REVIEW

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Tolerance to the Prophylactic Effects of Carbamazepine and Related Mood Stabilizers in the Treatment of Bipolar Disorders

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SUMMARY

Tolerance development after successful long-term treatment of bipolar disorder is under recognized, as are ways to prevent or show its occurrence or reverse it once it has occurred. We review the clinical literature which suggests that tolerance can develop to most treatment approaches in bipolar illness and present an animal model of tolerance development to anticonvulsant effects of carbamazepine or lamotrigine on amgydala-kindled seizures. In this model tolerance does not have a pharmacokinetic basis, but is contingent upon the drug being present in the brain at the time of amygdala stimulation. The occurrence of seizures in the absence of drug is sufficient to reverse tolerance and re-establish anticonvulsant efficacy. Based on the model, we hypothesize that some episode-induced compensatory adaptive changes in gene expression fail to occur in tolerant subjects and that episodes off medication re-induce these changes and renew drug effectiveness. Approaches that slow or reverse tolerance development in the animal model are reviewed so that they can be tested for their applicability in the clinic. Criteria for assessing tolerance development are offered in the hope that this will facilitate a more systemic literature about its prevalence, prevention, and reversal. Careful longitudinal monitoring of episode occurrence is essential to understanding tolerance development in the affective disorder and its treatment.

Introduction

Tolerance to the antinociceptive effects of carbamazepine (CBZ) in the long-term treatment of trigeminal neuralgia and related paroxysmal pain syndromes has been widely recognized as a substantial problem after initial evidence of acute efficacy in about 80% of patients [1–4]. Less well known is the potential for tolerance development during long-term treatment with CBZ and other anticonvulsants in seizure disorders and in patients with bipolar disorder.

However, close examination of the course of illness in initial good responders to CBZ in mono- or poly-therapy reveals that after years of sustained remission, episodes of mania and/or depression can begin to break through prophylaxis with increasing frequency, intensity, or duration in a pattern that is highly suggestive of the development of tolerance [5–8]. Similar tolerance patterns (i.e., loss of effectiveness of a treatment after a period of good initial responsivity) have also been reported for lithium (Li)[7,9], valproate (VPA), and lamotrigine (LTG) in bipolar disorder [8] as well as with antidepressant treatment in the prophylaxis of recurrent unipolar depression [10,11], Given this potential for loss of responsiveness after an initial period of sustained response to many drugs used in the long-term treatment of bipolar disorder patients, a closer examination of the phenomenon, potential mechanism, and therapeutic approaches appears indicated.

Differentiating the Development of Tolerance from Other Reasons for Loss of Effectiveness

A. *Nonresponse from the Outset*

For tolerance to be inferred there must be clear evidence of an initial successful treatment response and not just a spontaneous course of illness variation, such that the patient was not really a responder. For example, in those with a pattern of pretreatment rapid cycling bipolar disorder (four or more episodes/year), a period of several years without any episodes on a new treatment begins to be highly suggestive of effective prophylaxis. However, in someone showing a pattern of more intermittent episodes every 1–2 years, a very much longer time of prospective observation is required in order to reliably demonstrate initial treatment effectiveness and, subsequently, even longer periods of time to evaluate whether a tolerance pattern emerges.

B. *Another form of Acquired Loss of Responsiveness– Discontinuation-Related Refractoriness*

If an effective treatment is discontinued and episodes emerge, this is not evidence of tolerance, but likely reflects the reemergence of the illness in the absence of adequate treatment. Such episodes emerging off of treatment can also ultimately lead to the phenomenon of discontinuation-related refractoriness. When a good responder to Li, for example, stops the treatment and episodes reoccur, upon reestablishing the same Li treatment regimen, a good clinical response similar to that seen previously may not occur [7,8,12–14].

Such a phenomenon has also been observed in patients discontinuing long-term previously effective antidepressant prophylaxis in unipolar illness [8,15]. Several investigators have raised questions about the occurrence of this phenomenon in bipolar disorder [16,17], but their observations that most patients who discontinue treatment then reacquire their initial responsivity does not invalidate the systematic, detailed, and careful observations in a small percentage of individual patients who fail to rerespond [7,8,12,13,18,19]. Aside from clear-cut discontinuation-induced refractoriness, a mixture of this mechanism and apparent tolerance development may occur in some covertly noncompliant patients who repeatedly miss doses, drop their blood levels substantially, and show a progressive pattern of breakthrough episodes.

Clinical Tolerance Development

Tolerance to CBZ

In our initial studies of long-term prophylaxis involving regimens that utilized CBZ, we saw an initial 50–60% response rate even in highly treatment-refractory rapidly cycling patients, but then some 30–40% of these patients began to show a pattern of loss of efficacy consistent with the development of tolerance [6]. In the additional follow-up of a total of 44 patients for an average of 6.9 years, 29 individuals (65.9%) were highly responsive to CBZ in combination with other drugs, and tolerance developed in 13 of these patients, or 44.8%. Episodes began to breakthrough CBZ treatment after an average of 2.8–0.9 years of pharmacoprophylaxis. One such patient is illustrated in Figure 1.

Tolerance to VPA

In another group of patients initially treated with regimens involving VPA, we saw a lesser degree of tolerance development, that is, about 25% of the initially responsive patients lost their good effect after an average of 2–4 years (see example in Figure 2) [8].

Tolerance to Li

Patients admitted to our tertiary-referral clinical research unit at the National Institute of Mental Health (NIMH) almost always had a history of nonresponsiveness to Li and sought alternative protocols and treatment studies. When we systematically charted these patients' previous course of illness and medication response, a tolerance pattern had occurred in 34.3% of patients, while the phenomenon of discontinuation-related refractories was seen in another 13.6% [12]; 43.9% of the patients showed a pattern of unresponsiveness to acute and/or prophylactic Li from the outset, while 7.6% were sustained partial responders.

Tolerance to Other Anticonvulsants and Treatments Used in Long-term Prophylaxis of Bipolar Disorder

While we did not have a large enough series of patients followed prospectively on other anticonvulsants to give reliable percentages of tolerance development, in several instances we saw patients with clear-cut periods of treatment responsiveness who then began to show a pattern of gradual reemergence of episodes. An example of such apparent tolerance to gabapentin (GPN) observed prospectively with daily ratings on the NIMH-Life Chart Method™ (NIMH-LCM) [8] is illustrated in Figure 3, although the literature remains mixed as to the overall effectiveness of this agent in monotherapy or combination therapy [20].

In several instances when patients' prospective course of illness was rated on a daily basis, tolerance to LTG was observed. In this case the literature is highly supportive of the efficacy of LTG in the prevention of episodes of bipolar disorder, and it is FDA approved for this indication.

