Therapeutic Drug Monitoring of Levetiracetam in Select Populations

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ABSTRACT - Purpose: Levetiracetam (LEV) is a broad spectrum antiepileptic drug (AED) that has a more favorable side effect profile compared to older AEDs. Therapeutic drug monitoring (TDM) of LEV is generally unnecessary given its linear and predictable dose-serum concentration relationship, lack of drug-drug interactions, and broad therapeutic window. However, there is growing evidence showing that alteration of LEV pharmacokinetics (PK) may occur in special populations calling for the need for TDM. The purpose of this review was to summarize current literature surrounding altered LEV PK in special patient populations and determine if there is a need for levetiracetam TDM. **Methods**: A literature search of MEDLINE (1946 – November 2017) database of available evidence pertaining to altered LEV PK in humans was conducted. **Results:** A total of 51 articles were found. There has not been a positive correlation shown between LEV levels and efficacy or toxicity. Variable LEV levels are reported in the literature with respect to adverse effects, seizures and efficacy occurring below, within and above the supposed reference ranges. Age is a major contributor to altered pharmacokinetics of LEV as shown in elderly patients and pediatric patients. Compared to adults, clearance of LEV has been shown to be decreased by almost half in patients over 65 and increased by 30-40% in pediatric patients. LEV pharmacokinetics varied further when data from its use in neonates was explored. LEV clearance declined in a linear fashion with declining estimates of creatinine clearance but was variable in patients with end-stage renal failure or those requiring renal replacement therapy. In patients who were critically ill, LEV clearance may be augmented and these patients may require higher doses of medications to maintain drug levels. In patients who are pregnant, LEV levels are likely to decline as pregnancy progresses due to changes in glomerular filtration rate and remain variable in the post-partum period. **Conclusion:** Routine TDM of levetiracetam is not recommended for all populations, however, it may be beneficial to maintain an individual therapeutic range in patients where the PK of LEV may be altered, such as in patients who are critically ill patients, pregnant, pediatrics or elderly.

INTRODUCTION

Levetiracetam (LEV) is a broad spectrum antiepileptic drug (AED) that is effective against partial and generalized seizures (1). Aside from the possible psychiatric and behavioral side effects experienced by some patients, LEV has a more favorable side effect profile compared to older AEDs such as phenytoin, carbamazepine, valproic acid or phenobarbital (1). Among numerous adverse effects, too many to list, these AEDs are known to cause alterations in mental status, ataxia, skin rashes, endocrine and metabolic disturbances and cardiovascular effects to varying degrees including bradycardia, hypotension, hypertension, and arrhythmias. Valproic acid is known to cause significant weight gain, and all have been associated with congenital abnormalities when used in pregnancy. LEV is available in oral and parenteral formulations and can be rapidly loaded. It displays linear elimination kinetics; therefore, dose changes produce relatively predictable changes in serum Concentrations (1). The pharmacokinetics (PK) of LEV are summarized in Table 1. LEV is renally eliminated and metabolized by non-hepatic hydrolysis and not by the Cytochrome P450 (CYP) enzyme family. In addition, it does not induce or inhibit CYP enzymes, resulting in minimal drug-drug interactions (1). Therefore, therapeutic drug monitoring (TDM) of LEV is generally unnecessary given its linear and predictable dose-serum concentration relationship, lack of drug-drug interactions, and broad therapeutic window. However, there is growing evidence showing that alteration of LEV pharmacokinetics may occur in special populations such as pediatric patients and the critically ill calling for the need for TDM.

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ABBREVIATIONS
AED Antiepileptic Drug
AE Adverse Effect
ARC Augmented Renal Clearance
AUC Area Under the Curve
CL Oral Clearance
Cmax Maximum Concentration
CrCl Creatinine Clearance
CRRT Continuous Renal Replacement Therapy
CVVH Continuous Venovenous Hemofiltration
CYP Cytochrome P450
ECMO Extracorporeal Membrane Oxygenation
GCS Glasgow Coma Scale
GFR Glomerular Filtration Rate
ICU Intensive Care Unit
IM Intramuscular
IV Intravenous
LEV Levetiracetam
NR Not Reported
NS Nonsignificant
PK Pharmacokinetic(s)
RRT Renal Replacement Therapy
SE Status Epilepticus
TBI Traumatic Brain Injury
TDM Therapeutic Drug Monitoring
Tmax Time to Maximum Concentration

The purpose of this review was to summarize current literature surrounding altered LEV PK and to determine if there is a need for levetiracetam TDM in certain populations.

METHODS

A literature search (Figure 1) of the database MEDLINE (1946 – November 2017) was completed using the following search terms: "Levetiracetam","Keppra", "New Antiepileptics", "New Anticonvulsants". These terms were combined with (AND) and with the following search terms: "Pharmacokinetics", "Pharmacokinetic", "Kinetics", "Clinical Pharmacokinetics", "Therapeutic Drug Monitoring", "Drug Monitoring", "Drug Toxicity", "Therapeutic Monitoring", "Therapeutic Level", "Therapeutic Efficacy", "Reference Range", "Therapeutic Range", "Optimal Range", "Desirable Range", "Effective Range", "Target Concentration". The search was limited to human studies that are published in the English language. Title and Abstract screening was performed to eliminate irrelevant articles and duplicates. If relevance was in doubt, the article was included in the full-text review. This screening was completed independently by the two authors. Only original primary research was included. Commentaries, editorials, conference abstracts, and reviews were excluded. The full-text review was then completed to determine relevant articles for inclusion in this review. Articles that did not collect laboratory data were excluded. In addition, a manual search for additional relevant studies was performed by analyzing the reference lists of the relevant reviews and the selected studies. In case of any discrepancies between the reviewers, further discussion was undertaken to reach a consensus. In this review, a "reference range" is defined as the range of concentrations below which the AED is most likely ineffective and above which the AED will most likely cause adverse drug reactions or toxicity. On the other hand, an "individual therapeutic range" is defined as the range of concentrations that are most effective and least toxic for an individual patient.

RESULTS

The MEDLINE database search resulted in 421 articles. After duplicate removal, a total of 391 articles were screened. After title and abstract screening, 201 articles were assessed for inclusion and underwent a full-text review. A total 51 studies (mainly observational) and case reports were included in this review. Based on that, the available evidence is considered low or very low using the GRADE working group criteria (2). Table 2 depicts the results of the studies included in this review.

