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Variation in dose and plasma level of lamotrigine in patients discharged from a mental health trust

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Abstract

Background: The objectives of this study were to investigate the dose of lamotrigine when prescribed with an enzyme inhibitor or enzyme inducer in patients discharged from a mental health trust and to determine the corresponding lamotrigine plasma concentrations and the factors that may affect these.

Methods: All patients discharged on lamotrigine between October 2007 and September 2012 were identified using the pharmacy dispensing database. We recorded demographic details, lamotrigine dose and plasma levels and coprescribed medication.

Results: During the designated period, 187 patients were discharged on lamotrigine of whom 117 had their plasma levels recorded. The mean lamotrigine daily dose was 226.1 mg (range 12.5–800 mg) and the mean plasma level 5.9 mg/l (range 0.8–18.1 mg/l). Gender, ethnicity, diagnosis and smoking status had no significant effect on dose or plasma levels. Patients taking an enzyme-inducing drug (n = 6) had significantly lower plasma levels [mean (SD) 3.40 (1.54) mg/l] than those not taking enzyme inducers [n = 111; 6.03 (3.13) mg/l; p = 0.043]. Patients taking an enzyme-inhibiting drug (n = 23) had significantly higher levels [7.47 (3.99) mg/l] than those not taking an inhibitor [n = 94; 5.52 (2.75) mg/l; p = 0.035]. No significant difference was found between the doses of lamotrigine in patients taking an enzyme inhibitor and those not taking one (p = 0.376). No significant difference was found between the doses of lamotrigine in patients taking an enzyme-inducing drug and those not taking any (p = 0.574).

Conclusions: Current dosing recommendations indicate that lamotrigine doses should be halved in individuals taking enzyme inhibitors and doubled in those on enzyme inducers. In our survey these recommendations were rarely followed with the consequence that patients received too high or too low a dose of lamotrigine, respectively.

Keywords: drug interactions, lamotrigine, therapeutic drug monitoring

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Introduction

Lamotrigine is an anticonvulsant which entered the market in 1994 as an add-on treatment for seizure disorders. Currently it is licensed for the adjunctive or monotherapy treatment of various seizure disorders in both adults and children. In adults it is also indicated for the prevention of depressive episodes in bipolar I disorder [GlaxoSmithKline UK, 2016]. Also not uncommonly in mental health, lamotrigine is used off-license to augment clozapine in patients who have refractory schizophrenia and have shown an inadequate response to clozapine monotherapy [Tiihonen *et al.* 2003]. It is also employed to act as prophylaxis against seizures in susceptible patients when clozapine plasma levels are above 500–600 mg/l [Varma *et al.* 2011].

Lamotrigine is metabolized in the liver primarily by conjugating with glucuronic acid to form the inactive metabolite 2-N-glucuronide [Rambeck and Wolf, 1993]. Uridine 5′-diphospho-glucuronosyltransferase 1A4 (UGT1A4) and UGT2B7 are the enzymes involved in this reaction [Magdalou *et al.* 1992; Rowland *et al.* 2006]. Other drugs and their metabolites that involve

this metabolic route may show altered metabolism or affect the metabolism of lamotrigine due to competition for this pathway. As the metabolism of lamotrigine does not depend upon any cytochrome P450 enzymes, the possibility for drug interactions are generally limited [Rambeck and Wolf, 1993]. However, lamotrigine does have some clinically relevant interactions.

Upon starting lamotrigine for any indication, the dose needs to be titrated slowly to a maintenance dose to reduce the risk of developing a serious rash. The maintenance monotherapy dosage of lamotrigine in epilepsy ranges typically between 100 and 200 mg daily. However, when used with an adjunctive drug that inhibits lamotrigine glucuronidation (such as valproate) the titration of lamotrigine needs to be slower and lower maintenance doses of lamotrigine are required. Conversely, when lamotrigine is administered with a drug that can induce its glucuronidation (such as carbamazepine) the initial starting dose of lamotrigine is higher and the final maintenance dose of lamotrigine should also be higher than when an inducer is not administered.

