Lamotrigine in Adolescent Mood Disorders: A Retrospective Chart Review

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Abstract

Introduction: Treatment nonresponse in adolescent mood disorders is a major public health problem, as mood disorders in youth are associated with significant mortality by suicide, protracted course of illness, and recurrence into adulthood. Three studies with small sample sizes exist for lamotrigine in youth mood disorders. However, the risk of serious rash has limited its use in youth mood disorders. **Objective**: The aims of this study are to evaluate the preliminary effectiveness and safety of lamotrigine in adolescent mood disorders. **Methods**: Medical charts were retrospectively reviewed at three clinical sites for 42 adolescents treated with lamotrigine for a mood disorder. The Clinical Global Impression (CGI) Severity and Improvement scores were obtained at baseline and last visit. Treatment-emergent adverse effects were also obtained. **Results**: Improvement was seen in 22 subjects (52%). The mean daily lamotrigine dose was 114.8mg (SD 75.6), and the average duration of lamotrigine treatment was 29.1±31.8 weeks. The mean CGI-S score decreased from 4.9±1.0 at baseline to 3.5±1.4 at endpoint ($z=3.204$, $p<0.002$). Four subjects (10%) developed benign rash. **Conclusions**: This study provides preliminary data that lamotrigine may be effective in adolescents with mood disorders. However, this study revealed that lamotrigine might be associated with a significant risk of benign rash.

Key words: Lamotrigine, psychopharmacology, depression, mood, adolescent

Résumé

Introduction: La non-réponse au traitement des troubles de l'humeur chez les adolescents présente un sérieux problème de santé publique, car ces troubles s'accompagnent souvent de suicide, d'une prolongation de la maladie et de rechutes à l'age adulte. L'utilisation de la lamotrigine dans le traitement des troubles de l'humeur a fait l'objet de trois études portant sur un échantillonnage réduit. **Objectif général**: Évaluer l'efficacité et l'innocuité de ce médicament chez ces sujets. **Méthodologie**: Le dossier médical de 42 adolescents traités pour des troubles de l'humeur a été analysé rétrospectivement dans trois sites. L'indice de gravité générale clinique globale et l'indice d'amélioration ont été enregistrés au début et à la fin de l'étude. Les effets secondaires dus au traitement ont également été étudiés. **Résultats**: On a constaté une amélioration chez 22 sujets (52 %). La dose quotidienne moyenne était de 114,8 mg (SD 75,6), la durée de traitement moyenne de 29,1 ± 31,8 semaines. L'indice moyen de gravité générale est descendu de 4,9 ± 1,0 (valeur de début) à 3,5 ± 1,4 (valeur de fin) ($z=3,204$, $p<0,002$). Quatre sujets (10 %) ont souffert d'une légère éruption cutanée. **Conclusions**: Les données préliminaires de cette étude montrent que la lamotrigine est efficace dans le traitement des troubles de l'humeur chez les adolescents, mais qu'il existe un risque d'éruption cutanée bénigne.

Mots clés: lamotrigine; psychopharmacologie; dépression; humeur; adolescent

Introduction

Mood disorders in youth, which include major depressive disorder and bipolar disorder, are highly prevalent, and are associated with significant mortality and morbidity. A recent multi-site, methodologically sound study of fluoxetine with concurrent cognitive behavioral therapy in adolescents illustrated that approximately 30% had a partial or no response to treatment, thus classified as "treatment-resistant" (March et al, 2004). A meta-analysis of the six published, randomized, placebo-controlled trials of Serotonin Reuptake Inhibitors (SRI's) in depressed youth (not including the March Study) revealed an effect size of only 0.26 (Jureidini et al, 2004). This further illustrates the poor response of SRI's in youth depression. Treatment-resistant depression is associated with poor prognosis and high risk for suicide, indicating the need for more aggressive and clinically effective treatment than SRI's alone

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can provide. Bipolar disorder in youth is also associated with poor prognosis, and the standard mood stabilizers (lithium, valproate, carbamazepine, atypical antipsychotics) are associated with serious adverse effects. While Bipolar I Disorder is well recognized in adolescents, there is controversy about the boundaries of the bipolar spectrum. The National Institute of Mental Health (NIMH) has recommended a classification system to prospectively follow youth who have narrow, intermediate, or broad phenotype, in an attempt to assess the validity of each subtype in longitudinal studies (Leibenluft et al, 2003).