DISCUSSION

Therapeutic Drug Monitoring

The rationale for therapeutic drug monitoring (TDM) in the management of epilepsy has been well described (3). Seizure control, or a reduction in the number of seizures, while minimizing drug adverse effects, are the goals of therapy. Seizure occurrence is unpredictable and some medication side effects can be subtle in their presentation or indistinguishable from other conditions. Therefore, it can be challenging to determine if the current AED dosage is effective and safe in the long term. TDM has been employed with phenytoin, valproic acid, phenobarbital and carbamazepine, among other AEDs, to inform dose adjustments of AEDs to

address lack of seizure control and prevent toxicity within a narrow reference range. The rationale for TDM depends on the pharmacological characteristics of the AED in question. Drug concentrations of phenytoin, phenobarbital, valproic acid and carbamazepine are historically known to be highly variable and are subject to the effects of age, altered protein-binding, organ dysfunction and clinically significant drug interactions (3). Phenytoin can be particularly challenging to use as it exhibits non-linear pharmacokinetics and a saturatable metabolism that contributes further to drug concentration variability between patients (3). Unlike these classic AEDs, LEV has demonstrated a wide therapeutic range, a limited side effect profile and predictable pharmacokinetics and TDM has not been incorporated into its routine use. Consistent with other AEDs, there have not been any randomized controlled trials performed with LEV to determine whether TDM improves efficacy and tolerability compared to usual care. Furthermore, a robust correlation between efficacy and plasma concentrations of LEV has not been shown in either adults or children (4-8). Nevertheless, variable reference ranges have been suggested with the most commonly cited one being 12-46 mg/L (9). In the study by Stepanova and Beran, plasma concentrations of LEV and a target trough reference range of 20-40 mg/L have been used alongside clinical assessment to titrate levetiracetam therapy in adult patients without a comparison to usual practice (10). LEV levels ranged from 2-100 mg/L, averaging 28 mg/L, with one patient experiencing seizures thought to be demonstrative of LEV toxicity at a level of 86 mg/L. Sixty nine percent of subjects achieved seizure freedom at one year, compared to previous studies in which seizure freedom has been achieved in 50-60% of subjects with LEV as an add-on or monotherapy. The authors of this study have concluded that levetiracetam TDM achieved improvement in LEV efficacy when used to guide clinical decision making. We speculate that this improvement in efficacy could manifest as a result of more timely LEV dose changes, consideration of additional AEDs or improvements in patient compliance.

Four prospective observational studies have included LEV concentrations as part of routine monitoring but a correlation has not been noted between concentrations and efficacy or toxicity (7, 11-13). In the study by Mink et al., seizure prophylaxis with valproic acid therapy has been compared to LEV in 35 patients with aneurysmal subarachnoid hemorrhage and drug levels were taken daily (12). If plasma levels had been below the specified reference range (5-30 mg/L for LEV), a second anticonvulsant was used in addition to or to replace LEV and dose adjustments were not performed. Five of 35 patients experienced seizures after anticonvulsants were initiated, all with plasma levels within the specified reference range, and seizure incidence was not significantly different between LEV and valproic acid arms (12). Targeting a specified reference range did not prevent patients from having seizures. This underlines the fact that AED reference ranges should be used as tools rather than ultimate targets. It must also be considered that patients with refractory or treatment resistant seizures may continue to experience seizures despite drug levels within reference ranges. It would be reasonable, however, to identify an individual reference range if a reduction in the frequency of seizures occurred within a particular range. In the study by Iwasaki et al. in 24 patients aged 0.9 – 16 years with focal seizures, a significant association between efficacy and high LEV peak levels (approximately > 23 mg/L) was demonstrated 2 weeks and 1 year after LEV initiation, but not at 2 years (11). The authors suggested a LEV plasma concentration range of 20-30 mg/L to be an "optimal" range for focal seizures control (11). To aid in determining a common safety level, 3 case reports of LEV overdose were found in this review (14-16). Sedation, coma and respiratory depression were experienced in a 38-year-old patient after ingestion of 30 g of LEV with reported levels of 400, 72 and 60 mg/L at 6,18 and 20.5 hours post ingestion, respectively. Symptoms were resolved rapidly within 24 hours with supportive care (14). A 41-year-old patient experienced blurred vision, ataxia and transient leucopenia and thrombocytopenia after ingestion of 63 g of LEV. LEV levels 10 hours post ingestion were 220 mg/L and the patient's physical assessment was completely normal within 24 hours of observation (15). Lastly, cardiotoxicity evidenced by bradycardia and hypotension occurred after a 41year old ingested 60-80 g of LEV. LEV levels 8 hours post ingestion were 463 mg/L and heart rate and blood pressure returned to normal at the time of discharge 48 hours after ingestion (16). The variability in effects of toxicity as well as the lack of consistent correlation between LEV levels and efficacy and adverse effects support an individual therapeutic range for patients on LEV therapy.

Importantly, even at the supra therapeutic LEV levels seen in the above case reports, linear pharmacokinetics were maintained.

In addition to safety and efficacy, TDM has been used to address compliance concerns. TDM has been used to monitor for compliance to therapy in a prospective safety study of LEV for prevention of post-traumatic epilepsy in traumatic brain injury (TBI) patients (17). Severity of adverse effects did not correlate with trough levels in this study except for depression in patients greater than 65 years old. Drug levels per age group were not reported and average trough levels throughout the study ranged from 19.6-26.7 mg/L. Noncompliance was concluded when trough LEV levels fell below 7 mg/L and alterations in absorption and/or increases in renal clearance had been ruled out. Sixty percent of children and 85 % of adults were determined to be compliant (17). Compliance to therapy was also assessed using TDM in a retrospective study by Sheinberg et al (8). In this study, the use of TDM had revealed incidences of parents deliberately not providing the prescribed doses for children using LEV. Of note, in this study efficacy had not correlated with plasma concentrations however violent behavior had been found to significantly correlate with low LEV levels (8).

As demonstrated by the above evidence, correlations between efficacy and adverse effects are not consistent and are from observational studies with small sample sizes. Although TDM may be useful to guide decision making and assess compliance, the focus of TDM is therefore to guide dosage adjustments for populations where the pharmacokinetics of LEV are likely to be altered. TDM will be helpful in maintaining LEV concentration within an individual reference range (therapeutic range). Specific populations that have been identified to experience altered pharmacokinetic of LEV include older adults (18, 19), pediatric patients (6, 11, 13, 20-31), pregnant patients (32-36), patients with renal impairment (19, 37-42) and critically ill patients (17, 43-46). The evidence for use of LEV in these populations will be reviewed here as well as drug-drug (47-51) and formulation interactions (12, 52-54) with LEV that may have implications for TDM.

Drug-Drug and Drug-Formulation Interactions

The effects of other AEDs on LEV pharmacokinetics have been explored as LEV is often used in addition to other therapies to maintain seizure freedom. LEV is not hepatically metabolized, however, clearance of LEV has been shown to increase by 25-30% when administered with enzyme-inducing AEDs (EIAEDs) such as phenytoin, carbamazepine or phenobarbital (49, 51, 55). Although statistically significant, this increase is not likely to be clinically significant, and dose adjustments for LEV are not recommended when used with EIAEDs. Non-enzyme inducing AEDs and enzyme inhibiting AEDs such as valproic acid did not have an appreciable effect on LEV concentrations (47-49, 55). Of note, oral contraceptive use has not been shown to affect LEV concentrations (50). In the study by Mink et al., switching from parenteral to an enteral liquid formulation of LEV in critically ill patients at high risk for seizures has been associated with similar reductions of LEV concentration that have been associated with co-administration of EIAEDs (12). A significant 30% decline in LEV drug levels occurred after the change in formulation, proposed to be due to digestive and absorption issues in ICU patients; however, sample size was small (12). On the other hand, other studies have not found a difference between plasma levels when oral LEV tablets and liquid have been compared (52, 53) or when the intravenous or intramuscular administration of LEV have been compared (54). In keeping with the above evidence, we do not recommend routine LEV level monitoring when LEV is administered with other AEDs, oral contraceptives or when a formulation change is made. The magnitude of change in LEV levels in these situations is unlikely to be of clinical significance.