For maintenance treatment of bipolar I disorder 200 mg is the recommended target dose for lamotrigine [GlaxoSmithKline UK, 2016]. Although licensed only for the prophylaxis of bipolar I depression it is also used off-label for the acute treatment of this disorder. The advantage over antidepressants is that lamotrigine does not induce switching or rapid cycling [Taylor *et al.* 2015]. In practice, it is also used as an adjunct to other mood stabilizers. For clozapine augmentation doses of lamotrigine 25–300 mg have been recommended [Taylor *et al.* 2015].

A therapeutic plasma concentration target range is not established for lamotrigine. However, a therapeutic range of 2.5–15 mg/l has been suggested in epilepsy [Cohen *et al.* 1987; Johannessen *et al.* 2003; Kilpatrick *et al.* 1996; Lardizabal *et al.* 2003]. It is believed that levels above 15 mg/l may be associated with toxicity [Morris *et al.* 1998].

Routine blood monitoring of lamotrigine is not recommended. However, if ineffectiveness, poor adherence or toxicity is suspected blood plasma level monitoring is recommended [National Institute for Health and Care Excellence, 2016]. Likewise, when prescribed with an enzyme inducer or enzyme inhibitor plasma level monitoring is also suggested [GlaxoSmithKline UK, 2016].

The aim of this survey was to determine in a mental health setting to what extent lamotrigine dose is reduced or increased when prescribed with an enzyme inhibitor or enzyme inducer, respectively, and to determine the resulting plasma levels and the factors that may affect these.

Methods

Patients discharged on lamotrigine between October 2007 and September 2012 were identified from the pharmacy electronic dispensing database system (JAC) of the South London and Maudsley NHS Foundation Trust (SLaM). SLaM is an inner city Trust serving a diverse population of 1.2 million people with areas of high unemployment and immigration. The dose of lamotrigine and any co-administered medication were noted. Patient details such as age, diagnosis, smoking status and reasons for taking lamotrigine were obtained from the patient electronic clinical notes (electronic patient journey system). Lamotrigine plasma level and the levels of any other available co-administered medication were obtained from the patient plasma level record system (PROL).

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences SPSS version 22. Normal Q–Q plot was used to assess normality of the outcome variables. For descriptive statistics, categorical variables were presented as number of cases (n) and percentage (%), continuous variables as mean and standard variation. Student's t test (independent samples) was employed for the comparison of two groups. The analysis of variance (ANOVA) was used for the comparison of three groups or more for the continuous variables. The Pearson correlation test was employed to ascertain the association between the continuous variables. Significant results were shown by a p value < 0.05.

The Drugs and Therapeutics Committee of SLaM confirmed this as a service evaluation so ethics approval was not required. Data were collected by AB. All data were anonymized by PDH before analysis.

Results

The characteristics of study subjects are shown in Table 1. There were 189 patients discharged

Table 1. Characteristics of the study sample.

Demographics *n* = 187	
Characteristics	*N* (%)
Gender	
Male	122 (65.2)
Female	65 (34.8)
Ethnicity	
Asian	8 (4.3)
Black	23 (12.3)
White	156 (83.4)
Age, years	
Mean	46.6
Range	13–90
Standard deviation	17.4
Smoking status	
Smoker	99 (52.9)
Nonsmoker	49 (26.2)
Don't know	39 (20.9)
Reason for lamotrigine	
Bipolar affective disorder/TRD	52 (27.8)
Clozapine augmentation	40 (21.4)
Other	87 (46.5)
TRS AP augmentation	8 (4.3)
Diagnosis	
Bipolar affective disorder	46 (24.6)
Schizoaffective disorder	15 (8.0)
Schizophrenia/TRS	31 (16.6)
Other	95 (50.8)
Taking an enzyme inducer	
Yes	10 (5.3)
No	177 (94.7)
Taking an enzyme inhibitor	
Yes	27 (14.4)
No	160 (85.6)

TRD, treatment-resistant depression; TRS AP, treatment-resistant schizophrenia treated with an antipsychotic other than clozapine.