Current options for treatment-resistant depression in youth include optimizing the dose and duration of the current antidepressant, switching to another antidepressant within the same class, switching to another antidepressant in a different class, augmentation of the antidepressant, or combination (with lithium, thyroid hormone) (AACAP, 1998). More aggressive treatment includes monoamine oxidase inhibitors (MAOI) or electroconvulsive therapy (ECT). Overall, minimal data exists to guide clinicians in treating refractory depression in youth.

A few pilot studies have shown promising results for lamotrigine (LTG) in treatment refractory mood disorders in both youth and adults, especially for depressive symptoms (Carandang et al, 2003; Mandoki, 1997; Frye et al, 2000). The two youth pilot studies for refractory mood disorders (Carandang et al, 2003; Mandoki, 1997) illustrated that LTG was effective and well tolerated. One prospective study was recently published for LTG in adolescent bipolar disorder (Chang et al, 2006), where the majority of study patients responded and LTG was well tolerated. Lamotrigine (Lamictal®) is approved by the U.S. Food and Drug Administration (FDA) for maintenance treatment of bipolar disorder in adults (Prescribing Information, Lamictal®, 2006). However, the risk of serious rash associated with LTG has limited its use in youth with mood disorders. Studies of LTG in epilepsy indicate that the risk factors associated with serious rash and lamotrigine treatment include young age, high starting dose, rapid dose escalation, and addition of LTG to valproate (Guberman et al, 1999). Safety data regarding LTG in pediatric mood disorders is limited, as only three studies exist.

In the only prospective study of LTG in pediatric mood disorders, Chang and colleagues (2006) studied 20 youth with bipolar disorder, ages 12-17. The study patients presented with bipolar depression. Study patients received open-label LTG monotherapy or add-on (to lithium, valproate, carbamazepine, antipsychotics, or stimulants). Response was defined by a Clinical Global Impressions Improvement scale score of 1 or 2, and a 50% decrease of the Children's Depression Rating Scale-Revised (CDRS-R) from baseline. The mean final dose was 131.6mg/day, with 84% response as measured by the CGI-I, and 58% response as measured by the CDRS-R. No weight gain or rash was noted in the Chang study.

The other two LTG youth studies for pediatric mood disorders are non-controlled, retrospective studies. However, these studies provide valuable information regarding the safety and tolerability of LTG in refractory mood disorders in youth. In the first study, Mandoki retrospectively studied 10 children and adolescents with refractory bipolar disorder, in which LTG was added to valproate (Mandoki, 1997). The dose range for LTG was 50-200mg/day, while the range for VPA was 500-1500mg/day. Clinical Global Impressions (CGI) revealed improvement when LTG added to VPA. However, the author did not define the criteria for improvement as measured by the CGI. The age range and mean age were also not published. Rash was not reported by any subjects in the study.

In the second study, Carandang and colleagues reviewed 9 adolescents with refractory mood disorders retrospectively, where LTG was added or substituted when previous pharmacotherapy failed (Carandang et al, 2003). Diagnoses included: 6 with bipolar depression, 2 with unipolar depression, and 1 with mood disorder not otherwise specified. Their mean age was 16.4 years, ranging from 14 to 18 years. The mean daily LTG dose was 141.7mg, ranging from 25 to 250mg/day. Improvement was seen in 8 out of 9 subjects, as measured by the CGI-BP overall illness rating (Clinical Global Impressions-Bipolar Version). Responders included 7 who were rated as 'much improved' and 1 who was rated as 'very much improved.' One subject developed a benign rash, which remitted a few days after discontinuation of LTG. The specific aim of

this study is to provide more data on the safety and tolerability of LTG in adolescent mood disorders.