Elderly patients

Population studies of LEV have consistently shown that age has the most pronounced effect on the clearance of LEV. Clearance has been found to be significantly reduced by 40% in those 65-86 years of age when compared to adults ($P<0.01$) (56). A similar trend has been described in a prospective study of almost 300 subjects in which patients over the age of 65 had required lower LEV doses compared to adults (55). Based on this population data, we surmise that older patients, or patients over the age of 65 may benefit from TDM when using LEV. The physiologic changes of aging, as well as patient-specific factors, predispose this population to experiencing altered LEV PK. These patients are more likely to have reduced kidney function, have multiple comorbidities and therefore are likely to be

on multiple medications that increase risk for drug interactions. However, as noted previously, drug interactions with LEV have not been reported to be of clinical significance. Nevertheless, patients in this age group were excluded from clinical trials and PK data for LEV use in this population is scarce. It is therefore beneficial to determine if and in whom TDM should be employed when using LEV in elderly patients as they are a heterogeneous population. A retrospective study has looked at LEV PK in elderly patients with epilepsy compared to non-elderly patients (19). Clearance of LEV had been found to be reduced by 40-60% among elderly patients. This decrease was in parallel with the decrease in creatinine clearance with age, however creatinine clearance and the timing of dose and blood sampling were not known for all subjects. Adverse effects including drowsiness, psychiatric side effects (irritability, depression, anxiety), cognitive adverse effects, imbalance and dizziness had been experienced more commonly by those in the elderly group, although this difference was not statistically significant. Intolerability requiring discontinuation or dose decrease have been more common in the elderly group but only significant in those newly started on the medication. The retrospective design and incomplete study data limit definitive conclusions being made from this data alone. In addition, the PK of LEV in elderly patients has been prospectively explored and similar reductions in clearance have been seen (18). Those aged 66-80 had been classified as elderly and those aged 81-96 as very elderly. When compared to non-elderly epilepsy patients, aged 30-65, oral clearance of LEV is reduced by 33% in elderly subjects and by 52% in the very elderly (18). LEV concentrations remained linearly correlated to LEV dosage in each age group and were similar among those who had experienced adverse effects and those who had not. Based on this data, the authors have recommended a 30-50% levetiracetam dose reduction in elderly patients (18). The lack of correlation between drug level and adverse effects suggests TDM may be of little benefit to predict adverse events in elderly patients but it could also be attributed the lack of power to demonstrate a difference among study groups. Despite this, routine monitoring in all elderly patients newly started on LEV cannot be recommended as the above evidence supports a relatively predictable LEV pharmacokinetic trend in relation to creatinine clearance. Even with this predictability, estimation of kidney function in the elderly by calculating creatinine clearance or GFR can be fraught with uncertainty. Elderly patients may be frail with reduced muscle mass which may jeopardize the accuracy of such calculations and populations included in the modification of diet in renal disease (MDRD) studies were aged 18-70, leaving out a significant and growing portion of this patient population(57). Due to these potential inaccuracies in kidney function estimation, it cannot be assumed that LEV PK will be predictable in each elderly patient. Therefore, TDM can be used to guide dosage adjustments for efficacy and toxicity in elderly and very elderly patients to determine and maintain their individual therapeutic range.

Pediatrics

On the other end of the age spectrum, pediatric patients have emerged as another group that may benefit from TDM when using LEV. Clearance of LEV was significantly increased up to 60% in children younger than 10 years when compared to adults ($P<0.01$) (56). In a population PK study, higher doses per body weight, 20-60 mg/kg/day, in children have been compared to standard dosing of LEV in adults at 500mg twice daily up to 3000mg per day. Maximum concentrations and area under the curve (AUC) estimations in children had been similar to those seen in adults, consistent with an increase in drug clearance in children (29). Similarly, this trend has been described in a prospective study of almost 300 subjects in which children under the age of 12 had required larger doses per body weight compared to adults (55). This has been suggested to be due to glomerular filtration rate (GFR) changes that occur in children and their effect on the renal clearance of LEV. In children, GFR rapidly increases in the first 2 weeks of life and is generally thought to reach the rate consistent with adults by 6-12 months of age. It then exceeds adult rates during preschool years and finally reaches adult values at prepubertal age (around 6 years) (58). To assess the pharmacokinetics of LEV in children, an open-label study has been completed with 24 children aged 6 to 12 years old on a stable AED regimen (21). These children had been given a single 20mg/kg dose of LEV and drug concentrations were monitored over a 24-hour period. Children 6-12 years old had experienced peak concentrations and AUC values that are comparable to healthy adults when normalized for weight. Oral clearance, however, was 30-40% higher in children at 1.43 ml/min/kg compared to 0.96 ml/min/kg that has been previously

reported in adults (1) and a mean elimination half-life of LEV was 6.1 (range 4-8.2) hours versus 7.2 (range 6-8) hours reported previously in adults (1). An elimination half-life of approximately 5 hours has been the most consistently reported value in children (20, 27). Similarly, the trend of a 30-40% higher clearance in children has been supported by Toublanc et al. The authors have reported that the PK of LEV in children are similar to adults except that 30-40% higher doses are required in children to achieve similar drug exposure due to higher clearance (29). In general, children younger than 10 years of age have had the highest clearance, followed by those older than 11 and adults followed by elderly patients with the lowest level of clearance (6, 28). On the other hand, a pharmacokinetic study conducted on 361 Chinese children aged 6 months to 14 years with epilepsy have found LEV clearance to be 50% lower than that of Caucasian children with a reported average elimination half-life of 8.13 hours (30) similar to the half-life associated with adults and clearance values of 0.96 ml/min/kg(1). However, this could have been a result of the wide age range of the participants, including those past puberty, affecting the average clearance calculation. When younger and more narrow age ranges were studied by Glauser et al, LEV clearance was again found to be higher than that seen in adults(20). In this study, 12 children less than 4 years old with epilepsy had received a single dose of LEV and clearance was determined to be 1.57 and 1.23 ml/min/kg in those older than 6 months and those younger than 6 months of age, respectively(20). Although based on a small number of subjects, this study provides rationale to perform TDM for LEV in children as they age to maintain their individual therapeutic range.

LEV pharmacokinetics in neonates appears to be highly variable as well. In 8 neonate's who had been breastfed by mother's taking LEV, despite a milk to maternal serum ratio of 1, LEV had been barely detectable with levels <1.7 mg/L 3-5 days after delivery(25). The authors have suggested this could have been accounted for by the high level of LEV clearance in these infants. In contrast, LEV clearance has been reported to be much lower than adults and children in a case report of bottle-fed infant twins that had been exposed to LEV through cord blood alone. LEV clearance and half-life were reported to be 0.4-0.45 ml/min/kg and 16-18 hours, respectively (26). Similar elimination half-lives have been reported in 2 other neonates as well (31). Furthermore, two prospective studies have been completed in neonates that provide further clarity to LEV PK in this population. In the study by Merhar et al., the PK parameters of LEV have been determined in 18 neonates with ages ranging from 0 to 30 days receiving LEV in the neonatal intensive care unit. LEV clearance and elimination half-life have been reported to be 1.21 (0.47-2.89) ml/min/kg and 8.9 hours, respectively (23). Similarly, this trend has been documented in a second prospective study by Sharpe et al. in which the PK of LEV in 18 term neonates have been described comparing the PK on day 1 of life to day 7(24). On day 1, the average LEV clearance was 0.71 ml/min/kg and then increased to 1.31 ml/min/kg by day 7. The elimination half-life decreased from 18.5 hours to 9.1 hours over this same time period (24). Notably, in this study the plasma and urinary metabolite to LEV ratio had been determined at both time points as well and had remained stable throughout the 7 days, suggesting that as the kidneys mature the process of hydrolysis of LEV matures as well. As described above, significant variability of LEV clearance and serum concentration occurs as children grow and develop and can occur within an age group as is the case with neonates. This creates potential for variability in efficacy and toxicity if doses of LEV are not adjusted accordingly as children age.