Table 2. List of 'other' diagnoses for patients who were discharged on lamotrigine.

Other diagnoses *n* = 95
Anorexia nervosa
Asperger's syndrome
Cyclothymia
Dementia in Alzheimer's disease with late onset
Emotionally unstable personality disorder
Generalised anxiety disorder, agoraphobia, obsessive compulsive disorder
Mental retardation, pervasive development disorder
Mixed obsessional thoughts and acts
Mental and behavioural disorders due to use of cannabinoids/opioids/alcohol
Organic personality behavioural disorder
Post-traumatic stress disorder
Persistent delusional disorder
Recurrent depressive disorder with or without psychotic symptoms
Somatisation disorder

from SLaM on lamotrigine in the 5-year period from October 2007 and September 2012. Two patients were not included in the study because it was unclear whether lamotrigine was ever actually prescribed. Table 2 lists the 'other' diagnoses that were recorded.

The mean lamotrigine daily dose was 226.1 mg (range, 12.5–800 mg). Clozapine augmentation was associated with the largest mean dose of lamotrigine as plotted in Figure 1. Overall, 117 patients had their plasma levels recorded and the mean plasma level was 5.9 mg/l (range 0.8–18.1 mg/l). Table 3 records the mean lamotrigine daily dose and mean plasma levels for the different patient characteristics.

No association was found between patient's age and dose of lamotrigine (Pearson correlation $r = -0.063$; $p = 0.395$; $n = 187$). Similarly, no association was discovered between age and plasma concentration of lamotrigine ($r = -0.087$; $p = 0.350$; $n = 117$). A weak association was determined between lamotrigine dose and lamotrigine concentration ($r = 0.318$; $p = 0.001$; $n = 117$; see Figure 2).

Discussion

Main findings

The mean daily dose of lamotrigine was found to be 226.1 mg (range 12.5–800 mg) and the mean daily plasma level 5.9 mg/l (range 0.8–18.1 mg/l). A weak association was shown between lamotrigine daily dose and lamotrigine plasma levels. Our main finding was that patients taking an enzyme-inducing drug with lamotrigine had significantly lower lamotrigine plasma levels than those not taking one, despite receiving numerically higher doses. Conversely patients taking an enzyme-inhibiting drug had significantly higher levels than those not taking such drugs despite numerically lower doses (doses did not differ to a statistically significant degree). The reasons for being

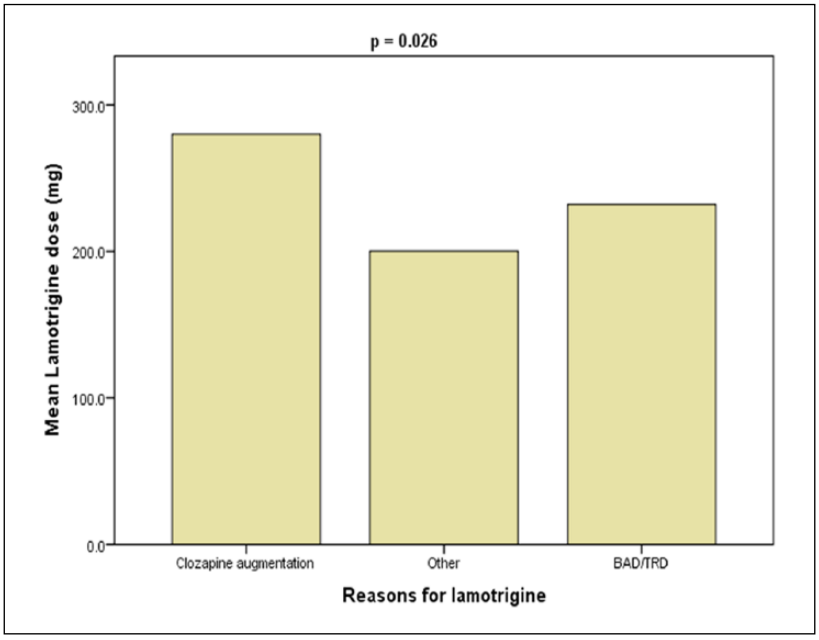

Figure 1. Mean daily dose of lamotrigine for the groups reason for taking lamotrigine.