Methods

A multi-site, retrospective chart review was completed on all adolescents (13-17 years old) treated with lamotrigine for a mood disorder at three tertiary mood disorder programs. No information was gathered directly from the patient or family. All patient identifiers were removed, and a study number was assigned to preserve confidentiality. Permission was obtained from the Institutional Review Board (IRB) at the two American sites and the Research Ethics Board (REB) at the Canadian site to review these charts for research purposes. The IRB and REB waived the need for informed consent from the patient and guardians. The following mood disorder diagnoses were included in the review: bipolar disorder (type I, II, and not otherwise specified), major depressive disorder, and mood disorder not otherwise specified. The data was collected by the investigators through chart reviews, which included the following: 1) age, diagnosis, and CGI-S (severity subscale) (Guy, 1976) of the patient before initiation of LTG, 2) treatment-emergent adverse effects while on LTG (especially observing for rash), 3) concurrent medications and final LTG dose at time of clinical effect or taper/discontinuation, 4) duration of treatment with LTG (or time to discontinuation), and 5) CGI-S and CGI-I (improvement subscale) of last point of contact with the patient while either stable on LTG or at discontinuation. Diagnoses were made by child psychiatrists using clinical interviews based on DSM-IV criteria and from all available collateral information. CGI-S and CGI-I were obtained from the clinician of record based on the chart notes. The CGI-S ratings at baseline and endpoint were analyzed using the Wilcoxon signed ranks test ($p<0.01$ as significant [two-tailed]).

Results

Forty-two adolescents (mean age 15.6 years, SD 1.3) with bipolar disorder or refractory depression who were treated with LTG were identified: 28 from an outpatient child and adolescent psychiatry clinic, 7 from a clinical research program, and 7 from a pediatric mood disorders clinic. The data on the patients are outlined in Table 1. Diagnoses included 21 (50%) with bipolar disorder, 12 (29%) with unipolar depression, and 9 (21%) with mood disorder not otherwise specified. The mean number of comorbid diagnoses was 0.8±0.7, and 29% of the sample was male (Table 2). Thirty-eight (90%) had failed prior medication trials with mood stabilizers and/or antidepressants. The average number of concurrent medications with LTG was 1.5±1.0 (Table 3). These included SRI (n=12, 29%), other antidepressants (n=3, 7%), other mood stabilizers (n=7, 17%), antipsychotics (n=22, 52%), stimulants (n=12, 29%), anxiolytics (n=3, 7%), no concurrent medications-LTG monotherapy (n=6, 14%), and ECT (n=1, 2%). The mean daily LTG dose was 114.8mg (SD 75.6), ranging from 10 to 300mg/day. The average duration of LTG treatment was 29.1±31.8 weeks. The mean CGI-S score decreased from 4.9±1.0 (markedly ill range) at baseline to 3.5±1.4 (mildly ill range) at endpoint (Wilcoxon signed ranks z-score=3.204, $p<0.002$) (Figure 1). Improvement was seen in 22 subjects (52%), as defined by a Clinical Global Impression-Improvement scale score of 1 (very much improved) or 2 (much improved) (Figure 2). Four subjects (10%) developed benign rash, which remitted after discontinuation of LTG. One additional subject developed severe generalized pruritis when she abruptly discontinued her oral conceptive (OC), which resolved when restarting the OC. Three subjects (7%) developed excessive sedation, which led to two discontinuations of LTG, and one subject was stable with no adverse effects at a lower LTG dose.

Discussion

Improvement was seen in 52% of study subjects on LTG. However, this study revealed that LTG may be associated with a significant risk of benign rash for adolescents with mood disorders. No serious rash (i.e. Stevens Johnson Syndrome, Toxic Epidermal Necrolysis) occurred. The sample in this study is similar demographically to a previous sample by Carandang and colleagues (2003), where one subject (11%) developed benign rash out of a total of 9 adolescents with mood disorders on LTG. When comparing the sample in this study with the Chang study (2006), Chang and col-