The utility of LEV TDM has been investigated by Iwasaki et al. The authors have found that at two weeks following LEV initiation, higher LEV levels were associated with greater efficacy and a peak target range of 20-30 mg/L was defined as "optimal" as all effective cases were within it. However, such correlation was not seen at 2 years. The authors attributed that to dose escalation in patients with ongoing seizures (11). Similarly, a prospective study of intravenous LEV in 30 children between the ages of 6 months and 15 years did not find a clear correlation between LEV levels and efficacy or tolerability. As would be expected with such a large age range, LEV concentrations varied widely (13). The data described above included pediatric patients with healthy kidney function and the variations in kinetics are likely to be greater in pediatric patients with kidney dysfunction. The above data does not point to a specific reference range to be targeted; however, as with other AEDs, an individual therapeutic range can be determined for pediatric patients and doses adjusted accordingly as LEV clearance changes with age and changing GFR.

Renal and Hepatic Impairment

LEV is primarily cleared by the kidneys with 66 % of the drug removed by renal excretion. A dose reduction of 50% is recommended in patients with creatinine clearance less than 60 ml/min (1). As LEV is minimally protein bound and does not undergo hepatic metabolism, it would be expected that the effects of renal or hepatic impairment on the pharmacokinetics of LEV be limited to the extent that the glomerular filtration rate or estimates of creatinine clearance are reduced. The pharmacokinetics of LEV in renal impairment have been examined in patients with varying degrees of renal impairment (59). The single and multiple dose studies have looked at 11 patients with mild to severe renal impairment and LEV clearance was found to be directly proportional to renal clearance. LEV elimination half-life was 10.4 and 24.1 hours in patients with mild and severe renal impairment, respectively. Definitions of "mild" and "severe" impairment were not available, however, creatinine clearance ranged from 5.6 to 84 ml/min (59). In congruence with the LEV clearance being proportionally affected by changes in creatinine clearance, Hirsch et al. have found that in both younger and older adults, creatinine clearance and LEV clearance were positively correlated (19). Additionally, the authors concluded that the decrease in LEV clearance in older adults paralleled that of the decline in creatinine clearance and age-related reductions in kidney function are solely accountable for reductions in LEV clearance (19). A proportional and linear relationship between LEV clearance and creatinine clearance was also seen in the study by Yamamoto et al. (37). Japanese adults with renal impairment had been administered LEV dose adjusted in accordance with estimated creatinine clearance and recommendations in the product monograph (1, 37). Clearance of LEV decreased linearly with decreasing creatinine clearance and was reduced by approximately 50% in patients with severe renal impairment (CrCl <30ml/min). The elimination half-life increased to approximately 20 hours in these patients with severe renal impairment, compared to 6 to 8 hours in those with normal renal function. The elimination half-life increased to 40 hours in those patients with end-stage renal disease receiving hemodialysis, however, the max concentration and time to max concentration when dosed according to the monograph recommendations were similar to that seen in patients with normal renal function, suggesting renal impairment did not affect absorption of LEV. As LEV levels increase linearly with decreasing creatinine clearance, TDM in mild to moderate renal impairment is not likely to be of benefit. TDM, however, would be a benefit in patients with severe renal impairment.

Another factor contributing to LEV PK variability in patients with renal disease is the extracorporeal removal of levetiracetam in patients undergoing dialysis. LEV's low molecular weight and insignificant protein binding allow it to readily diffuse through dialysis filters and renal replacement devices (60). Thus, hemodialysis and continuous renal replacement therapies (CRRT) are expected to significantly contribute to LEV clearance. To illustrate, a 4-h hemodialysis run results in 70% reduction in LEV concentration (37). Three further case reports have described the use of LEV in patients undergoing CRRT (39-41). In all the three cases, LEV dose of 1000 mg every 12 hours resulted in serum concentrations ranging from 13.9 to 19 mg/L. LEV PK parameters were similar to those in patients with normal renal function with an estimated half-life of 8-10 h. The authors suggested high LEV doses in patients undergoing CRRT. However, the extent of extracorporeal LEV removal by renal replacement therapies not only depends on the drug characteristics but also on the type and settings of the renal replacement therapy and patients' residual renal function making proper dosing predictions a challenge. TDM might be useful in these situations. It is important to note that peritoneal dialysis is not expected to provide significant drug clearance and drug dosing is generally estimated for creatinine clearance or GFR of less than 15 ml/min, in keeping with end-stage renal disease (38, 61).

Since levetiracetam does not undergo hepatic metabolism, one can surmise that liver dysfunction does not have an appreciable effect on LEV PK. In a PK study of single dose 1000mg levetiracetam in patients with cirrhosis, LEV PK in patients with Child-Pugh class A and B were not significantly different from healthy subjects (42). In patients with more severe liver dysfunction (Child-Pugh C) the elimination half-life of LEV was increased to 18.4 hours. The ratio of metabolite to active drug did not differ between levels of liver dysfunction, and this decrease in clearance of LEV was likely due to reduced renal clearance in these subjects. Renal function may be overestimated in severe liver disease due to reduced muscle mass, low protein diet, decreased creatine production and fluid overload (62-64). In such patients where renal function may

be complicated to quantify adequately, TDM may be employed with LEV use to guide therapy and avoid toxicity.

Critically Ill

Critically ill patients are those who require admission to the intensive care unit due to life-threatening medical conditions such as respiratory failure, septic shock and severe traumatic brain injury. In those patients, the phenomenon of augmented renal clearance (ARC) has been well described (65) and may present a challenge for the use of LEV in these patients as it is cleared primarily by the renal route. ARC, otherwise known as glomerular hyperfiltration or enhanced renal clearance, indicates an increase in kidney function that results in an augmentation of drug clearance and the possibility of treatment failure. If ARC is present in a patient requiring LEV therapy, this could result in subtherapeutic LEV levels and subsequent seizures. Creatinine clearance estimations defining ARC have varied, but generally patients who have a creatinine clearance of >120-160 ml/min are deemed to be experiencing ARC. ARC may be both due to changes in the body as a result of being critically ill or the therapies commonly received by ICU patients, such as IV fluids, vasopressors, and inotropes. The higher amount of monitoring in critically ill ICU patients may also account for higher identification of ARC in this patient population. Nevertheless, for patients who are critically ill with traumatic brain injuries (TBI) requiring seizure prophylaxis, the PK data for LEV use is conflicting. In a controlled, open-label trial of children and adults with TBIs and intracranial hemorrhage, drug exposure, as demonstrated by AUC, have been found to be similar to those seen in healthy patients (44). Patients in this study received a dose of 55 mg/kg/day and a similar trend was observed as in other studies with a trend towards higher AUC in those over 65 years old and a lower trend in AUC among children (44). In a prospective trial of 12 patients in status epilepticus (SE), LEV had been used as add-on therapy at a single intravenous dose of 2500 mg (45). PK data were only available for 10 patients, but were similar to those seen in healthy subjects with an average maximum concentration of 85 mg/L and an average elimination half-life of 9.7 hours, ranging from 5.8 to 13.9 hours. Conversely, a case of augmented renal clearance causing lower than expected LEV concentrations has been described in a patient with a traumatic subarachnoid hemorrhage (46). This patient had required a 4000mg intravenous load and an eventual maintenance dose of 1500mg every eight hours. In addition, a prospective study of 12 critically ill patients with neurologic injuries requiring seizure prophylaxis have reported a LEV half-life of approximately 5 hours and doses of 1000-1500 mg every eight hours were required to maintain trough LEV levels above 6 mg/L (43). Although the limited number of subjects impacts applicability, this data suggests that the PK of LEV in the critically ill may be altered and unpredictable. To ensure LEV levels are within the reference range most associated with effectiveness, TDM is recommended for patients who are critically ill.