In long-term treatment of 27 patients with the high-potency benzodiazepine clonazepam, Kishimoto el al. [21] reported an initial response rate of 84%, but then observed a very high rate of loss of efficacy via tolerance. In patients with refractory epilepsy with a good initial response to the high-potency benzodiazepine clobazam, a loss of efficacy occurs rapidly in a large proportion of patients limiting the utility of this treatment [22].

In a prospective follow-up of 525 patients during naturalistic treatment, 195 (37.1%) were clear-cut responders for a minimum of 6 months. Of these 16.4% showed a tolerance pattern to treatment with an average of three drugs in combination after a mean of 14.8 ± 7.5 months of response [23]. Thus tolerance can occur not only to individual medications, but also to their use in complex combinations.

Preclinical Tolerance Studies: Implications for Clinical Tolerance

Contingent Tolerance to the Anticonvulsant Effects of CBZ and LTG on Amygdala-Kindled Seizures

Animals given once-daily amygdala-kindled stimulations above their after discharge (AD) threshold will eventually develop reliable seizures [24,25]. CBZ and LTG are highly effective in preventing these fully developed amygdala-kindled seizures when the drugs are administered between 15 min and 1 h prior to amygdala stimulation. However, after repeated daily pretreatments with these drugs (Figure 4), animals increasingly begin to show breakthrough seizures and eventually completely lose their anticonvulsant response to CBZ or LTG [26–32].

This is a pharmacodynamic effect because animals that are repeatedly treated with the same dose of drug immediately after a kindled seizure has occurred on a daily basis do not develop

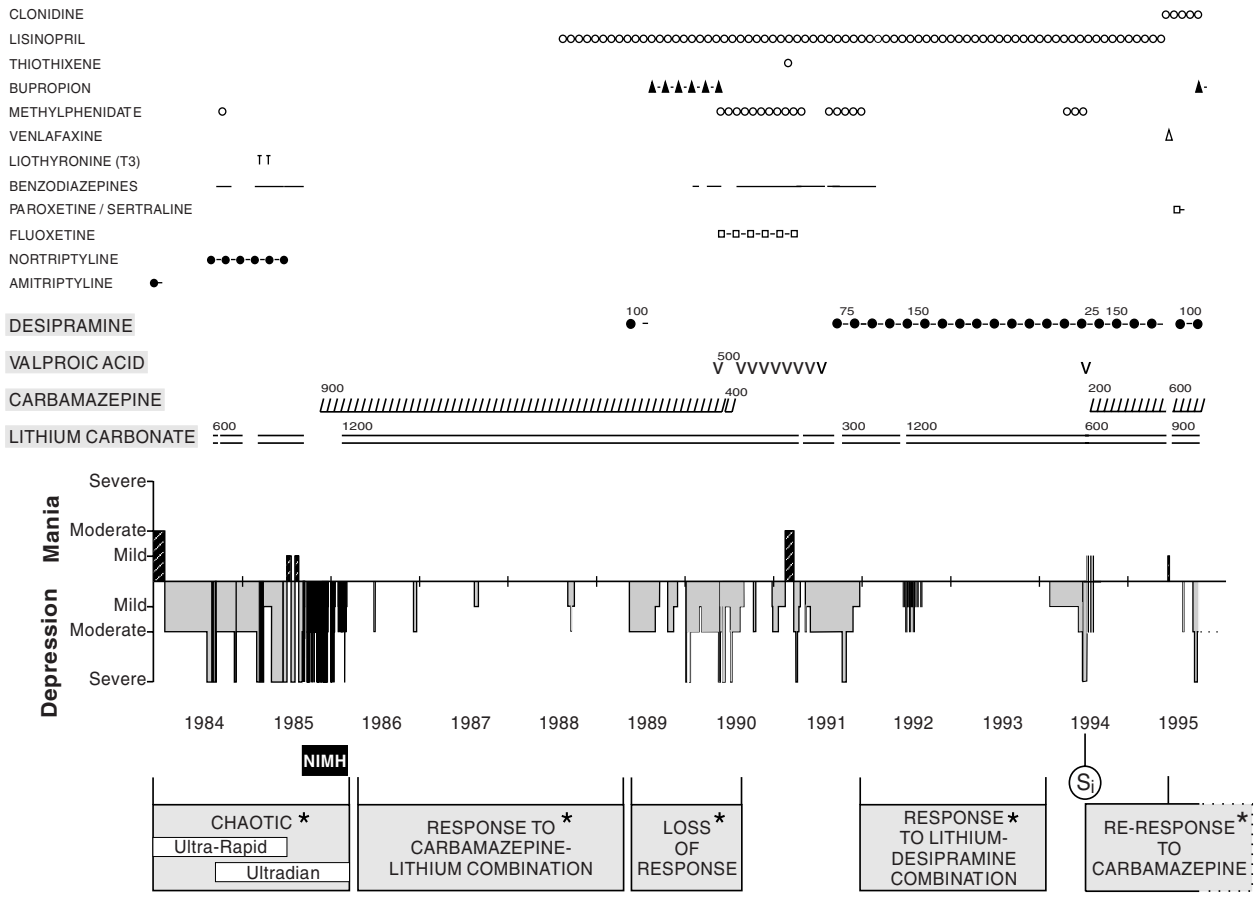

Figure 1 Phases in illness evolution and treatment response in a bipolar female. This patient's course of illness progressed from a pattern characterized by isolated, intermittent episodes (not illustrated) to a continuous, rhythmic phase with ultrarapid and ultradian cycling in 1985. Manic severity is rated above the line and depression severity below; years are on the abscissa. After 3 years well on carbamazepine (plus lithium which had previously been ineffective in monotherapy), she began to show a tolerance pattern of intermittent mild, then moderate, then severe breakthrough depressions in 1989 and 1990. She did not respond to valproate (either because of cross-tolerance to carbamazepine or an entire lack of responsivity to it). She did well for a period with the addition of desipramine, but made a severe suicide attempt in 1994, and then appeared to have a renewed response to carbamazepine.

tolerance when the drug is switched to a prestimulation time frame. Thus, the development of tolerance is contingent upon the drug being present in the brain at the time of electrical stimulation of the amygdala. Similar tolerance has been observed with other drugs, including benzodiazepines and alcohol [33–36].

This contingent tolerance phenomenon has the property that it can be overcome or reversed if the animal is given several days of amygdala-kindled seizures in the absence of drug [26]. Even more remarkably, if animals that have become tolerant to the anticonvulsant effects of CBZ or LTG continue to receive the drug on a once-daily basis, but immediately *after* the kindling stimulation and the occurrence of a seizure, this too is associated with the renewal of anticonvulsant efficacy. This tolerance reversal despite continued daily drug administration further demonstrates the contingent and pharmacodynamic mechanisms involved in this type of tolerance.