prescribed lamotrigine were significantly associated with the mean lamotrigine dose, with clozapine augmentation being associated with the highest mean dose. Gender, ethnicity and smoking status were found to have no significant effect on lamotrigine's dose or plasma levels. This study also highlighted the range of use of lamotrigine in several psychiatric illnesses. In fact, its use in the large majority of cases was off-label; bipolar affective disorder accounted for 24.6%, schizoaffective disorder 8.0%, schizophrenia 16.6% and others 50.8%.

Lamotrigine's plasma concentrations

The Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie guidelines [Hiemke *et al.* 2011] acknowledges that there are no established plasma level target range for lamotrigine's mood-stabilizing effects. They do, however, recommend therapeutic drug monitoring and suggest a range of 3–14 mg/ml, the same as what is suggested for monitoring lamotrigine's anticonvulsant effects. For the bulk of our patients who had had their lamotrigine levels measured, their levels fell within this suggested range. However, 17 patients had lamotrigine plasma levels below the suggested therapeutic threshold of 3 mg/l. The implications for having plasma levels this low is unknown.

Our study suggested a weak association between lamotrigine dose and lamotrigine plasma level but clearly the impact of enzyme inducers and inhibitors is important here.

Lamotrigine's relevant clinical interactions potentially requiring dose adjustments

The interaction between lamotrigine and valproate is widely known. The dosing regimen for lamotrigine is changed substantially when these two drugs are prescribed together. Both drugs share glucuronidation *via* UGT as a major metabolite pathway and the interaction is thought to result from competitive inhibition of this enzyme group. The magnitude of the interaction was first quantified in a cross-over study of 18 volunteer subjects who received valproate (as divalproex) and three doses of lamotrigine 50, 100 and 150 mg/day [Anderson *et al.* 1996]. It was shown that when compared with previous studies where subjects received only lamotrigine, the co-administration of valproate increased lamotrigine's half-life from 26.4 to 69.6 h and the clearance values were decreased from 0.48 to 0.20 ml/min/kg, respectively. The addition of lamotrigine to valproate, however, also resulted in the increased clearance of valproate with a 25% decrease in its plasma concentration. The nature of this bidirectional interaction cannot be

Table 3. Mean daily dose and mean plasma level of lamotrigine for different patient characteristics.

Characteristic	Lamotrigine dose (mg)			Lamotrigine concentration (mg/l)		
	Mean (SD)	*t* test (df)	*p* value	Mean (SD)	*t* test (df)	*p* value
Gender						
Female	225.39 (156.47)	−0.078 (185)	0.938	5.93 (3.34)	0.151 (115)	0.093
Male	227.31 (164.69)			5.84 (2.62)		
Ethnicity						
Black and Asian	210.49 (167.43)	−0.596 (185)	0.552	6.83 (2.64)	1.28 (185)	0.552
White	229.15 (157.58)			5.76 (3.17)		
Enzyme inducer						
Yes	270.00 (249.39)	0.583 (9.386)*	0.574	3.40 (1.54)	−2.047 (115)	**0.043**
No	223.57 (152.97)			6.03 (3.13)		
Enzyme inhibitor						
Yes	200.93 (138.59)	−0.888 (185)	0.376	7.47 (3.99)	2.218 (27.337)*	**0.035**
No	230.30 (162.13)			5.52 (2.75)		
Smoking status						
Yes	240.51 (170.58)	1.692 (146)	0.093	5.88 (2.91)	0.282 (89)	0.779
No	192.86 (140.22)			5.70 (3.01)		
Diagnosis						
Scz/SA	250.27 (172.41)	0.746 (2,184)#	0.476	5.95 (2.59)	2.641 (2,114)#	0.076
BAD	212.72 (145.95)			6.86 (3.97)		
Other	226.06 (158.60)			5.27 (2.71)		
Reasons for lamotrigine						
BAD/TRD	231.92 (160.18)	3.708 (2,184)#	**0.026**	6.57 (3.78)	1.381 (2,114)	0.256
Clozapine augmentation	280.00 (182.68)			5.75 (2.46)		
Other	200.13 (142.41)			5.47 (2.87)		