Pregnancy

Pregnancy is known to affect the pharmacokinetics of numerous AEDs and LEV has been shown to be no exception. Glomerular filtration rate is known to increase in pregnancy along with other physiologic changes, including increased volume of distribution and enhancement of metabolic processes. The majority of LEV clearance is renal; therefore, LEV levels are likely to decrease below pre-pregnancy levels and this may compromise efficacy. The use of TDM of LEV in pregnancy has been recommended prior to conception, and with each trimester to determine the need for dose adjustments to prevent potentially harmful breakthrough seizures (66). As previously described, prospective trials have confirmed the decline of LEV levels in pregnancy. LEV levels of 19 pregnant women were investigated during their pregnancy (34). The extent of the decline in LEV concentrations in the third trimester varied widely, but on average, patients experienced a 50% decline in drug levels and 7 out of 19 women experienced an increased frequency of seizures; in 5 patients, this increase occurred in the third trimester. A clear correlation between lowered drug levels and breakthrough seizures was not determined. A similar trend was seen in 14 pregnant women using LEV where the decline in LEV concentrations was approximately 60% with clearance increasing significantly in the third trimester (35). Complete data sets were only available for 7 patients and a similar decline in LEV concentrations were seen in both the 2 patients that experienced breakthrough seizures and the 5 that remained seizure free. In addition to these previously reviewed trials, a small prospective trial of 5 pregnant patients describes the changes in LEV concentrations during pregnancy and in the post-partum period (36). Reductions in

LEV levels between the first and third trimester varied from 17.6% to 47.8% and post-partum levels tended to be higher than late-term and pre-pregnancy baseline levels, with one case seeing a 30.4% rise in drug levels at 2 months post-partum. Seizure frequency did not change for 4 out of 5 patients whose doses were unchanged. Additionally, 2 cases of breakthrough seizures possibly associated with increased LEV clearance and sub-therapeutic levels have been published (32, 33). Dose increases were required in both cases with final maintenance doses of 5000 mg and 3375mg per day achieved, respectively. Both patients remained seizure free for the remainder of the pregnancy, however the patient requiring 5000mg per day experienced a seizure at 2 weeks post-partum with a corresponding trough drug level of 69.8 mg/L, nearly double the trough concentrations maintained during the pregnancy (32). This newer data further supports the recommendation to perform TDM when using levetiracetam during pregnancy. Furthermore, it would be prudent to continue monitoring in the post-partum period and remain cognizant of any dose increases that may have been required during pregnancy to avoid potential toxicity during this time.

Other Pharmacokinetic Considerations

The altered pharmacokinetics of LEV identified in this review have been largely attributed to changes in drug clearance and its inverse relationship with drug elimination half-life. Other considerations such as gender, acid-base alterations or changes in body composition may have meaningful impact on LEV PK. Volume of distribution of a drug is another important factor that could significantly alter the drug's elimination half-life as well as drug plasma concentrations (67). Neonates, pediatrics, pregnant patients and those that are critically ill have been all previously identified as populations in which volume of distribution of drugs may be increased. Compared to adults, neonates and pediatric patients have a higher percentage of their body weight in the form of water (68). Pregnant patients experience significant plasma and red blood cell volume expansion throughout pregnancy and a subsequent decline in the postpartum period (69, 70). Patients who are critically ill may experience fluid shifts, or "third spacing", in septic states due to increased capillary permeability and decreased oncotic pressure. This is further potentiated by the use of crystalloids to maintain intravascular space (71). As a highly hydrophilic drug, the changes in LEV plasma concentrations and elimination seen in the reviewed evidence may be a result of changing volume of distributions as well. On average, LEV in adult patients has a volume of distribution of 0.5-0.7 L/kg (1). Volume of distribution was infrequently reported in the evidence reviewed, however in 2 studies in pediatric patients, LEV volume of distribution was reported to be 0.63±0.08 L/kg in infants and children under the age of 4 (20) and 0.72±0.12 L/kg in children 6 to 12 years of age (21) which may account in part to differences seen in LEV plasma concentrations compared to adults. Additionally, to our knowledge, there were no reports of clinically significant acid-base alterations that could affect LEV clearance. LEV is eliminated by the kidneys via glomerular filtration with consequent active tubular reabsorption (1, 73, 74). In addition, the PKa of levetiracetam cannot be accurately estimated due to the instability of the protonated form (1). However, it is reported to be unionized over the PH range of 0-14 (75). Therefore, we speculate the LEV is less likely to be affected by urinary acid base alterations. Notably, although not extensively reported in the data reviewed, no gender differences in LEV concentrations or PK were observed (21, 49, 55).

Limitations

The evidence identified in this literature review, although compelling, are subject to inherent bias due to the fact that the majority are from observational studies without randomization or blinding and are subject to confounding variables (72). Further, the majority of the studies are of small size and may lack the power to demonstrate meaningful differences or present differences that are merely the result of chance (72). As such, the recommendations in this review should not be applied empirically, but rather in tandem with clinical judgement individualized to patients' specific medical needs.

CONCLUSION

At present, timely access to LEV plasma concentration monitoring is limited at some centers. This is understandable considering that monitoring of LEV levels is not routine practice. This review outlines select populations that may benefit from monitoring of LEV levels. The evidence identified in this review, however, is limited to observational and PK studies of small sizes and case reports, making

definitive conclusions challenging. Despite this fact, the following trends were identified and may inform the use of TDM of LEV: In elderly and pediatric patients, kidney function will change as they age and monitoring of LEV levels to maintain an individual therapeutic range as these changes occur is recommended. As elderly patients are a heterogeneous group, assessment of renal function on an individual basis will guide for whom to initiate LEV level monitoring. In patients with end-stage renal disease and those who are critically ill, LEV pharmacokinetics are unpredictable and monitoring in all patients requiring LEV in these populations is recommended. Lastly, LEV level monitoring has previously been recommended in pregnant patients and we recommend extending this monitoring to include the post-partum period as LEV pharmacokinetics have shown to be variable during this time as well.

