

FINK! STILL AT LARGE

Exposure to violent media results in brain changes that might desensitize teen boys to aggression. Should we advise patients in therapy to stay away from violent media?

Research tends to narrow a question to a researchable conclusion. The question above is not only of concern to those of us in psychiatry; it worries parents and teachers alike.

The question refers to an article published last month ("On-Screen Violence May Desensitize Teen Boys," *CLINICAL PSYCHIATRY NEWS*, November 2010, p. 19). That article was based on a study published online (*Soc. Cogn. Affect. Neurosci.* 2010 [doi:10.1093/scan/nsq079]) that traces these matters to the brain and leaves out environmental, social, and psychological possibilities.



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Instead of approaching the issue from a biopsychosocial point of view, it is immediately medicalized, and conclusions and solutions are derived from the major premise.

I am a great believer in the biopsychosocial ethos and our need to rise above the rest of medicine.

Even if these researchers are correct in their findings, this is just a tiny corner of the data we have on the causes of adolescent violence. Desensitization is important, but its causes are many. One example is growing up in a house devoid of empathy, so that the child has no one to whom he can talk and receive an empathetic response. Empathy is learned and only can be achieved through love. If the child has not felt love, he cannot be empathic. It is a critical factor when we try to understand how an adolescent could take the life of another. He has no ability to put himself in the other person's shoes.

This area of youth violence is one that I have been working in for almost 2 decades, and I am pleased to have some biological evidence about aggression. Experiments using neuroimaging are always engaging, but they still leave many psychosocial discoveries as peripheral to the central biological theses.

For example, we have discovered markers for murdering someone or getting murdered. These include bullying; dropping out of school; being a chronic truant – often leading to illiteracy; and getting suspended from school multiple times. None of these markers correlate with parts of the brain underlying these kinds of behaviors.

Perhaps researchers in the future will be able to trace each of these markers to functional magnetic resonance imaging (fMRI) changes, which, in turn, could help develop methods for reducing these behaviors. But I doubt it.

Bullying has recently received much attention, especially the phenomenon of cyberbullying, which has resulted in numerous suicides across the country. In

each of the markers I have mentioned, multiple factors are driving the child to make them happen.

Negative self-image is a major factor that causes adolescents to strike out, retaliate, take action to preserve their manhood, and find ways to feel better about themselves.

A young man went to apply for a job

and kept saying to his mentor after the interview: "They'll never hire me," over and over again. It was an inappropriate reaction, but his self-esteem was so poor that he could only have a negative response. Feeling worthless is not a genetic trait. It is imbedded in the child from early life. If a mother tells her son: "You can't do it"; "You're worthless"; "Every-

thing you touch is ruined," the child's sense of value is permanently damaged.

Many aggressive adolescents are angry – very angry! The most important reason for their anger is the absence of a father in their lives. They feel it keenly. If their father was never there, is in jail, or is on the streets, the child feels it. The key is

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Please see Brief Summary, including Boxed Warning, for LAMICTAL XR and Brief Summary, including Boxed Warning, for LAMICTAL Tablets, LAMICTAL Chewable Dispersible Tablets, and LAMICTAL ODT Orally Disintegrating Tablets on adjacent pages.

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the absence of a relationship or interaction between the two. I recommend that every psychiatrist see an outstanding documentary called "Oh Father... Where Art Thou?" It is a provocative movie filmed across two continents that demonstrates the value of a father or male mentor in the life of a young boy.

Another reason for the anger is the continual punishment a child receives, perhaps for an aggressive act. The failure on the part of the adult to understand why the child did what he did is a key fac-

tor that stimulates anger. I have written many times about the negative effects of corporal punishment and physical abuse. I am saddened to report that 95% of American children experience hitting. Many children expect to get beaten and talk about it as adults with a sense of pride. But it carries a price (as does verbal shaming).