Table 1. Patient Data

Subject	Age (years)*	Gender	Mood D/O Diagnosis	Comorbid Diagnoses	Number of comorbid diagnoses	LTG Dose (mg/day)†	LTG Duration (weeks)†	Prior Medication Trials	Concurrent Medications†	Number of Concurrent Medications with LTG	CGI-S Pre-LTG TX	CGI-S Post-LTG TX†	CGI Improvement†	Adverse Effects†
1	13	M	Mood D/O NOS	ADHD	1	50	7	Fluoxetine, aripiprazole, methylphenidate, risperidone, atomoxetine	Methylphenidate 90mg, quetiapine 75mg	2	5	3	2	None
2	13	M	Bipolar D/O NOS	ADHD, Psychosis	2	50	13	Olanzapine, clonidine	Divalproex 750mg, aripiprazole 20mg	2	5	2	2	None
3	13	F	MDD	PDD, GAD	2	200	36	Sertraline, buspirone	Escitalopram 10mg	1	5	3	2	None
4	13.5	M	Bipolar I D/O	None	0	25	8	Mirtazapine, buproprion, lithium, carbamazepine, divalproex, risperidone	Oxcarbazepine 1500mg, aripiprazole 30mg	2	6	6	4	None
5	14	F	MDD	None	0	25	1.5	Divalproex, venlafaxine	Divalproex 750mg	1	3	3	4	Rash occurred when LTG 25mg added to VPA at week 1.5-remitted on D/C of LTG
6	14	F	Bipolar D/O NOS	None	0	100	104	None	None	0	3	1	2	None
7	14	M	Mood D/O NOS	ADHD	1	100	132	Sertraline, risperidone, l/d-amphetamine, atomoxetine	None	0	4	3	3	None
8	14	F	MDD with psychosis	None	0	200	36	Aripiprazole	Sertraline 200mg, quetiapine 200mg	2	6	2	1	None
9	14.5	F	Bipolar D/O NOS	None	0	25	40	None (lithium offered, but refused blood draws)	Quetiapine 100mg	1	5	3	2	None
10	15	F	Bipolar I D/O	ADHD	1	100	36	Fluoxetine, citalopram, risperidone, methylphenidate	Loxapine 5mg, benztropine 2mg	2	4	3	3	None
11	15	M	MDD	ADHD	1	100	24	Buproprion, atomoxetine	Citalopram 30mg, OROS:MPH 72mg	2	6	3	1	None
12	15	F	Mood D/O NOS	ADHD	1	200	10	Fluoxetine, sertraline, escitalopram, buproprion, l/d-amphetamine	Quetiapine 100mg, OROS:MPH 72mg	2	5	3	2	None
13	15	F	Bipolar D/O NOS	None	0	25	0.3	Sertraline	Quetiapine 125mg	1	5	5	4	Rash occurred day 2 at 25mg-remitted on D/C of LTG
14	15	F	Bipolar D/O NOS	ADHD, Psychosis	2	100	28	Aripiprazole, atomoxetine, clonazepam	Quetiapine 25mg, OROS:MPH 18mg	2	5	3	2	None
15	15	F	Mood D/O NOS	None	0	200	104	Citalopram, venlafaxine, buproprion, paroxetine, risperidone	Fluoxetine 60mg, aripiprazole 10mg, OROS:MPH 72mg	3	5	4	3	None
16	15	M	Mood D/O NOS	None	0	200	12	Sertraline, paroxetine, venlafaxine, lithium, quetiapine, olanzapine, risperidone, alprazolam	Fluoxetine 20mg	1	4	3	3	none
17	15.5	M	Bipolar I D/O	ADHD	1	25	0.3	Risperidone, d/l-amphetamine, dextroamphetamine	Olanzapine 20mg, guanfacine 6.5mg, gabapentin 2400mg, benztropine 1.5mg	4	7	7	4	Rash occurred day 2 at 25mg-remitted on D/C of LTG
18	16	F	MDD	None	0	100	32	None	None	0	3	1	2	None
19	16	F	Bipolar II D/O	Substance Abuse	1	25	8	None	Divalproex 500mg	1	4	4	4	None
20	16	F	Bipolar D/O NOS	ADHD	1	175	32	Sertraline, venlafaxine, buspirone, ziprasidone, aripiprazole, topiramate	Olanzapine 2.5mg, l/d-amphetamine 10mg, OCP	2	6	4	2	Severe generalized pruritis after OCP D/C'ed; remitted when OCP restarted
21	16	F	MDD	PTSD, ADHD	2	200	18	Sertraline, escitalopram, venlafaxine, lithium, ziprasidone	Buproprion 450mg, venlafaxine 225mg, OROS:MPH 72mg	3	6	6	4	None
22	16	F	Mood D/O NOS	Substance Abuse	1	100	6	Citalopram, buproprion, divalproex	Aripiprazole 10mg	1	5	4	3	Excessive sedation at 100mg led to D/C at week 6