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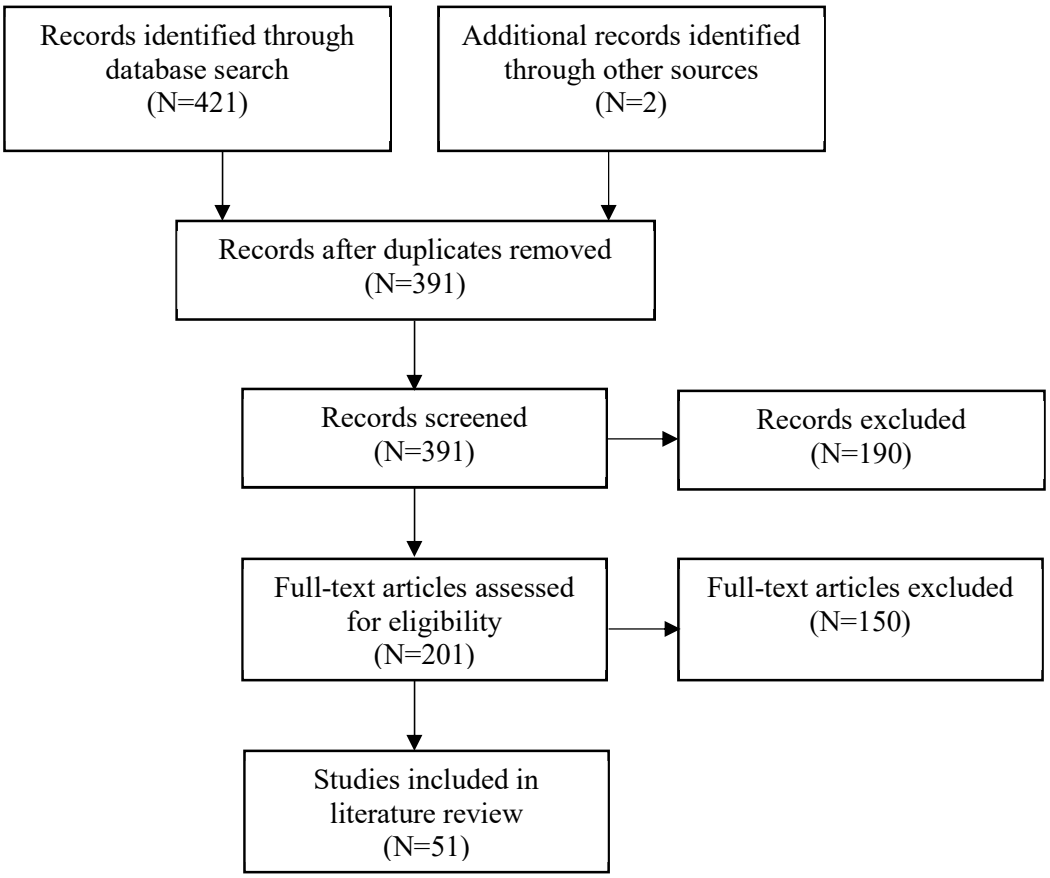

FIGURE 1. Literature review flow diagram.

Table 1. Summary of levetiracetam pharmacokinetics (1)

Adult dosage range	• Dose: 1000-3000 mg/day divided Twice Daily
Molecular weight	• 170.21 g/mol
Absorption	• Absorption is rapid and almost complete; oral bioavailability 100%
	• Food decreases the rate but not the extent of absorption; T_{max} 1.3 h (2.8 h with food)
Distribution	• Volume of distribution (V_d) 0.5-0.7 L/kg
	• Protein binding: 10%
Metabolism	• Percent metabolism: 24 % to inactive metabolites
	• Mode of metabolism: enzymatic hydrolysis (not liver cytochrome P450 mediated)
Excretion	• Percent renal excretion: 66% as unchanged drug
	• Half-life ($T_{1/2}$): 6-8 hours, increased in renal impairment
	• Total Body Clearance (CL/F) 0.96 ml/min/kg

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
Therapeutic Drug Monitoring								
Stepanova and Beran, 2014 (10)	Prospective observational	Adults patients with epilepsy (Focal 52%; Generalized 40%; unspecified 8%)	52	19-69 (42±14)	40	250-6000 mg/d	Aims: To assess the efficacy of LEV plasma concentration range of 20-40 mg/L and potential drug interactions with concomitant AEDs in people with epilepsy. Main results: LEV levels ranged from 2 -100 mg/L. Sixty nine percent of subjects achieved seizure freedom at one year. Authors concluded that TDM of LEV improved efficacy when used to support clinical decision-making.	20-40 mg/L
Lancelin et al, 2007 (4)	Retrospective observational	Patients with epilepsy (Focal 96%; Generalized 3%; unspecified 1%)	69	13-60 (33±13)	57	500-3000 mg/d	Aims: To develop an HPLC method for LEV plasma level monitoring and determine if a correlation exists between LEV plasma levels and therapeutic response or adverse effects in patients with refractory partial seizures. Main Results: LEV trough levels ranged from 1.1-33.5 mg/L. There were no significant differences in LEV plasma concentrations between responders (≥50% reduction seizure frequency) and non-responders or between patients who did or did not experience adverse effects. Seventy three percent of responders and 29% of non-responders had plasma concentrations > 11 mg/L	11 mg/L (determined)
Giroux et al, 2009 (5)	Retrospective and prospective observational	Pediatrics with refractory epilepsy (Generalized 41%; Focal 59%)	37	2-18 (11.45±0.8)	54	10-50 mg/kg/d	Aims: To assess the therapeutic efficacy and safety of LEV in children with refractory epilepsy and to determine if there is a correlation between plasma concentration and efficacy. Main Results: LEV trough levels ranged from 24.44-30.44 mg/L. There was not a significant correlation between LEV plasma concentrations and efficacy. Drowsiness was the most commonly reported adverse effect and was typically transient.	5-40 mg/L

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
Mathew et al, 2012 (7)	Prospective observational	Pediatrics with epilepsy (Focal 38%; Generalized 58%; Focal with secondary generalization 4%)	69	1-16 (NR)	NR	100-2000 mg/d	Aims: To determine the effect of EIAED and valproic acid on LEV concentrations. To determine if there is a correlation between LEV concentration and clinical response in children with generalized and focal epilepsy. Main Results: The median serum LEV concentration was 50% lower in patients on EIAEDs (7.3 mg/L) than those on non-inducing (16.6 mg/L) or enzyme inhibiting AEDs (14.4 mg/L). No significant difference in median LEV concentrations existed between responders(≥50% reduction seizure frequency) and non-responders.	NR
Sheinberg et al, 2015 (8)	Retrospective observational	Pediatrics with refractory epilepsy (Generalized 42%; Focal 38%; NCSE 12%, Absence 4%, Lennox-Gaustaut 1%; Infantile spasms 1%)	50	0.9-21 (10.3±5.5)	48	250-4000mg/d	Aims: To evaluate if there is a correlation between serum LEV concentrations and efficacy and tolerability in children with refractory epilepsy with various seizure types. Main Results: Neither efficacy nor tolerability correlated with serum LEV concentrations (range 2.5-38.5mg/L)	NR
Levetiracetam Overdose Reports								
Barrueto et al, 2002 (14)	Case report	Adult (Bipolar Disorder)	1	38 (NA)	F	30 g	Aim: To describe a case of 30 gm LEV overdose in an adult female patient using LEV as a mood stabilizer for bipolar disorder. Main Results: Sedation, coma and respiratory depression occurred after ingestion and resolved in 24 hours with supportive care. Levels of 400 mg/L, 72 mg/L and 60 mg/L were reported at 6, 18 and 20.5 hours after ingestion respectively.	10-37 mg/L
Chayasirisobhon et al, 2010 (15)	Case report	Adult with epilepsy (Focal Seizures)	1	41 (NA)	M	63 g	Aim: To describe a case of 63 gm LEV overdose in a 41-year-old patient with epilepsy. Main Result: Mild blurred vision, ataxia and transient leucopenia and thrombocytopenia	3-37 mg/L