A related phenomenon of contingent inefficacy has also been demonstrated for both CBZ and LTG. These drugs are not effective in preventing the initial, developmental phase of kindling which occurs from the onset of stimulations to the first full blow amygdala-kindled seizure [26,31,37] However, if either drug is given prior to (but not after) each amygdala stimulation in this initial developmental phase of kindling, the drugs will no longer be effective in treating the full-blown kindled seizures once they emerge. In this case using a drug when it is otherwise ineffective may have adverse consequences for later responsiveness when it would ordinarily be effective.

Potential Mechanisms of Contingent Tolerance Development and its Reversal with Seizures in the Medication-Free State

In an effort to examine the molecular mechanisms involved in tolerance development, we treated one group of animals with once-daily CBZ until tolerance had developed and full-blown seizures had reemerged, and a second group with CBZ given only

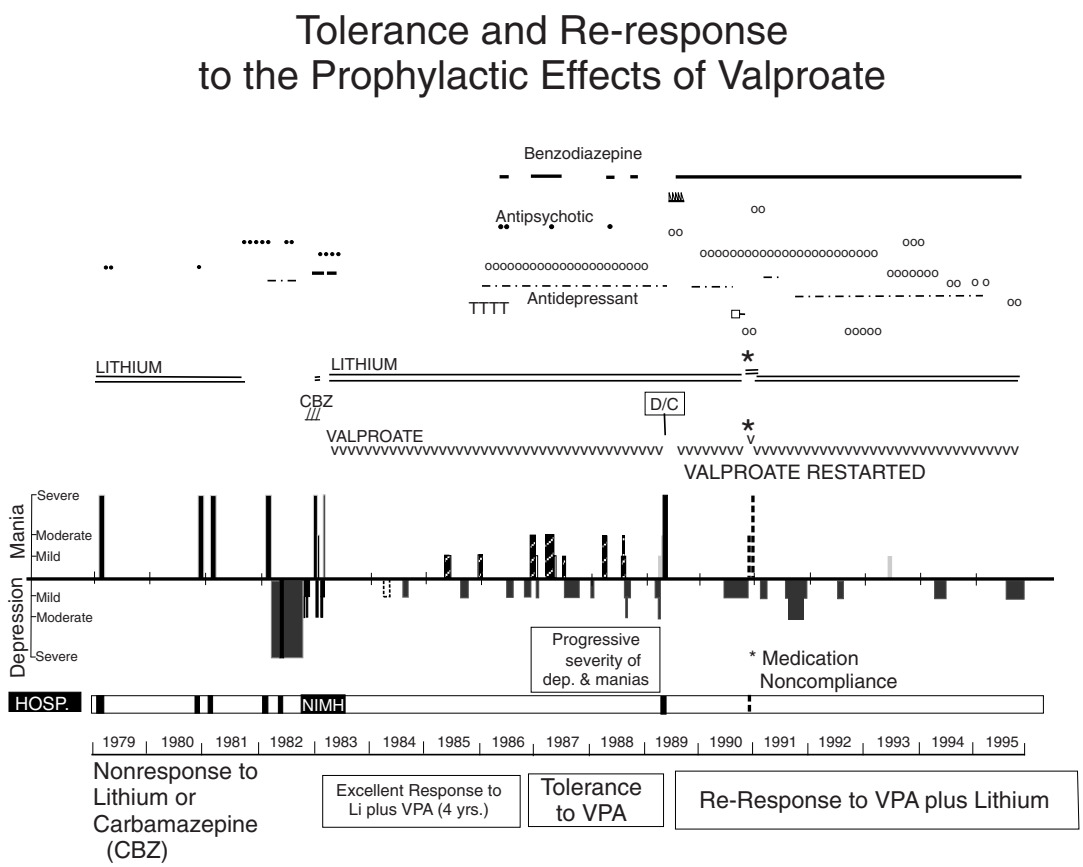

Figure 2 This lithium-nonresponsive patient (1979–1981) showed an excellent response to the addition of valproate (1983–1986), but manias of increasing frequency and moderate severity and mild to moderately severe depressions began to break through treatment (especially in 1987 and 1988) despite attempts at adjunctive treatment with antipsychotics, antidepressants, and benzodiazepines. A severe mania ensued off valproate in 1989 despite continued treatment with lithium, but after several months off valproate, the drug was reintroduced, and the patient appeared to regain responsiveness to it (1990–1995).

after seizures had occurred so that they were not tolerant (even though they had had the same number of stimulations and drug administrations) [26]. Another group of animals were given kindled seizures without any medications, and a fourth group was implanted but received only sham stimulation. We found that amygdala-kindled seizures in the absence of drug and in the animals given CBZ after their seizures had occurred (such that they were not tolerant), both manifested robust seizure-induced increases in the mRNA for thyrotropin-releasing hormone (TRH) which has putative anticonvulsant properties [38]. In contrast, in the CBZ tolerant animals, their full-blown seizures were not associated with an increase in TRH mRNA in the dentate gyrus of the hippocampus.

A similar failure of seizure-induced adaptations to occur selectively in animals that become tolerant to the anticonvulsant effects of CBZ was observed in studies of the GABA-A receptor and its alpha-4 subunit [26,39]. This was a highly selective occurrence as other subunits (beta 1 and 3) continued to be induced after kindled seizures in the CBZ -tolerant animals.

We surmised that it was these seizure-induced endogenous anticonvulsant adaptations (such as increases in TRH and GABA-A receptor subunits) that were usually enabling the anticonvulsant effects of CBZ, and that when these adaptations failed to occur despite an induced seizure, CBZ was no longer effective, that is, tolerance is manifest [37]. Consistent with this interpretation, when TRH was administered bilaterally into the hippocampus of animals who were tolerant to CBZ, anticonvulsant effectiveness was restored [40].

Table 1 lists the series of biochemical entities that we explored in animals which were CBZ -tolerant animals compared to those medication-free or nontolerant (when CBZ was given immediately after the seizures). Since many of the mRNA and receptor changes that fail to occur following seizures in CBZ -tolerant animals are for substances with known anticonvulsant effects, their combined failure could contribute to the manifestation of tolerance [26,37].