Significant results are in bold ($p < 0.05$).
*Welch's *t* test; #Analysis of variance (ANOVA) *F* test.
BAD, bipolar affective disorder; df, degrees of freedom; SA, schizoaffective disorder; Scz, schizophrenia; TRD, treatment-resistant depression.

explained by competitive inhibition alone. It was later studies by Rowland and coworkers that showed that glucuronidation of lamotrigine was metabolized by both UGT1A4 and UGT2B7 [Rowland *et al.* 2006]. Valproate is a known substrate of UGT2B7 but was shown not to affect the function of UGT1A4. The authors concluded that valproate decreased lamotrigine's clearance *via* inhibition of UGT2B7 and lamotrigine increased valproate's clearance possibly by induction of UGT1A4.

In practice, the coprescribing of valproate should provoke a halving of the lamotrigine dose. Our study found that there was no significant difference between the doses of lamotrigine in patients taking an enzyme inhibitor and those not taking one. The enzyme-inhibiting group's mean lamotrigine dose was 200.93 mg daily which indicates that many patients were taking a higher dose than 200 mg daily. The Summary of Product Characteristics (SPC) for lamotrigine recommends a maximum dose of 200 mg daily of lamotrigine when taken with valproate [GlaxoSmithKline UK, 2016]. Valproate was the main inhibitor taken by patients in our study (two patients were taking an enzyme-inhibiting drug other than valproate). Our findings indicate that current guideline recommendations are not being followed. In one case a patient given valproate was also prescribed 400 mg daily of lamotrigine; this patient's lamotrigine level was 15 mg/l.

When a known inducer of lamotrigine metabolism, such as carbamazepine, phenytoin or hormonal contraceptives is taken with lamotrigine the lamotrigine dose should be doubled [GlaxoSmithKline UK, 2016]. In our survey no significant difference was found between the doses of lamotrigine in patients taking an

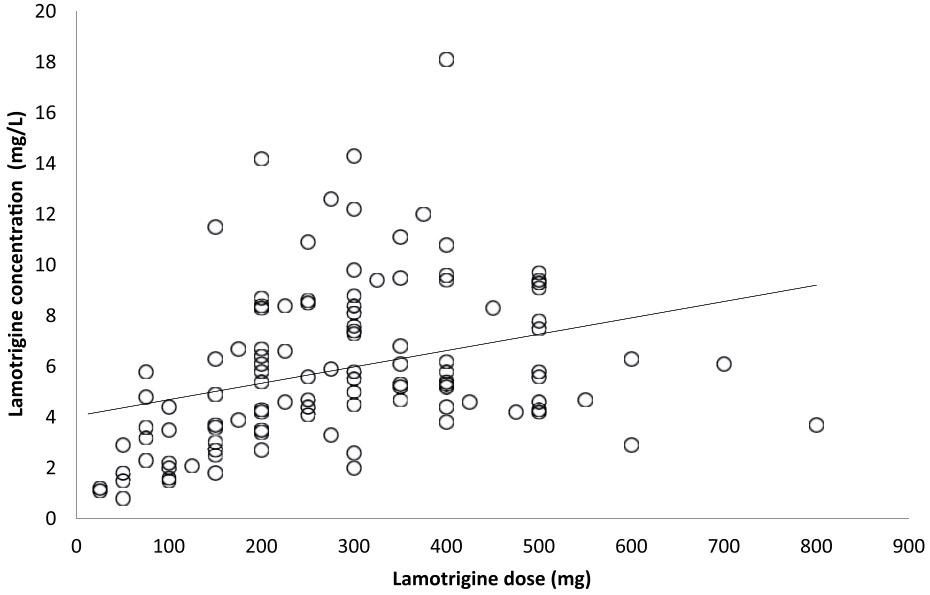

Figure 2. Scatterplot for lamotrigine dose and plasma concentration ($r = 0.318$; $p = 0.001$).

enzyme-inducing drug and those not taking any. The doses were numerically higher in the enzyme-inducing group but only for one patient was the dose doubled. Not doubling the dose of lamotrigine in these circumstances can be predicted to afford subtherapeutic plasma levels.