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
							occurred after ingestion. Physical assessment was normal after 24 hours of observation and blood counts normalized by 2 months. LEV levels of 220 mg/L were reported 10 hours after ingestion.	
Page et al, 2016 (16)	Case report	Adult with epilepsy (unspecified seizure type)	1	43 (NA)	M	60-80 g	Aim: To describe a case of cardiovascular toxicity after 60-80 gm LEV overdose in a 43-year-old patient with epilepsy Main Result: Persistent bradycardia and hypotension occurred and responded to supportive measures and normalized in 48 hours. LEV levels of 463 mg/L were reported 8 hours post ingestion	10-40 mg/L
Drug-Drug and Drug-Formulation Interactions								
Coupez et al, 2003 (47)	Prospective open label crossover study	Healthy Volunteers	16	22-52 (NR)	42	1500mg Day 1, 10 VPA 500mg BID Day 3-11	Aims: To determine if the PK of LEV is impacted by the co-administration of valproic acid. Main Results: Neither the PK of single dose LEV or steady state valproic acid therapy was affected by co administration. Average LEV levels alone 39.6±9.9 mg/L and 41.4±9.7 mg/L with VPA.	NR
Strolin Benedetti et al, 2003 (48)	Prospective PK study	Healthy Volunteers	4	31-51 (43.25)	100	479-480mg once	Aims: To investigate the PK of LEV in healthy volunteers and determine the impact of co administration of valproic acid and an esterase inhibitor (paraoxon). Main Results: Valproic acid administration did not alter the PK of LEV. Paraoxon inhibited hydrolysis almost completely (>92%) *(In Vitro)*.	NR
Contin et al, 2004 (49)	Prospective PK study	Adults with epilepsy (unspecified)	100	20-38 (31±5 inducers) (29±9 non-inducers)	32	500-5000mg/d	Aims: To assess the effect of concomitant AED therapy on steady-state plasma LEV concentrations as add-on treatment in patients with epilepsy on chronic AED therapy Main Results: CL was significantly higher (~25%) in patients receiving EIAEDs (1.93 ml/min/kg) compared to non-EIAEDs or valproic acid (1.45 ml/min/kg). CL was not significantly	NR

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
							different between patients receiving non-EIAEDs and valproic acid. No significant gender related differences were observed.	
Sabers et al, 2011 (50)	Retrospective observational	Women with epilepsy (unspecified)	53	17-48 (29 non-users, 25 users)	0	500-2500mg without OC 500-4000mg with OC	Aims: To determine whether oral contraceptive (OC) use resulted in altered LEV concentrations. Main Results: There was not a significant difference in mean plasma concentrations or concentration-to-dose ratios between OC and non-users. (p=0.80)	NR
Freitas-Lima et al, 2011 (51)	Prospective observational	Patients with epilepsy (unspecified)	30	19-52 (39.4±9.8 EIAED; 39.3±10.1 Control)	53	1000mg single dose	Aims: To compare the LEV plasma levels in patients receiving EIAEDs with matched controls not receiving EIAEDs. Main Results: There was a significantly lower AUC (234.4±55 mg h/L vs. 295±86.1; p=0.02), significantly higher CL (1.17±0.3 ml/min/kg vs. 0.93±0.22; p=0.01) and significantly shorter terminal half-life (6.1±1 h vs 7.3±1.5h) in patients receiving EIAEDs.	NR
Fay et al, 2005 (52)	Prospective open label crossover study	Healthy Volunteers	10	NR (28.9±6.5)	60	500 mg	Aims: To compare the PK of an intact tablet to a crushed LEV tablet mixed with applesauce or enteral nutrition and administered orally Main Results: No significant difference in AUC (p=0.38), Cmax (p=0.07) and Tmax (p=0.25) occurred between the three groups.	NR
Mink et al, 2011 (12)	Prospective observational	Critically Ill (subarachnoid hemorrhage)	35	NR (51±11.7)	11	3000mg/d	Aims: To compare the efficacy of valproic acid to LEV in neurocritical care patients with aneurysmal subarachnoid hemorrhage. Main Results: No difference in incidence of seizures was seen between patients on valproic acid (12%) or LEV (17%) therapy. A significant 30% decline in LEV concentrations occurred when patients were switched from IV LEV (27.2±8.7 mg/L) to enteral liquid (19.2±9.7 mg/L) p<0.05.	5-30 mg/L

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
Coupez et al, 2003 (53)	Phase 1 Randomized open label Bioavailability/ Bioequivalence study	Healthy Volunteers	24	18-55 (33.4±9.78)	50	750mg single dose	Aims: To determine whether the tablet and solution formulations of LEV were bioequivalent. Main Results: Bio equivalency between the two formulations was concluded. Solution 21.1±4 mg/L vs Tablet 20.3±3.9 mg/L.	NR
Leppik et al, 2010 (54)	Randomized double-blind controlled trial	Healthy Volunteers	10	18-60 (34.8±NR)	50	500mg single dose	Aims: To determine the safety, tolerability and bioavailability of IM administration of LEV. Main Results: More pain was associated with IM LEV than IM saline but no AE were reported. There were no significant differences between IV (Cmax 11.57 mg/L, t1/2 9.37h) or IM (7.51 mg/L, t1/2 8.25h) LEV PK, p>0.05.	NR
Elderly Patients								
Contin et al, 2012 (18)	Prospective observational	Adults with epilepsy (unspecified)	272	30-96	53	1000-2125mg/d	Aims: To determine and compare the CL of LEV in elderly (age 66-80) and very elderly (age 81-96) patients to these in non-elderly adults (age 30-65). Main Results: median CL/F decreased by 33% in elderly (0.83 ml/min/kg) and 52% in very elderly (0.59 ml/min/kg) patients when compared to non-elderly (1.23 ml/min/kg). There was not a significant association between AE and drug levels and AE incidence was similar between age groups.	NR
Hirsch et al, 2007 (19)	Retrospective observational	Adults with epilepsy (unspecified)	308	16-88	NR	125-4625mg/d	Aims: To compare the PK and tolerability of LEV between older (age 55-88) and younger (age 16-31) adults. Main Results: Older patients (0.775 ml/min/kg) had a 40% lower LEV CL than younger patients (1.31 ml/min/kg). Younger patients were less likely to experience intolerable AE.	NR

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
Pediatrics								
Iwasaki et al, 2015 (11)	Prospective observational	Pediatrics with epilepsy (Focal Seizures)	24	0.7-16.7 (9.8±NR)	63	10mg/kg/d increased to 30-40mg/kg/d (max 60mg/kg/d)	Aims: To evaluate the efficacy of LEV in pediatric patients with focal seizures and determine the utility of therapeutic drug monitoring. Main Results: A positive correlation between drug levels and efficacy was seen at 2 weeks and 1 year but was not present at 2 years. An optimal range of 20-30 mg/L was chosen because effective cases had levels within this range without adverse effects. Average peak level 16.4-31.3 mg/L.	20-30 mg/L (determined)
Naik et al, 2015 (6)	Retrospective observational	Patients with epilepsy (Unspecified)	330	1-8 (4.26±2.27) 9-17 (13.07±2.41) 18-62 (32.31±12.5)	NR	5.95 – 100 mg/kg/dose	Aims: To describe the use of drug level monitoring of LEV and lamotrigine and determine the proportion of patients who achieved concentrations within the therapeutic range and the effects of co medication with EIAEDs. Main Results: No correlation between serum trough concentrations and clinical response or toxicity was seen. 57% of patients were within the reference range, 43% were below, none were above. Children < 9 years of age had higher LEV CL (2.6 mg/kg/min) than those >10 years of age (1.49 mg/kg/min) and adults ≥18 years of age (1.03 mg/kg/min).	12-45 mg/L
Glauser et al, 2007 (20)	Prospective open label PK study	Pediatrics with epilepsy (Focal 76.9%; Generalized 23.1%; Infantile spasms 38.5%)	12	2.3-46.2 months (19.9±14.16)	54	20mg/kg/dose	Aims: To determine the PK of LEV in children with epilepsy aged 1 month to 4 years old. Main Results: Children older than 6 months had the highest CL (1.57 ml/min/kg) while those 6 months and younger had the lowest (1.23 ml/min/kg).	NR