At the same time, these observations could explain why several seizures induced in the absence of CBZ or LTG are sufficient to reverse the tolerance process. These seizures would, again, induce TRH, the alpha-4 subunit of the GABA-A receptor and the other endogenous anticonvulsant substances listed in Table 1 which would restore anticonvulsant effectiveness. That is, we postulate that CBZ and LTG require the presence of a certain amount

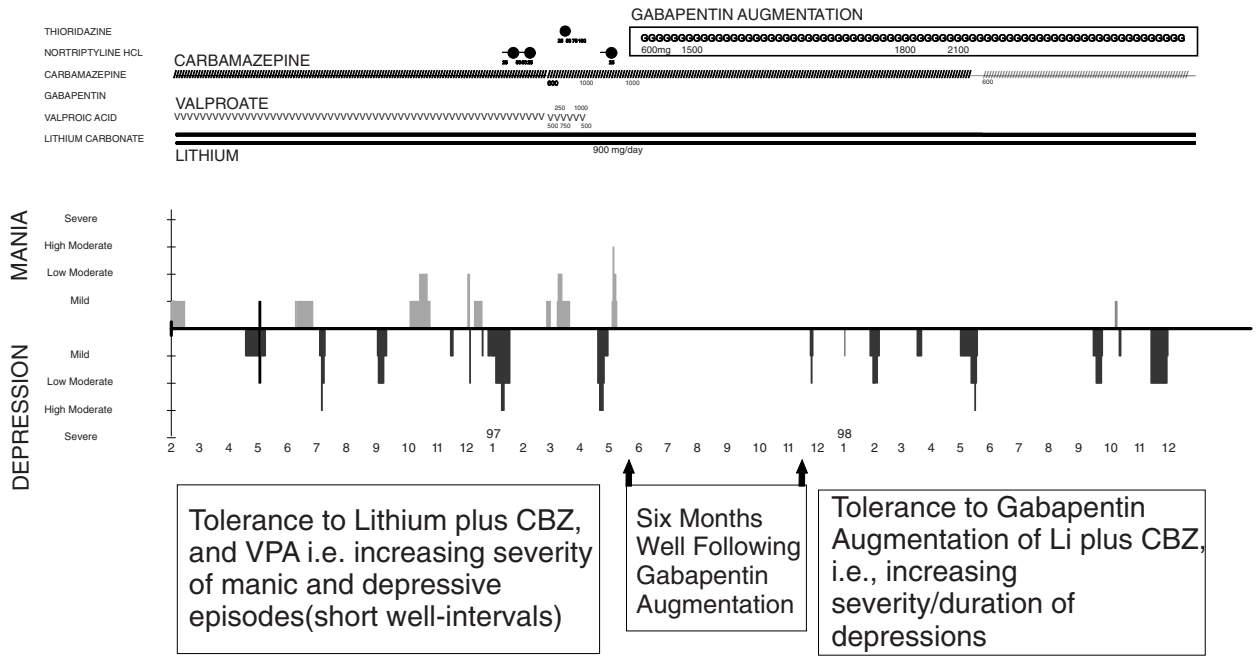

Figure 3 In June 1997, gabapentin augmentation resulted in sustained antimanic effects, but after a period of 6 months without depressions, depressive episodes of increasing duration again began to manifest in 1997 and 1998 as they had prior to gabapentin in 1996 and 1997. Note while depressions returned, manias did not, suggesting differential vulnerability to tolerance development between the two mood poles.

of endogenous anticonvulsant modulators in order to be effective against amygdala-kindled seizures.

Consistent with this viewpoint are the observations of a "time-off from last seizure" effect [26]. The increase in TRH mRNA leads to increases in TRH protein that remain for some 3–5 days after a seizure [41]. If the increases in TRH and related substances are important to the anticonvulsant effects of CBZ and LTG, the drugs should work well in the first several days after the last seizure has occurred, but should fail to exert anticonvulsant effects if animals are given a time-off vacation from kindled seizures for a period of at least 5 days. By this time the transient seizure-induced increases in TRH protein would have dissipated, and, accordingly, these drugs would lose their anticonvulsant effectiveness.

Ratio of Pathological to Adaptive Factors as a Determinant of Cyclicity

Given these observations, one is in a position to postulate some of the mechanisms involved in the cyclic reemergence of seizures leading to full-blown loss of efficacy [42–45]. The initial application of CBZ prior to a kindled seizure would result in an anticonvulsant effect on each of the first several days of treatment (Figures 4 and 5). However, seizures might begin to break through this effective prophylaxis based on three phenomena. One is the addition of further kindled stimulations that would hypothetically increase illness drive (increase the pathological kindled memory trace). The second is the failure of these seizures in treated animals to induce the usual range of endogenous adaptations that would normally occur as listed in Table 1. The third is that with the passage of time, whatever seizure-induced endogenous adaptations had occurred would now begin to dissipate.

As illustrated in Figure 5, this would render the combined effects of the exogenous medication and endogenous anticonvulsant actions inadequate to continue to convey anticonvulsant efficacy. However, with the recurrence of several breakthrough seizures even in partially tolerant animals, some of the endogenous anticonvulsant substances might be sufficiently induced in order to renew efficacy for a short period of time, but then as the endogenous adaptations begin to dissipate, seizures would again break through, and this process would be reiterated until complete tolerance occurred [43,44].

Based on this analysis, we have suggested that parallel principles and processes could occur in bipolar disorder (in very different time frames and in different neuroanatomical and neurotransmitter systems) following effective treatment when episodes begin to reemerge with increasing frequency, severity, or duration as

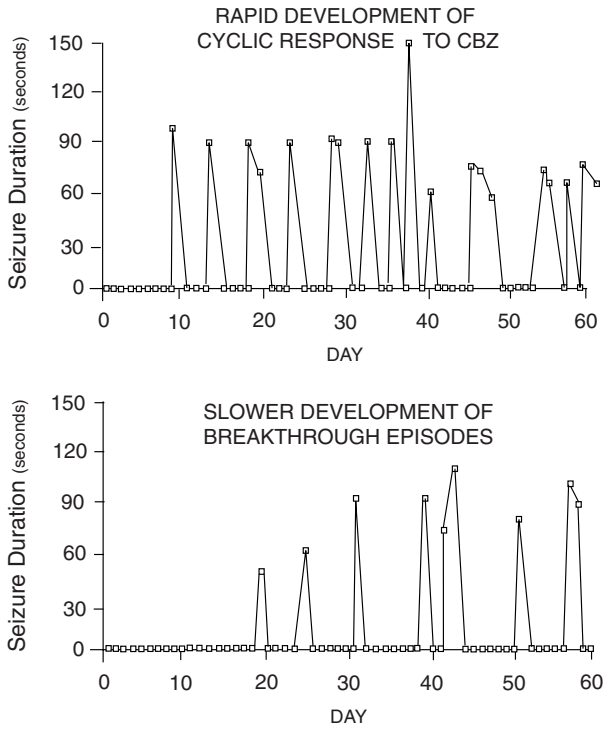

Figure 4 Variable and oscillating patterns of tolerance emergence to carbamazepine's anticonvulsant effects is illustrated in two individual rats. Kindling stimulation was administered daily for 1 second at 400 μA and was preceded by carbamazepine (15 mg/kg i.p.). Motor seizure duration is plotted on the ordinate and days of electrical stimulation (with drug treatment) are plotted on the abscissa. Breakthrough seizures appeared rapidly in an episodic fashion (top) or only partially after a long delay (bottom) in these two individual animals.

tolerance develops. We posit it is the ratio of endogenous pathological alterations (the "bad guys") to endogenous adaptive alteration (the "good guys") combined with the exogenous effects of drugs that determines whether or not affective episodes are suppressed, occur episodically, or occur regularly as complete tolerance develops [43,44].

