduce the hypothermic response to morphine and vice versa (Lê et al., 1980), but tolerance to the analgesic effect of alcohol does not attenuate morphine analgesia (Bell et al., 1998). The attenuation of the hypothermic effect may represent a form of cross-adaptation or physiologic tolerance, as opposed to tolerance (Lee et al., 2019). Thus, it is clear that the mechanisms behind what is commonly called cross-tolerance vary with the agents and effects being measured. The term itself appears intuitively obvious and serves the purpose of providing a label for observations across various agents. Distinguishing the mechanisms for cross-tolerance is certainly valuable in specific settings. At the same time, the practical implications of the existence of cross-tolerance would appear to be independent of the mechanism by which it occurs.

### Pseudotolerance

Loss of drug effect during treatment can also occur due to factors unrelated to any type of adaptive responses to drug administration. These are best viewed as forms of *pseudotolerance*. At times, patient noncompliance results in a loss of symptom

control, which, if not discovered, may be viewed and responded to as tolerance, with adverse consequences. Disease progression can also result in a loss of observed effect that may or may not be responsive to increased doses. Alternatively, emerging pathology may give rise to loss of therapeutic control. This scenario is exemplified by the loss of effect with antidepressants, which may not be responsive to increased doses (Katz, 2011). Although the underlying mechanisms of this phenomenon remain uncertain, emergence of latent or undiagnosed bipolar disorder is believed to be responsible for at least some of the cases (Fornaro et al., 2019). For reasons undiscoverable to this author, this loss of control is commonly referred to in the psychiatric literature as tachyphylaxis, despite taking months to develop (Kinrys et al., 2019). Indeed, a search via Google Scholar by the author identified over a hundred articles referring to antidepressant tachyphylaxis. This is among the illogical uses of the term, and the loss of control would be better labeled as pseudotolerance.

### Refractory Response

Nonresponsiveness in a previously responsive preparation or organism was first observed with sympathomimetic agents. Mechanistically, it is obvious that if stores of a cellular signaling molecule are fully depleted, cell response will be lost. Hence, a refractory response can be seen in the setting of tachyphylaxis, dependent upon the initial dose and timing of subsequent dose. There are, however, other mechanisms by which a cell may become refractory. For example, resistance to cancer chemotherapeutic or antimicrobial agents can develop (see below), rendering a cell nonresponsive to the drug. A loss of response to antidepressant drugs has also been observed clinically, a phenomenon that likely arises as a consequence of pseudotolerance (discussed in the previous section). Hence, a refractory state is an empirical observation that may be caused through a variety of mechanisms and is not reflective of a particular type of repeated dose attenuation in response.

### Resistance versus Tolerance

The use of drugs in the treatment of cancer represents an unusual pharmacologic endpoint, as the goal is to generate a lethal response in mammalian cancer cells. The use of combination regimens for the treatment of cancer is largely necessitated by the development of nonresponsiveness to drugs during the course of treatment. This occurrence of repeated dose attenuation to cancer chemotherapeutic agents has commonly been referred to as *resistance*. Cancer cell resistance to these agents involves both selective pressure (i.e., selective death of sensitive cells in the population leading to overgrowth of resistance cells) and cellular adaptation due to exposure to chemotherapeutic agents (Fodale et al., 2011; Mollaei et al., 2021).

Similarly, antimicrobials, herbicides, and pesticides have a lethal objective, and repeated dose attenuation is observed with mechanisms akin to that seen with cancer chemotherapeutic agents. Although one might, therefore, classify all of these agents as provoking both pseudotolerance (selective pressure) and tolerance (cellular adaptation), the unique pharmacologic objective and mechanisms of these agents justify the use of a different term to describe the phenomenon. Hence, characterizing the attenuation of response to repeated doses of

cancer chemotherapeutics, antimicrobials, herbicides, and pesticides as resistance rather than tolerance is strongly justified.

## Summary of Recommendations

The varying uses of terms to describe attenuation of response after repeated administration of drugs has led to widespread imprecise usage of labels for this phenomenon. Although true tachyphylaxis always occurs rapidly, tolerance may also emerge quite quickly. Hence, time is insufficient to distinguish these responses. It is proposed that tachyphylaxis be reserved for attenuation that occurs in response to cellular depletion, whereas tolerance be used to describe attenuations that arise from cellular adaptations. Related categories of behavioral tolerance, physiologic tolerance, and dispositional tolerance are useful means to categorize attenuation that arises outside the target cell. Desensitization should be reserved for responses wherein immunologic tolerance is induced. Finally, it should be recognized that pseudotolerance, secondary to patient noncompliance, disease progression, or emergence of latent pathology, may also mimic tolerance. Distinguishing among these phenomena has important implications for therapeutic strategies when attenuation of drug response occurs in patients during treatment.

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