Punishment in the home is only part of it. Punishment in school also is quite common: In many U.S. states, corporal punishment remains legal and acceptable in schools. About 25% of adolescents continue to absorb blows from adults –

which singularly is a humiliation that is antagonistic to the child's developmental goal of autonomy. Unfortunately, suspension is used as punishment, and, as I stated earlier, multiple suspensions from school are markers for getting killed. In Philadelphia, a 17-year-old boy accumulated 57 suspensions from school before he was murdered.

The street also is a place where children are punished by bullying from their peers and "older heads"; they also are chased by neighbors and others who do not want "bad kids" crowding their streets.

Another cause for adolescent male aggression involves their continual search for respect, which I interpret as a search for someone – a peer, adult, mentor, teacher – with whom they can talk. It is imperative that we adults learn how to talk to young people.

We are frightened of them. We don't listen to them or even express curiosity about their feelings – assuming that they have none. This is an enormous flaw in our society when it comes to our children.

Another locus for punishment is the public-safety sector – lawyers, courts,

LAMICTAL[®] XR™ (lamotrigine) Extended-Release Tablets

BRIEF SUMMARY

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: SERIOUS SKIN RASHES

LAMICTAL[®] XR™ can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving the immediate-release formulation of LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking the adjunctive immediate-release formulation of LAMICTAL, there was 1 rash-related death. LAMICTAL XR is not approved for patients under the age of 13 years. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with the immediate-release formulation of LAMICTAL. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR. Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL XR. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL XR with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL XR, or (3) exceeding the recommended dose escalation for LAMICTAL XR. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by the immediate-release formulation of LAMICTAL have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes are also caused by LAMICTAL XR, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, LAMICTAL XR should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring [see *Warnings and Precautions* (5.1)].

4 CONTRAINDICATIONS: LAMICTAL XR is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients [see *Boxed Warning, Warnings and Precautions* (5.1), (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin Rashes [see *Boxed Warning*]: The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with the immediate-release formulation of LAMICTAL [see *Boxed Warning*]. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR.

Pediatric Population: The incidence of serious rash associated with hospitalization and discontinuation of the immediate-release formulation of LAMICTAL in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy with immediate-release lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate. LAMICTAL XR is not approved in patients under the age of 13 years.

Adult Population: Serious rash associated with hospitalization and discontinuation of the immediate-release formulation of LAMICTAL occurred in 0.3% (11 of 3,348) of adult patients who received the immediate-release formulation of LAMICTAL in premarketing clinical trials of epilepsy. In worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate. Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, and hematologic and hepatologic abnormalities. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered the immediate-release formulation of LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered the immediate-release formulation of LAMICTAL in the absence of valproate were hospitalized.

Patients With History of Allergy or Rash to Other AEDs: The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation of LAMICTAL is exceeded and in patients with a history of allergy or rash to other AEDs.

5.2 Hypersensitivity Reactions: Hypersensitivity reactions, some fatal or life-threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL XR should be discontinued if an alternative etiology for the signs or symptoms cannot be established. Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

5.3 Acute Multiorgan Failure: Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving the immediate-release formulation of LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received the immediate-release formulation of LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause. Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after the immediate-release formulation of LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with the immediate-release formulation of LAMICTAL was discontinued.

5.4 Blood Dyscrasias: There have been reports of blood dyscrasias with the immediate-release formulation of LAMICTAL that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

5.5 Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including LAMICTAL XR, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,963 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanism of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients With Events Per 1,000 Patients	Drug Patients With Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients With Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing LAMICTAL XR or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Potential Medication Errors: Medication errors involving LAMICTAL have occurred. In particular, the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the Medication Guide [see *Patient Counseling Information* (17.10)]. Each LAMICTAL XR tablet has a distinct color and white center, and is printed with "LAMICTAL XR" and the tablet strength. These distinctive features serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30 tablets. The label on the bottle includes a depiction of the tablets which further communicates to patients and pharmacists that the medication is LAMICTAL XR and the specific label strength included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle label features serves to identify the different presentations of the drug and thus may help to reduce the risk of medication errors. To avoid the medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL XR each time they fill their prescription.