23	16	M	Mood D/O NOS	GAD	1	100	40	Divalproex, risperidone	Citalopram 30mg, clonazepam 1.5mg	2	4	2	2	None
24	16	M	Bipolar I D/O with psychosis	None	0	25	5	Escitalopram	Lithium 450mg, aripiprazole 5mg	2	6	7	5	None
25	16	F	Bipolar II D/O	ADHD	1	300	40	Sertraline, l/d-amphetamine	Aripiprazole 10mg, OROS:MPH 54mg, OCP	2	5	3	2	None
26	16	F	MDD	Substance Abuse	1	150	11	Multiple SRI's per hx, lithium, ziprasidone	Escitalopram 20mg, topiramate 50mg, clonazepam 1mg	3	5	4	3	None
27	16	F	Mood D/O NOS	None	0	10	2	Fluoxetine, risperidone, lithium	None	0	6	4	2	None
28	16.5	F	MDD with psychosis	ADHD	1	100	76	Citalopram, lithium, risperidone	Mirtazapine 30mg, aripiprazole 30mg, l/d-amphetamine 15mg	3	5	2	1	None
29	16.5	F	MDD with psychosis	None	0	200	104	Paroxetine, citalopram, venlafaxine, lithium, risperidone, l/d-amphetamine	Aripiprazole 40mg, benztropine 1mg, ECT (monthly)	2	7	3	1	None
30	16.5	F	Bipolar D/O NOS	None	0	100	16	None	None	0	4	3	3	None
31	17	F	MDD	ADHD, Dysthymia	2	150	40	Sertraline, citalopram, venlafaxine, aripiprazole, lithium, buspirone, dextroamphethamine	Buproprion 300mg, l/d-amphetamine 30mg	2	5	4	3	None
32	17	F	Bipolar II D/O	Substance Abuse	1	100	28	Sertraline	None	0	4	2	2	None
33	17	M	Bipolar II D/O	Panic Disorder	1	200	12	Lithium, olanzapine/fluoxetine (Symbyax®)	Olanzapine 5mg, clonazepam 3mg	2	6	3	1	None
34	17	F	Mood D/O NOS	Conduct D/O, Psychosis	2	50	5	Divalproex	Citalopram 40mg, OROS:MPH 72mg	2	4	6	6	Rash at 50mg at week 5-remitted on D/C of LTG
35	17	F	Bipolar D/O NOS	None	0	250	44	Lithium, ziprasidone	Olanzapine 2.5mg	1	4	2	2	None
36	17	M	Bipolar D/O NOS	Psychosis	1	50	12	Olanzapine, ziprasidone, aripiprazole	Quetiapine 800mg	1	5	3	2	None
37	17	F	Bipolar D/O NOS	PTSD	1	100	4	Escitalopram, risperidone, quetiapine, haloperidol, trazodone	Sertraline 50mg	1	4	4	4	None
38	17	F	Bipolar II D/O	None	0	200	52	Sertraline, escitalopram	Quetiapine 100mg, d/l-amphetamine 10mg	2	5	2	1	None
39	17	F	Bipolar II D/O	ADHD, Substance Abuse	2	10	4	Fluoxetine, sertraline, OROS:MPH	Quetiapine 50mg	1	5	3	2	Excessive sedation at 25mg; no sedation on 10mg
40	17	F	MDD	Panic Disorder	1	50	4	Dextroamphetamine	Sertraline 100mg	1	5	5	4	Excessive sedation at 25mg led to D/C at week 4
41	17	F	Bipolar I D/O	None	0	150	16	Sertraline, paroxetine, risperidone	None	0	4	3	3	None
42	17	M	MDD	Dysthymia	1	200	20	Citalopram, buproprion, OROS:MPH	Escitalopram 10mg, trazodone 100mg	2	4	4	4	None
Mean	15.6				0.8	114.8	29.1			1.5	4.9	3.5	2.7	
SD	1.3				0.7	75.6	31.8			1.0	1.0	1.4	1.2	