An important clinical and theoretical implication of the postulate would be that any neurobiological abnormality observed in the affective disorders would need to be differentiated into at least two categories, each with differential therapeutic implications [42,45]. Abnormalities representing the primary pathological processes driving illness progression (i.e., the "bad guys"), such as increases in corticotropin-releasing hormone (CRH), should be targeted for amelioration or prevention. In contrast, those representing secondary adaptive ones (i.e., the putative "good guys"), such as increases in TRH, should be further enhanced by therapeutic interventions. Another obvious implication of these principles is that the illness and its neurobiology is constantly in flux, such that any cross-sectional neurobiological assessment can only provide a snapshot of what is likely a highly variable and ultimately a potentially progressive process [45,46].

In the case of tolerance development to drugs on amygdala-kindled seizures, some animals lose anticonvulsant efficacy very rapidly and completely, while others sustain responsivity to a drug for substantial periods of time before losing it in a slow intermittent or cyclic fashion (see Figure 4). A similar wide individual variability is seen in clinical tolerance development in the affective disorders. In both of these instances, one would postulate that the individual differences in rate of tolerance development might relate to both an individual's baseline and episode-related ratio of pathological to adaptive factors [44,45].

In this analysis we have highlighted the changing ratio of pathological versus adaptive alterations that occur at the level of changes in gene transcription. A new level of modulation of these changes has recently been documented in epigenetic alterations, based on environment- and drug-induced changes in DNA methylation and histone acetylation and methylation [46–50]. Such changes which affect the ease of gene transcription could account for the induction or suppression of a whole array of neurobiological alterations such as those illustrated in Table 1.

Potential Clinical Approaches to Slowing Tolerance Development: Implications from Preclinical Models

Decreasing the forces that propel the pathological processes involved in the kindled memory trace is one way to slow tolerance development. This involves stimulating animals with less intense current or less frequently [26,37]. However, while these ways of lowering illness drive are available in the experimental situation, in clinical approaches to patients with recurrent mood disorders, lowering illness drive is obviously more problematic. However, it could include decreasing the impact of stressful life events and decreasing substance use, as well as intervening early to prevent episode accumulation [50]. Clearly, most of the clinical attempts at slowing tolerance development based on the rodent kindling model would rely on alterations in the medication strategy, as listed in Table 2A. If anticonvulsant treatment is started early in the course illness development after only one or two full-blown kindled seizures have occurred, this results in less rapid development of tolerance compared with animals that have had scores of amygdala-kindled stimulations [26].

We can ask whether this and the other principles observed in the preclinical kindling model are applicable to tolerance development in the affective disorders. In our clinical data on CBZ tolerance cited, the 13 patients who did develop tolerance had an average of 5 hospitalizations for mania compared to only 2.8 in those who remained responsive. Thus, clinically, illness drive as reflected in the number of prior episodes may relate to the likelihood of tolerance development. Also there are a wealth of data indicating that Li is less effective in those with more prior compared to fewer prior episodes [8], and whether some of this poorer long-term responsivity relates to ultimate tolerance development remains to be clarified.

We have also seen that using stable higher doses of CBZ, that is, well above the animal's seizure threshold, results in less rapid tolerance development compared with minimally effective doses. This principle would have very obvious clinical implications in the treatment of affective disorders wherein clinicians routinely attempt to treat patients with the lowest effective dose of drug.

Table 1 Selective failure of some kindled seizure-induced neurochemical changes during contingent tolerance to the anticonvulsant effects of carbamazepine (CBZ)

In nontolerant animals,[a] seizure-induced alterations include:	In tolerant animals, some seizure-induced alterations either:		* = Putative endogenous anticonvulsant effect is lost
	Continue to occur	Fail to occur	
↑ c-fos mRNA		↑ c-fos	
↑ Diazepam receptors	↑ Diazepam-R		
↑ GABA-A receptors [3–1-1] musimol		↑ GABA A-R	*
↑ $\propto$4 subunit		↑ μ4 subunit	*
↑ Beta 1 & 3 subunits	↑ beta 1 & 3 subunits		
↑ TBPS binding		↑ TBPS	*
↑ Glucocorticoid RmRNA		↑ Glucocorticoid R	*
↑ Mineralocorticoid RmRNA	↑ Mineralocorticoid R		
↑ BDNF mRNA		↑ BDNF	
↓ NT3 mRNA	↓ NT3		
↑ TRH mRNA		↑ TRH	*
↑ CRH mRNA		↑ CRH	
↑ CRH-BP mRNA		↑ CRH-BP	
↑ NPY mRNA		(↑ NPY)	*
↑ Enkephalin mRNA		(↑ Enkephalin)	
↓ Dynorphin mRNA	↓ Dynorphin		

CBZ, carbamazepine; DZP, diazepam; GABA, γ-aminobutyric acid; TBPS, [35S]t-butylbicyclophosphorothionate; BDNF, brain-derived neurotrophic factor; NT3, neurotrophin-3; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; CRH-BP, corticotropin-releasing hormone binding protein; NPY, neuropeptide Y; (), partial loss; R, receptor.

Data based on studies summarized in Weiss et al., 1995.

[a]Treated with no drug or with CBZ after each daily amygdala-kindling stimulation; these nontolerant animals were matched for amount of drug and number of seizures seen in tolerant animals (columns 2 and 3).

This strategy may turn out to be counterproductive in some instances, and use of higher doses that are still well tolerated may be a more conservative strategy for preventing tolerance development to most treatment agents. However, in the case of LTG, use of high doses paradoxically appears to hasten tolerance development and various characteristics of LTG and CBZ tolerance development are quite different despite the fact that they show similar contingent inefficacy and bidirectional cross tolerance [27,28,30,31,44] (see Table 3).

In addition, if one uses only marginally effective doses of CBZ or VPA, tolerance to their anticonvulsant effects on amygdala-kindled seizures occurs more rapidly. However, administration of minimally effective dose of these two drugs in combination results in a much slower development of tolerance than to either drug alone [26]. Thus, it would appear that combinations of drugs, particularly those with different mechanisms of action may be of some utility in slowing tolerance development [51]. Each of these suggestions from the preclinical findings requires further exploration in the clinic.