5.7 Concomitant Use With Oral Contraceptives: Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine [see *Clinical Pharmacology* (12.3) of the full prescribing information]. Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL XR [see *Dosage and Administration* (2.1) of the full prescribing information]. During the week of inactive hormone preparation ("pill-free" week) of oral contraceptive therapy, plasma lamotrigine levels are expected to rise, as much as doubling at the end of the week. Adverse reactions consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

5.8 Withdrawal Seizures: As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of at least 2 weeks (approximately 50% reduction per week) [see *Dosage and Administration* (2.1) of the full prescribing information].

5.9 Status Epilepticus: Valid estimates of the incidence of treatment-emergent status epilepticus among patients treated with immediate-release lamotrigine are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 7 of 2,943 adult patients had episodes that could unequivocally be described as status epilepticus. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

5.10 Sudden Unexplained Death in Epilepsy (SUDEP): During the premarketing development of the immediate-release formulation of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure). Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0033 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for immediate-release lamotrigine, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving immediate-release lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving immediate-release lamotrigine and those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in similar populations. Importantly, that drug is chemically unrelated to lamotrigine. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

5.11 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate: Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half that required in its absence.

5.12 Binding in the Eye and Other Melanin-Containing Tissues: Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine binding to melanin is unknown [see *Clinical Pharmacology* (12.2) of the full prescribing information]. Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmological effects.

5.13 Laboratory Tests: The value of monitoring plasma concentrations of lamotrigine in patients treated with LAMICTAL XR has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs including AEDs (see Table 2), monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary. Treatment with LAMICTAL XR caused an increased incidence of subnormal (below the reference range) values in some hematology analytes (e.g., total white blood cells, monocytes). The treatment effect (LAMICTAL XR % - Placebo %) incidence of subnormal counts was 3% for total white blood cells and 4% for monocytes.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label: Serious skin rashes [see *Warnings and Precautions* (5.1)]; Hypersensitivity reactions [see *Warnings and Precautions* (5.2)]; Acute multiorgan failure [see *Warnings and Precautions* (5.3)]; Blood dyscrasias [see *Warnings and Precautions* (5.4)]; Suicidal behavior and ideation [see *Warnings and Precautions* (5.5)]; Withdrawal seizures [see *Warnings and Precautions* (5.8)]; Status epilepticus [see *Warnings and Precautions* (5.9)]; Sudden unexplained death in epilepsy [see *Warnings and Precautions* (5.10)].

6.1 Clinical Trial Experience with LAMICTAL XR for Treatment of Partial Onset Seizures: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most commonly observed adverse reactions (≥4% for LAMICTAL XR and more common on drug than placebo) in a double-blind, placebo-controlled trial of adjunctive therapy with LAMICTAL XR for the treatment of partial onset seizures were, in order of decreasing treatment difference (LAMICTAL XR % - Placebo %) incidence: dizziness, tremor/intention tremor, cerebellar coordination/balance disorder, nausea, asthenic conditions (asthenia, fatigue, malaise), vertigo/positional vertigo, and diplopia. Nine of 118 patients (8%) treated with LAMICTAL XR who participated in the double-blind, placebo-controlled trial in the treatment of partial onset seizures discontinued treatment due to adverse reactions compared to 2 of 121 patients (2%) who received placebo. Dizziness, nausea, and nystagmus were the most common adverse reactions (based upon treatment difference of ≥2%) that led to the withdrawal of subjects in the group treated with LAMICTAL XR. The following listing provides the incidence of adverse reactions in a 19-week, double-blind, placebo-controlled study of patients with partial onset seizures.