* At initiation of LTG

† At the time of the chart review

ADHD = Attention Deficit Hyperactivity Disorder; CGI = Clinical Global Impressions; D/C = discontinue; D/O = Disorder; ECT = electroconvulsive therapy; GAD = Generalized Anxiety Disorder; LTG = lamotrigine; MDD = Major Depressive Disorder; NOS = not otherwise specified; OCP = oral contraceptive pill; OROS:MPH = Concerta®; PDD = Pervasive Developmental Disorder; PTSD = Post Traumatic Stress Disorder; SRI = Serotonin Reuptake Inhibitor; TX = treatment; VPA = valproate

Table 2. Clinical Characteristics of the Sample (N=42)

Variable	Mean_SD
Age (years)	15.6_1.3
Number of comorbid diagnoses	0.8_0.7

	N	(%)
Gender (% male)	12	29%
Bipolar disorder	21	50%
Unipolar depression	12	29%
Mood disorder NOS	9	21%

Table 3. Concurrent Medications of the Sample (N=42)

Variable	Mean_SD
Number of concurrent medications	1.5_1.0

	N	(%)
SRI	12	29%
Other antidepressants	3	7%
Other mood stabilizers	7	17%
Antipsychotics	22	52%
Stimulants	12	29%
Anxiolytics	3	7%
LTG monotherapy	6	14%
ECT	1	2%

leagues studied bipolar depressed adolescents exclusively. This study focused on treatment-resistant depression in adolescents, who have either unipolar depression, bipolar affective disorder, or mood disorder NOS. There certainly is overlap, but the population in this study includes unipolar depression and mood disorder NOS, which is different from the Chang sample. To summarize, the focus in this study is LTG in adolescents with treatment-resistant depression, which is innovative to date.

The initial titration schedule for most subjects in this study was in accordance with FDA-recommended dosing guidelines for adult bipolar disorder: start 25mg daily for weeks 1 and 2, 50mg daily for weeks 3 and 4, 100mg daily for week 5, and 200mg daily for week 6 (Prescribing Information, Lamictal®, 2006). The current FDA guidelines for lamotrigine titration may be too aggressive for adolescents with mood disorders, as 10% of the sample in this study developed benign rash (a possible harbinger for serious rash). The risk of rash is decreased by initiating lamotrigine at a low dose, and titrating slowly over several weeks. Doubling the FDA recommended titration schedule for adult bipolar disorder may decrease the risk of rash in adolescents (Tables 4 and 5), as also recommended in the Connor and Meltzer text (2006). From the LTG studies in adolescents with mood disorders (including this study), the suggested average target dose for LTG is between 115mg to 142mg daily (Carandang et al, 2003; Chang et al, 2006).

Additional precautions should be taken when prescribing LTG in females taking oral contraceptives (OC's). Oral contraceptives can decrease LTG levels (Sabers et al, 2003). This can be problematic when OC's are abruptly