Management of Tolerance Once It Has Occurred

If tolerance has already developed, there are several potential approaches to attempting to reacquire therapeutic efficacy. Again, none of these seen in the preclinical model has been systematically tested in the clinical arena, although in some cases there are case vignettes and small series [8,52] suggesting the utility of a given approach, but each needs to be more systematically explored. In the face of tolerance development, it would make the most sense to switch to other drugs with different mechanisms of action, particularly ones that do not demonstrate cross-tolerance in animal models.

Table 4 lists drugs that have been demonstrated to show cross-tolerance in the amygdala-kindling model, while others do not show cross-tolerance and their use is associated with renewed anticonvulsant efficacy [28,30,32,44,51,53,54]. For example, there is clear-cut cross-tolerance between animals that have lost efficacy to the anticonvulsant effects of CBZ and then are administered LTG and vice-versa.

Surprisingly, animals that have become tolerant to the anticonvulsant effects of CBZ also show cross-tolerance to VPA [54]. Even though the mechanism of action of these two drugs is quite different, one could imagine that the reduction in GABA-A receptor number and the amount of its alpha-4 subunit induced by seizures in CBZ -tolerant animals could contribute to the loss of effectiveness of VPA, which is thought to act in part by increasing brain GABA levels (and may require adequate GABA-A receptors), but the precise mechanisms for this cross-tolerance remain to be seen. We have seen a bipolar patient who became tolerant to CBZ show apparent cross-tolerance to VPA (Figure 1) [8].

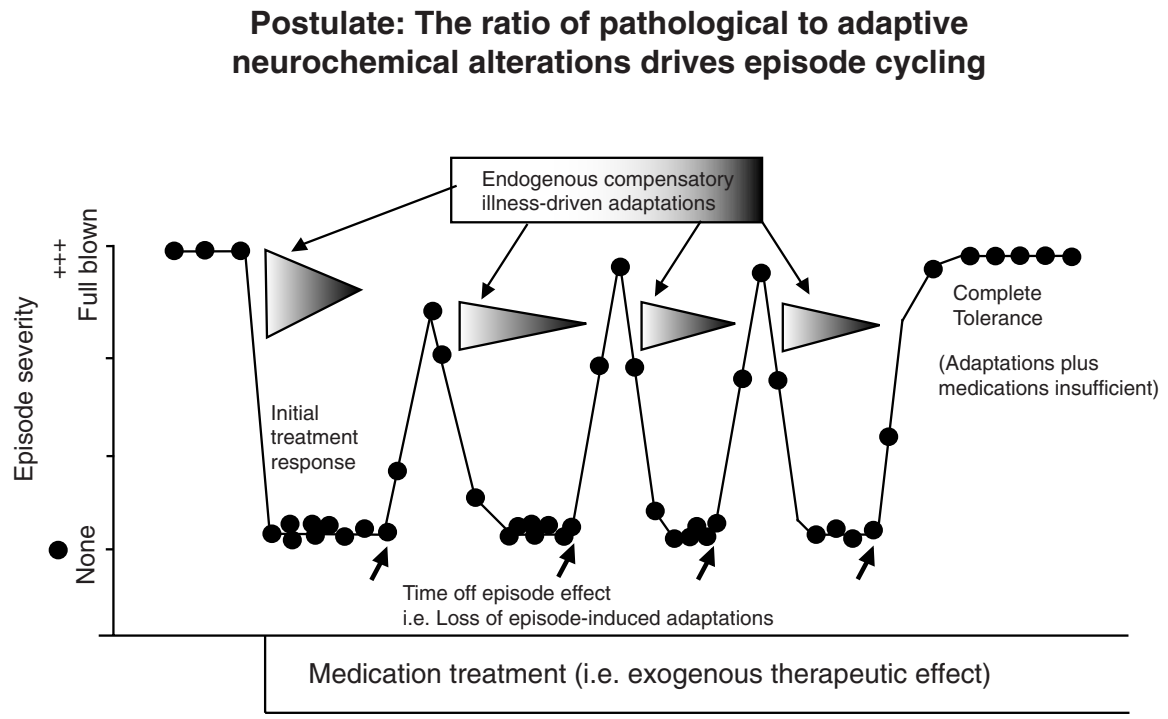

Figure 5 Full-blown seizures while medication-free generated endogenous anticonvulsant adaptation (first triangle). Anticonvulsant medications produce a good effect for about 1 week, then seizures start to break through as adaptations wear off. Full-blown seizures occurring during medication tolerance generate fewer endogenous anticonvulsant adaptations (smaller triangles) and finally full loss of effect occurs.

One of the first clinical reflexes in the face of tolerance development is to increase the dose of drug and, in some instances, this may be helpful. However, in the preclinical model, such gradual dose escalation of CBZ (or the benzodiazepines) usually results in the relatively rapid development of tolerance, and for this reason and especially in the face of dose-limiting side effects other strategies may be needed. One highly experimental approach in the face of inefficacy to a drug that has previously been effective (i.e., cases of clear-cut tolerance) is to discontinue the use of that drug and have some of the seizure or affective episodes continue to occur off that medication in the hope that this would reengender episode-driven adaptations, and thus renew efficacy once the drug is again administered.

We have seen several patients with CBZ tolerance rerespond after a period of time off the drug (Figure 1) [8,52] and another with tolerance to VPA (and Li) rerespond for a prolonged period of time after episodes occurred off drug (Figure 2); [8]. In these cases the episodes in absence of drug would presumably be reinducing positive or therapeutic endogenous adaptations that had been suppressed during tolerance development as seen in the preclinical model.

Consistent with this therapeutic perspective, Azar et al. [55] observed in a series of 43 patients with epilepsy that brief anticonvulsant withdrawal resulted in highly significant seizure interval prolongation once the drugs were restarted. This interval prolongation tended to be greater (25.7 days without a seizure) in those with a prior history of antiepileptic drug (AED) tolerance than in those without a tolerance history (14.0 days) [55].

An obvious negative attribute of the attempted drug-free interval as a way of reversing the tolerance process is that it requires the further experience of additional episodes (seizures or affective episodes) off drug. However, since the fully tolerant patient has already developed major breakthrough episodes on drug, the recurrence of several more episodes off drug may not be as pernicious as it might initially appear. However, this liability makes the alternative approach noted previously of attempting to find other drugs that do not show cross-tolerance a generally preferable clinical and conceptual strategy. This is further the case, as even the successful reestablishment of efficacy after a medication-free interval suggests the likelihood that tolerance would again occur in the not too distant future. This would require yet another off-medication period for transient efficacy renewal, and this requirement might repeatedly occur (Figure 6).