Treatment-Emergent Adverse Reaction Incidence in a Double-Blind, Placebo-Controlled Adjunctive Trial of Patients With Partial Onset Seizures (Adverse Reactions ≥ 2% of Patients Treated With LAMICTAL XR and More Common on Drug Than Placebo). Adverse reactions are listed by body system with the percent incidence of LAMICTAL XR (n=118) followed by placebo (n=121): **Ear and Labyrinth Disorders:** vertigo/positional vertigo (4, 0); **Eye Disorders:** vision blurred (4, 2), diplopia (4, 0); **Gastrointestinal Disorders:** diarrhea (8, 5), nausea (7, 2), abdominal pain/discomfort (6, 4), vomiting (4, 2), constipation (3, 1), dry mouth (3, 2); **General Disorders and Administration Site Conditions:** asthenic conditions (asthenia, fatigue, malaise) (9, 5), chest pain/discomfort (3, 1), gait disturbance (2, 0), pain (2, 1); **Infections and Infestations:** influenza/flu-like illness (3, 2), sinusitis (3, 1); **Metabolic and Nutritional Disorders:** anorexia/decreased appetite (3, 2), weight increased (2, 1); **Musculoskeletal and Connective Tissue Disorders:** myalgia (3, 0); **Nervous System:** dizziness (19, 5), somnolence (7, 5), tremor/intention tremor (7, 2), cerebellar coordination/balance disorder (5, 0), nystagmus (3, 1); **Psychiatric Disorders:** depression (4, 1), anxiety (3, 0); **Respiratory, Thoracic, and Mediastinal Disorders:** pharyngolaryngeal pain (3, 2), epistaxis (2, 1), sinus congestion (2, 0); **Skin and Subcutaneous Tissue Disorders:** rash* (2, 1), alopecia (2, 1); **Vascular Disorder:** hot flush (3, 0). *All types of rash. In clinical trials evaluating the immediate-release formulation of LAMICTAL, the rate of serious rash was 0.3% in adults on adjunctive therapy for epilepsy [see *Boxed Warning*].

Adverse reactions were also analyzed to assess the incidence of the onset of an event in the titration period, and in the maintenance period, and if adverse reactions occurring in the titration phase persisted in the maintenance phase. The incidence for many adverse reactions caused by LAMICTAL XR treatment was increased relative to placebo (i.e., LAMICTAL XR % - Placebo

judges, police – where the right questions are not asked and punishment is the end point. Whether it's jail, probation, rough treatment, or whatever the adults want to do or say, the child is subject to them.

Much more important than these violent videotapes is the failure to engage the child and make him feel like he matters. There is an element of ageism here that I find troubling, too. Adults think: "He's the child; I'm the adult. I'll straighten him out." In these situations, the adolescent comes out feeling badly treated and needing, and practically

pleading for an adult who will talk to him. I can't tell you how many times I've heard a young person say: "It's not fair." The thing is, when they describe what happened, it sounds unfair, indeed. Our society needs to change our attitudes toward and treatment of our young people.

When thinking about youth violence, we first must consider the psychological, familial, environmental, as well as biological factors that can come together in one child to take him down the road of aggression and violence, often landing him in a morgue or behind bars.

So many young men end up in jail for life with no opportunity to get anywhere near their goals, use their natural talents and skills, or speak out on their own behalf. When we deal with a young man who is caught up in either the courts or the mental health system, we must first ask: "What happened to you?" We must find out about the traumas, abuses, losses, and punishments he has endured, and help him forgive himself.

And we must remember to treat him with respect, an act that can open up the door to trust. These are children who never trusted anyone – let alone an adult.

To reverse that, we need to look at all of the factors in their lives that led to their current predicament.

Too often, we jump to conclusions and end up oppressing the child because of our prejudices.