Figure 1. CGI Severity, Pre- and Post-Treatment

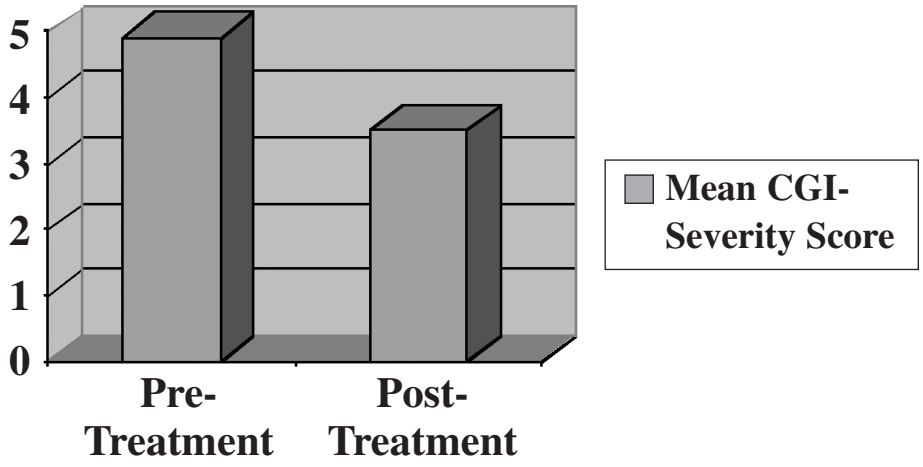

Figure 2. CGI-Improvement

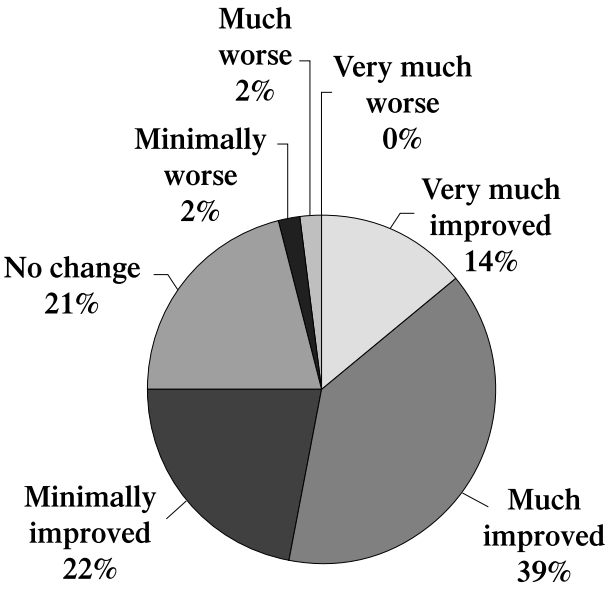

Table 4. Recommended Lamotrigine Titration in Adolescents

12.5mg daily for weeks 1 and 2
25mg daily for weeks 3 and 4
50mg daily for week 5
100mg daily for week 6
Target dose: Consider 115mg to 142mg daily

Table 5. Recommended Lamotrigine Titration Added to Valproate Regimen

12.5mg every other day for weeks 1 and 2
12.5mg daily for weeks 3 and 4
25mg daily for week 5
50mg daily for week 6
Target dose: Consider 50mg to 75mg daily

discontinued, as the resultant sudden increase in LTG levels can increase the risk of rash. When prescribing LTG, the known risk factors for rash (young age, high starting dose, rapid dose escalation, and concurrent valproate) and drug interactions (especially with OC's, valproate) should be discussed as part of the informed consent process. Clinicians should also be aware that LTG has a USA FDA Blackbox warning, which states "because the rate of serious rash is greater in pediatric patients than in adults, it bears emphasis that Lamictal is approved only for use in pediatric patients below the age of 16 years who have seizures associated with the Lennox-Gastaut Syndrome or in patients with partial seizures (Prescribing Information, Lamictal®, 2006)." However, when confronted with the poor prognosis and suicide risk associated with treatment-resistant depression, LTG can be considered as a 3rd-line treatment option, as the benefits may outweigh the risks.

Limitations

This study is limited by the lack of a comparison group, the lack of a gold-standard diagnostic instrument (K-SADS: Schedule for Affective Disorders and Schizophrenia for School Aged Children), the lack of a rating scale to systematically report treatment-emergent adverse effects, the use of a range of concomitant medications, and a small sample size. Methodological problems include the retrospective nature of chart reviews, highly variable lengths of treatment, heterogeneous sample (mood disorder spectrum rather than mood disorder subtypes), and unclear impact of comorbid conditions. It is also highly likely that adverse effects were underreported, as the adverse effects were spontaneously reported and not systematically obtained. It is also difficult to ascertain whether the improvements were due to lamotrigine, placebo effect, or the concurrent medications. These complicating factors limit the validity and reliability of the findings. Prospective, controlled studies are clearly indicated to definitely assess the safety and efficacy of lamotrigine in adolescent mood disorders.

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