We found significantly lower lamotrigine plasma levels in patients taking an enzyme-inducing drug than those not taking an enzyme inducer. Conversely, in patients taking an enzyme-inhibiting drug with lamotrigine we found significantly higher plasma levels of lamotrigine than those not taking an enzyme inhibitor. These findings indicate that therapeutic drug monitoring of lamotrigine would be helpful before and after an enzyme-inducing or an enzyme-inhibiting drug is added to an established dose of lamotrigine. The dose of lamotrigine could then be adjusted accordingly after the enzyme-modifying drug is established. This in fact is what is currently recommended in lamotrigine's SPC [GlaxoSmithKline UK, 2016].

Clozapine augmentation

In our study clozapine, augmentation was associated with the largest mean dose of lamotrigine. This was unexpected as guidelines recommend lower doses (50–200 mg) of lamotrigine for clozapine augmentation [Taylor *et al.* 2015]. Lamotrigine has been shown not to affect the plasma levels of clozapine significantly [Spina *et al.* 2006] and *vice versa* [Reimers *et al.* 2005].

Effect of age, ethnicity, sex and smoking status

Age, gender, ethnicity and smoking status were found not to have any significant effect on lamotrigine dose or plasma levels in our study.

Reimers and colleagues [Reimers *et al.* 2005] found male gender and being 70 or over to be associated with greater lamotrigine plasma concentrations. They state that this significant effect of age was not found in previous studies as low numbers of elderly subjects were included. In our study we had 17 patients aged 70 or over. In their study, they had 70 subjects aged 70 or over. With regards to gender even though a statistically significant effect was found the numerical value was low at 7%. The researchers postulate that this finding maybe coincidental or due to males tending to have a larger weight than females however acknowledging that evidence of weight effects and lamotrigine is lacking. They also suggest hormonal factors may explain this difference and call for more research on the effect of gender and body weight.

Reinsberger and colleagues [Reinsberger *et al.* 2008] found smoking to have a significant effect on lamotrigine's plasma levels and propose induction of UGT2B7 by tobacco as a possible

mechanism. Smokers had lower levels than non-smokers. The clinical relevance of this interaction was not elucidated.

Limitations

This study had a number of limitations. No data were collected about clinical efficacy and adverse effects. Smoking status was underreported and not all patients had lamotrigine plasma levels done. The extent to which patients were adherent to all their prescribed medication was unknown. The duration of lamotrigine treatment was not determined; it is known that low lamotrigine levels could be observed in the first few weeks of taking due to lamotrigine auto-induction. This could be confounded with the small doses needed at the start of treatment or co-administration with an enzyme-inducing drug.

Conclusion

Current dosing recommendations in the formal Product Licence indicate that lamotrigine doses should be halved in individuals taking enzyme inhibitors and doubled in those on enzyme inducers. In our survey these recommendations were not always followed with the consequence that patients receive too high or too low a dose of lamotrigine, respectively. Therapeutic drug monitoring of lamotrigine's plasma concentrations is recommended to assist in optimizing the dosing of lamotrigine particularly in patients taking co-administered enzyme-inducing or enzyme-inhibiting drugs. Prescribers used different doses of lamotrigine for different indications and lamotrigine was used almost entirely for off-label indications.

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Conflict of interest statement

DT has received payments for lectures and advisory boards from Eli Lilly, Lundbeck, Bristol Myers Squibb, Astra Zeneca, Sunovion and Otsuka. FG has received payments for lectures and advisory boards from Lundbeck, Roche, Sunovion, Bristol Myers Squibb and Otsuka and has a family member with professional links to Eli Lilly and GlaxoSmithKline. Other authors declare no potential conflicts of interest.