The current movie, "Conviction," is a perfect example of these dynamics. Our young people need an even playing field – and a chance. ■

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LAMICTAL® XR™ (lamotrigine) Extended-Release Tablets

% = treatment difference $\geq 3\%$) in either the titration or maintenance phases of the study. During the titration phase, an increased incidence (shown in descending order of % treatment difference) was observed for diarrhea, nausea, vertigo/positional vertigo, somnolence, myalgia, and hot flush. During the maintenance phase, an increased incidence was observed for dizziness, tremor/intention tremor, cerebellar coordination/balance disorder, vomiting, and diplopia. Some adverse reactions developing in the titration phase were notable for persisting (>7 days) into the maintenance phase. These "persistent" adverse reactions included somnolence, dizziness, and headache. In addition, some adverse reactions had an increased likelihood of recurring. Headache recurred predominantly in the titration period and vertigo and nausea recurred throughout the whole treatment period. There were inadequate data to evaluate the effect of dose and/or concentration on the incidence of adverse reactions because although patients were randomized to different target doses based upon concomitant AED, the plasma exposure was expected to be generally similar among all patients receiving different doses. However, in a randomized, parallel study comparing placebo and 300 and 500 mg/day of immediate-release formulation of LAMICTAL, the incidence of the most common adverse reactions ($\geq 5\%$) such as ataxia, blurred vision, diplopia, and dizziness were dose-related. Less common adverse reactions ($<5\%$) were not assessed for dose-response relationships. There were insufficient data to evaluate the effect of gender, age, and race on the adverse reaction profile for LAMICTAL XR.

6.2 Other Adverse Reactions Observed During the Clinical Development of the Immediate-Release Formulation of LAMICTAL: All reported reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug. **Adjunctive Therapy in Adults With Epilepsy:** In addition to the adverse reactions reported above from the development of LAMICTAL XR, the following adverse reactions with an uncertain relationship to lamotrigine were reported during the clinical development of the immediate-release formulation of LAMICTAL for treatment of epilepsy in adults. These reactions occurred in $\geq 2\%$ of patients receiving the immediate-release formulation of LAMICTAL and more frequently than in the placebo group. **Body as a Whole:** Fever, neck pain. **Musculoskeletal:** Arthralgia. **Nervous:** Insomnia, convulsion, irritability, speech disorder, concentration disturbance. **Respiratory:** Rhinitis, pharyngitis, cough increased. **Skin and Appendages:** Pruritus. **Urogenital:** (female patients only) Vaginitis, amenorrhea, dysmenorrhea.

Other Clinical Trial Experience: The immediate-release formulation of LAMICTAL has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients. **Body as a Whole:** Infrequent: Allergic reaction, chills, and malaise. **Cardiovascular System:** Infrequent: Flushing, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation. **Dermatological:** Infrequent: Acne, hirsutism, maculopapular rash, skin discoloration, and urticaria. **Rare:** Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson syndrome, and vesiculobullous rash. **Digestive System:** Infrequent: Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. **Rare:** Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, and tongue edema. **Endocrine System:** Rare: Goiter and hypothyroidism. **Hematologic and Lymphatic System:** Infrequent: Eosinophilia and leukopenia. **Rare:** Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia. **Metabolic and Nutritional Disorders:** Infrequent: Aspartate transaminase increased. **Rare:** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia. **Musculoskeletal System:** Infrequent: Arthritis, leg cramps, myasthenia, and twitching. **Rare:** Bursitis, muscle atrophy, pathological fracture, and tendinous contracture. **Nervous System:** Frequent: Confusion and paresthesia. **Infrequent:** Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonnia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, stupor, and suicidal ideation. **Rare:** Choreoathetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis. **Respiratory System:** Infrequent: Yawn. **Rare:** Hiccups and hyperventilation. **Special Senses:** Frequent: Amblyopia. **Infrequent:** Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. **Rare:** Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect. **Urogenital System:** Infrequent: Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, and urinary incontinence. **Rare:** Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency.