In the face of clinical tolerance to the mood-stabilizing anticonvulsants such as CBZ, VPA, or LTG in the affective disorders, one might also consider the utility of using nonanticonvulsant drugs, such as Li or atypical antipsychotics. These agents have very different mechanisms of action and, in some cases, they may be sufficient to renew efficacy in the tolerant patient, even without having to withdraw the drug to which the patient has become tolerant. Once the mechanisms of the pharmacodynamic (contingent) tolerance process have been further clarified, it may also be

Table 2

A. Testable clinical predictions about therapeutic approaches to slowing or preventing tolerance development based on the preclinical model	
Preclinical study findings in Rx of daily amygdala-kindled seizures in rodents	Future studies could assess whether there are parallel findings for clinical tolerance in epilepsy (likely) or affective illness (questionable)
Tolerance to anticonvulsant effects SLOWED by:	Would tolerance in humans be SLOWED by:
1. Higher doses (except with LTG)	1. Maximum tolerated doses rather than minimally effective doses
2. Not escalating doses	2. Stable dosing
3. More efficacious drugs (VPA > CBZ > LTG)	3. Valproate compared with carbamazepine or lamotrigine
4. Treatments initiated early rather than late in the course of kindled seizures	4. Early treatment more effective than that after many episodes have occurred**
5. Combination treatment (CBZ+VPA and LTG+GPN)	5. Combination treatment rather than monotherapy (as seen with VPA+Li; VPA+LTG)
6. Reducing illness drive (stimulation intensity)	6. Treatment or prevention of episodes, comorbidities, and stressors
7. Alternating high and low doses of lamotrigine	
B. Testable clinical predictions about therapeutic approaches to reversing tolerance once it has occurred	
Preclinical study findings in Rx of daily amygdala-kindled seizures in rodents	Future studies could assess whether there are parallel findings for clinical tolerance in epilepsy (likely) or affective illness (questionable)
Treatment response in tolerant animals RESTORED by:	Would treatment response in humans be RESTORED by:
1. Period of drug discontinuation, then reexposure	1. Period of time off CBZ or VPA in tolerant patients, then re-treatment (supported by clinical vignettes)
2. Agents with different mechanisms of action that do not cause cross-tolerance (see Table 3)	2. Anticonvulsant cross-tolerances may or may not be predictive of cross-tolerances in affective illness

VPA, valproic acid; CBZ, carbamazepine; LTG, lamotrigine; GPN, gabapentin; Li, lithium.

**This prediction has been partially validated for lithium, LTG, and naturalistic treatment.

Table 3 Differential effects of carbamazepine (CBZ) and lamotrigine (LTG) on the development of tolerance to their anticonvulsant effects*

	CBZ (15 mg/kg)	LTG (15 mg/kg)
Rapid tolerance to anticonvulsant effects (amygdala kindling)	+++	+++
Cross tolerance to other drug	+++	+++
"Time-off" effect (seizures enhance efficacy)	(4–5 days)	(4–5 days)
Seizure threshold change with tolerance	↓↓↓	↑↑ (possible residual drug effect)
High doses	Slow tolerancedevelopment	Speed tolerance and are proconvulsant
Alternating high and lowdoses	?	Slows tolerance
Chronic non-contingent drug dosing	Slows tolerance	?
MK801 on tolerance development	No effect	Slows (NMDA implicated)
Cross tolerance to valproate	Yes	No
Valproate combination	Slows tolerance	?
Gabapentin augmentation (2 hrs pre-treatment)	?	Slows tolerance
(Half hr. pretreatment)	?	↓↓ Stage VI seizures
(Tolerance Reversal)	?	+++

NMDA, N-methyl-D-aspartate.
+++ = robust effect; ↓↓↓ = robust decrease; ↓↓ = substantial decrease; ↑↑ = substantial increase; ? = not tested.
*These differences (despite many similarities in tolerance development and cross tolerance) suggest the importance of examining potential therapeutic interventions in the clinic based on those hypothesized from the specific drug and preclinical model.

possible to target them more directly, potentially even at the level of epigenetic manipulations.

Conclusions

While tolerance development has readily been recognized in the case of CBZ in the treatment of trigeminal neuralgia or clobazam treatment of refractory seizure disorders, in the recurrent affective disorders, tolerance phenomena are not as well characterized in part because of the very long time frame of observation required for patients with highly intermittent episodes. Thus, precise history taking and, preferably, the development of a systematic retrospective and prospective mood chart [8], may be one of the best ways of achieving appropriate pattern recognition that can discriminate initial nonresponsiveness to a treatment regimen from that which is acquired by a tolerance process (Figures 1–3) or by

Table 4 Cross-tolerance demonstrated in anticonvulsant effects on once daily amygdala-kindled seizures (from Post et al. 2005)

Tolerance on:	Shows cross-tolerance with:	Efficacy remains to:
Carbamazepine (CBZ)	PK 11195	Clonazepam
	CBZ-10, 11-epoxide	Diazepam
	Lamotrigine	Phenytonin
	Valproate[a]	Levetiracetam[b]
Lamotrigine (LTG)	Carbamazepine	Valproate
		MK 801[c]
		Gabapentin[c]
Levetiracetam (LEV)	Carbamazepine[b]	
Clonazepam (CLZ)	Carbamazepine[d]	

[a]Possibly mediated by CBZ tolerance decreasing GABA-A receptors and itsalpha-4 subunits.
[b]Unidirectional cross-tolerance LEV to CBZ, but not CBZ to LEV.
[c]These drugs slow LTG tolerance development.
[d]From Kim et al. 1992 also suggesting unidirectional cross-tolerance.

the completely different mechanism of discontinuation-induced refractoriness [12,13].

Some investigators question whether either the occurrence of tolerance or discontinuation-induced refractoriness may be an artifact of poor evaluation of the prior course of illness and the degree of treatment responsiveness [17]. Thus, it would appear useful to develop some consensus guidelines about the general rules of thumb that would characterize and differentiate these phenomena. Since the rate of loss of effectiveness in a tolerance-like process differs greatly as a function of the baseline pretreatment rapidity of recurrence of episodes, a single absolute temporal rule does not suffice.