References

Anderson, G., Yau, M., Gidal, B., Harris, S., Levy, R., Lai, A. *et al.* (1996) Bidirectional interaction of valproate and lamotrigine in healthy subjects. *Clin Pharmacol Ther* 60: 145–156.

Cohen, A., Land, G., Breimer, D., Yuen, W., Winton, C. and Peck, A. (1987) Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. *Clin Pharmacol Ther* 42: 535–541.

GlaxoSmithKline UK. (2016) *Summary of Product Characteristics: Lamictal*. Available at: https://www.medicines.org.uk/emc/medicine/4228

Hiemke, C., Baumann, P., Bergemann, N., Conca, A., Dietmaier, O., Egberts, K. *et al.* (2011) AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* 44: 195–235.

Johannessen, S., Battino, D., Berry, D., Bialer, M., Kramer, G., Tomson, T. *et al.* (2003) Therapeutic drug monitoring of the newer antiepileptic drugs. *Ther Drug Monit* 25: 347–363.

Kilpatrick, E., Forrest, G. and Brodie, M. (1996) Concentration-effect and concentration-toxicity relations with lamotrigine: a prospective study. *Epilepsia* 37: 534–538.

Lardizabal, D., Morris, H., Hovinga, C. and Del Mar Carreno, M. (2003) Tolerability and pharmacokinetics of oral loading with lamotrigine in epilepsy monitoring units. *Epilepsia* 44:536–539.

Magdalou, J., Herber, R., Bidault, R. and Siest, G. (1992) In vitro N-glucuronidation of a novel antiepileptic drug, lamotrigine, by human liver microsomes. *J Pharmacol Exp Ther* 260: 1166–1173.

Morris, R., Black, A., Harris, A., Batty, A. and Sallustio, B. (1998) Lamotrigine and therapeutic drug monitoring: retrospective survey following the introduction of a routine service. *Br J Clin Pharmacol* 46: 547–551.

National Institute for Health and Care Excellence. (2016) *Bipolar disorder: assessment and management: Clinical Guidance 185* (February 2016 update). Available at: https://www.nice.org.uk/guidance/cg185

Rambeck, B. and Wolf, P. (1993) Lamotrigine clinical pharmacokinetics. *Clin Pharmacokinet* 25: 433–443.

Reimers, A., Skogvoll, E., Sund, J. and Spigset, O. (2005) Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. *J Clin Psychopharmacol* 25: 342–348.

Reinsberger, C., Dorn, T. and Kramer, G. (2008) Smoking reduces serum levels of lamotrigine. *Seizure* 17: 651–653.

Rowland, A., Elliot, D., Williams, J., Mackenzie, P., Dickinson, R. and Miners, J. (2006) In vitro characterization of lamotrigine N2-glucuronidation and the lamotrigine-valproic acid interaction. *Drug Metab Dispos* 34: 1055–1062.

Spina, E., D'Arrigo, C., Migliardi, G., Santoro, V., Muscatello, M., Mico, U. *et al.* (2006) Effect of adjunctive lamotrigine treatment on the plasma concentrations of clozapine, risperidone and olanzapine in patients with schizophrenia or bipolar disorder. *Ther Drug Monit* 28: 599–602.

Taylor, D., Paton, C. and Kapur, S. (2015) *Maudsley Prescribing Guidelines in Psychiatry*, 12th edn. Oxford: Wiley Blackwell.

Tiihonen, J., Hallikainen, T., Ryynanen, O., Repo-Tiihonen, E., Kotilainen, I., Eronen, M. *et al.* (2003) Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 54: 1241–1248.

Varma, S., Bishara, D., Besag, F. and Taylor, D. (2011) Clozapine-related EEG changes and seizures: dose and plasma-level relationships. *Ther Adv Psychopharmacol* 1: 47–66.