6.3 Postmarketing Experience with the Immediate-Release Formulation of LAMICTAL: The following adverse events (not listed above in clinical trials or other sections of the prescribing information) have been identified during postapproval use of the immediate-release formulation of LAMICTAL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Blood and Lymphatic:** Agranulocytosis, hemolytic anemia. **Gastrointestinal:** Esophagitis. **Hepatobiliary Tract and Pancreas:** Pancreatitis. **Immunologic:** Lupus-like reaction, vasculitis. **Lower Respiratory:** Apnea. **Musculoskeletal:** Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions. **Neurology:** Exacerbation of Parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics. **Non-site Specific:** Progressive immunosuppression.

7 DRUG INTERACTIONS

Significant drug interactions with lamotrigine are summarized in Table 2. Additional details of these drug interaction studies, which were conducted using the immediate-release formulation of LAMICTAL, are provided in the Clinical Pharmacology section [see Clinical Pharmacology (12.3) of the full prescribing information].

Table 2. Established and Other Potentially Significant Drug Interactions

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine	Decreased lamotrigine levels approximately 50%.
Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine ? CBZ epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase CBZ epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

↓ = Decreased (induces lamotrigine glucuronidation).

↑ = Increased (inhibits lamotrigine glucuronidation).

? = Conflicting data.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Teratogenic Effects: Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m² basis, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6

times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased. A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m² basis, respectively. Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m² basis. When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m² basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between day 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study. Although lamotrigine was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects: As with other AEDs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Exposure Registry: To provide information regarding the effects of in utero exposure to LAMICTAL XR, physicians are advised to recommend that pregnant patients taking LAMICTAL XR enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org>. Physicians are also encouraged to register patients in the Lamotrigine Pregnancy Registry; enrollment in this registry must be done prior to any prenatal diagnostic tests and before fetal outcome is known. Physicians can obtain information by calling the Lamotrigine Pregnancy Registry at 1-800-336-2176 (toll-free).

8.2 Labor and Delivery: The effect of LAMICTAL XR on labor and delivery in humans is unknown.

8.3 Nursing Mothers: Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL XR is not recommended.

8.4 Pediatric Use: LAMICTAL XR is indicated as adjunctive therapy for partial onset seizures with or without secondary generalization in patients ≥ 13 years of age. Safety and effectiveness of LAMICTAL XR for any use in patients below the age of 13 have not been established. The immediate-release formulation of LAMICTAL is indicated for adjunctive therapy in patients ≥ 2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures. Safety and efficacy of the immediate-release formulation of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). The immediate-release formulation of LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, Placebo 5%), and respiratory adverse reactions (LAMICTAL 26%, Placebo 5%). Infectious adverse reactions included: bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.

8.5 Geriatric Use: Clinical studies of LAMICTAL XR for epilepsy did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects or exhibit a different safety profile than that of younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study with the immediate-release formulation of LAMICTAL in 24 patients with mild, moderate, and severe liver impairment [see Clinical Pharmacology (12.4) of the full prescribing information], the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response [see Dosage and Administration (2.1) of the full prescribing information].

8.7 Patients With Renal Impairment: Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of the metabolites being recovered in the urine. In a small study comparing a single dose of immediate-release lamotrigine in patients with varying degrees of renal impairment with healthy volunteers, the plasma half-life of lamotrigine was significantly longer in the patients with renal impairment [see Clinical Pharmacology (12.3) of the full prescribing information]. Initial doses of LAMICTAL XR should be based on patients' AED regimens; reduced maintenance doses may be effective for patients with significant renal impairment. Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine. Because there is inadequate experience in this population, LAMICTAL XR should be used with caution in these patients [see Dosage and Administration (2.1) of the full prescribing information].

10 OVERDOSAGE

10.1 Human Overdose Experience: Overdoses involving quantities up to 15 g have been reported for the immediate-release formulation of LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

10.2 Management of Overdose: There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed; usual precautions should be taken to protect the airway. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdose of LAMICTAL XR.

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May 2009

LXR-1BR8