Rather, we suggest the utility of making the assessments of long-term efficacy based on the achievement of a response and well-interval that is much longer than the previously observed baseline pretreatment well-intervals. One could adopt a criterion that a bonafide response should show a well-interval of at least two or three times the duration of the previous or average

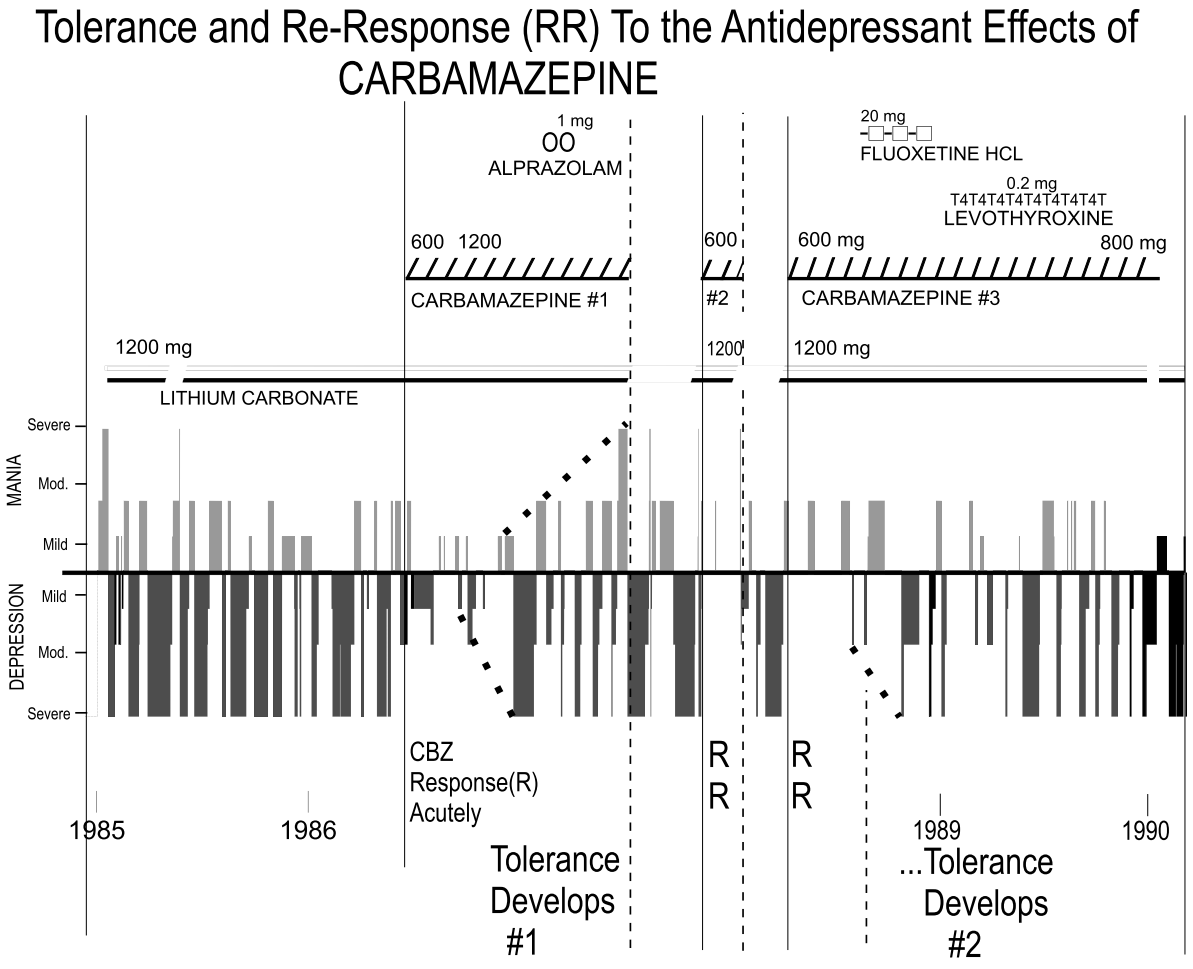

Figure 6 After several years of ultrarapid cycling of extremely severe BPII depressions despite lithium treatment, the patient had a partial response to the addition of carbamazepine for about 6 months (1986-1987). However, severe depressions reemerged, as did manias of increasing severity in a pattern suggestive of tolerance. Two brief periods of reresponse (RR) to carbamazepine occurred after several months off drug and the reemergence of new episodes of depression of several months' duration while medication free.

well-intervals [56]. In the recurrent affective disorders, once breakthrough episodes begin to occur, they may rapidly emerge with greater severity, frequency, or duration, such that the original patterns of illness progression of episodes (seen prior to any treatment or during inadequate treatment) are replicated or they may reemerge in an even more accelerated fashion. However, in other instances, the rate of breakthrough of episodes reflecting tolerance may proceed extremely slowly, over the course of months to years, and this makes the prospective charting of mood episodes of particular importance in the assessment of both initial degree of effectiveness of a treatment regimen (i.e., the duration of time improved or well) and whether such effectiveness begins to wane despite continued treatment via a tolerance process.

The rate of tolerance development can be assessed using the slope of a line drawn at the beginning of the first breakthrough episode to that occurring when full-blown episodes (of a severity to that previously observed) have emerged (Figure 6). The slope of this intersecting line, in the context of the prior rapidity of cycling, might then reflect the relative proneness to tolerance development of that individual. Such an intersecting tangential line could be drawn for the rate (slope) of breakthrough manic episodes and depressive episodes separately, as each phase may develop tolerance with different time frames. Such a differential rate would depend on the relative manic versus depressive illness drive in conjunction with the relative antimanic versus antimanic effectiveness of the treatment (Figure 6). Hopefully, with increasing recognition of different patterns of acquired loss of efficacy– tolerance versus discontinuation-related refractories– occurring in the course of the recurrent affective disorders, a more systematic literature about ways of preventing or slowing tolerance development will become possible, as well as assessment of the best therapeutic approaches to its reversal once it has occurred.

It is obviously a tenuous proposition to make inferences about clinical tolerance development in mood-disordered patients whose affective episodes and well-intervals may last weeks to months or even years compared with rodents, whose kindled seizures last about 60 seconds and duration of treatment response with stimulation given every 24 h is on the order of days to weeks. The study of the tolerance process and its avoidance and treatment would advance more rapidly if more adequate animal models of manic and depressive episodes were available where there were homologous behaviors and time frames as well as analogous drug effectiveness to that seen clinically.

Given these acknowledged shortcomings of the preclinical model of anticonvulsant tolerance development on amygdala-kindled seizures, we nonetheless hope that some of the principles observed from its study and the clinical and research questions it helps formulate will be valuable. The model helps focus attention on the detailed evaluation of the longitudinal course of the recurrent mood disorders and on the need for early and sustained prophylactic treatment intervention [44,45,50]. Examining this preclinical tolerance model may thus be a useful first step in beginning to approach the description and therapeutics of tolerance development in the affective disorders.

Conflict of Interest

The authors have no conflict of interest.

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