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
Pellock et al, 2001 (21)	Prospective open label PK study	Pediatrics with epilepsy (Focal Seizures)	24	6-12 (9.4±2.2)	75	19.6±4.6mg/kg single dose	Aims: To determine the PK of LEV and its metabolite in children with seizure disorders. Main Results: CL of LEV was 30-40% higher in children (1.43±0.36 ml/min/kg) compared to what has been previously been reported for adults. No age (study population) or gender differences in PK were seen.	NR
Chhun et al, 2009 (22)	Prospective open label PK study	Pediatrics with refractory epilepsy (unspecified)	44	4-16 (10.7±3.1)	50	10mg/kg/d then in 2 weeks 20mg/kg/d then in 2 weeks 40mg/kg/d	Aims: To develop a PK model to evaluate determinants of LEV PK and to determine recommended doses of LEV in children. Main Results: Body weight was the only covariate that explained individual variability in CL and volume of distribution. 20mg/kg BID had the highest probability of achieving troughs of 6-20mg/L (90%).	6-20 mg/L
Fountain et al, 2007 (27)	Prospective open label PK study	Pediatrics with epilepsy (Focal seizures)	14	4-12 (10.2±2.2)	8	10mg/kg/d then in 2 weeks 20mg/kg/d then in 2 weeks 40mg/kg/d	Aims: To characterize the PK of LEV in children following administration of escalating doses of LEV (20,40,60 mg/kg BID) and determine the effect of carbamazepine and valproic acid on PK of LEV. Main Results: LEV serum concentrations increased linearly and proportionally with dose and the elimination half-life was 4.9 hours, unchanged by escalating doses. CL of LEV was slightly higher in the carbamazepine group (1.23 ml/min/kg vs 1.08 ml/min/kg), but levels of carbamazepine and valproic acid did not differ significantly from baseline.	NR
Dahlin et al, 2010 (28)	Retrospective observational	Pediatrics with epilepsy (Focal 57%; Generalized 46%)	103	0-18 (10.2±4.8)	50	NR	Aims: To examine the influence of age on LEV CL in children with epilepsy and the of impact of LEV and concomitant AEDs on the CL of both LEV and other AEDs. Main Results: LEV CL was higher in youngest age group (0-4y, 3.7 ml/min/kg) compared to other age groups. (5-11y, 2.85 ml/min/kg; 12-17y, 2.15 ml/min/kg, p=0.0014). LEV serum	NR

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
							concentrations increased by 30% on average in patients taking EIAEDs.	
Toublanc et al, 2008 (29)	Retrospective Data pooling, PK study	Pediatrics with epilepsy (unspecified)	228	0.25-18 (NR)	NR	20-60mg/kg/d	Aims: To determine the PK of LEV as adjunctive therapy in children with epilepsy and to evaluate dosing regimens and covariates that may affect LEV PK. Main Results: Children required LEV doses that, when normalized for weight, were 30-40% higher than those used in adults to achieve similar trough values.	12-46 mg/L
Ng et al, 2010 (13)	Prospective observational	Pediatrics with epilepsy (Focal 30%; Generalized 30%; Focal-generalized 3%; Absence 20%; Atonic, Mixed, Myoclonic 17%)	30	0.5 - <15 (6.3±NR)	50	50mg/kg/d	Aims: To evaluate the safety and the efficacy of IV LEV in pediatric patients with epilepsy. Main Results: LEV was well tolerated and there was not a clear correlation between LEV levels and adverse effects or efficacy.	NR
Wang et al, 2012 (30)	Prospective PK study	Pediatrics with epilepsy (unspecified)	361	0.5-14 (6.34±NR)	44	20-60 mg/kg/d	Aims: To determine a population PK model of LEV in Chinese children with epilepsy. Main Results: Weight was the most important covariate that explained inter-individual variability of LEV CL. CL was approximately 50% lower in Chinese children (0.69 ml/min/kg) than previously published in Caucasian children and the elimination half-life was 8.9 hours.	NR
Blonk et al, 2010 (31)	Prospective PK study	Neonates (Electrographic epileptic seizures)	2	>37 wks GA	NR	Neonate 1: 64mg x 2 doses Neonate 2: 74mg x 2 doses	Aims: To validate a LEV plasma concentration quantification method in small volumes of plasma and describe the PK of IV LEV in 2 neonates with electrographical epileptic seizures. Main results: LEV clearance and elimination half-life were reported to be 0.43 ml/min/kg and 21	12-46 mg/L

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
							hours respectively in neonate 1 and 0.63 ml/min/kg and 14 hours in neonate 2.	
Merhar et al, 2011 (23)	Prospective observational	Neonates (unspecified)	18	≥32 wks GA, ≤30 days	56	14.4-39.9 mg/kg/d	Aims: To determine the PK of LEV in neonates with seizures and gather preliminary safety data for LEV use in this population. Main results: Neonates had a lower CL (1.21 ml/min/kg), higher volume of distribution (0.89 L/kg) and a longer elimination half-life (8.9 hours) than what has been reported for older children and adults.	NR
Sharpe et al, 2012 (24)	Prospective observational	Neonates (unspecified)	18	37 – 41 wks	50	20-40 mg/kg bolus dose, then 5-10 mg/kg/d	Aims: To investigate the PK of LEV in neonates with seizures and to determine its safety and efficacy in this population. Main results: LEV CL nearly doubled over the span of 7 days from 0.71 ml/min/kg on day 1 to 1.31 ml/min/kg on day 7. AE possibly related to LEV were mild sedation, feeding difficulty, mild apnea, mild bradycardia and decreased urine output.	6-20 mg/L
Johannessen et al, 2005 (25)	Prospective PK study	Neonates (NA)	8	3-5 days	NR	Maternal dose 1500-3500mg/d	Aims: To determine the PK of LEV at birth, during lactation and in the nursed infants of mothers taking LEV. Main results: Despite extensive transfer of LEV into breast milk, breast fed infants had low LEV serum concentrations (<1.7mg/L).	NR
Allegaert et al, 2006 (26)	Case report	Neonate twins (NA)	2	Up to 36 hrs	NR	Maternal dose 1500mg BID	Aims: To report on the PK of LEV in bottle fed neonates at birth after exposure to LEV during gestation. Main results: LEV clearance was 0.4-0.45 ml/min/kg and elimination half-life was 16-18 hours.	NR
Renal and Hepatic Impairment								
Yamamoto et al, 2014 (37)	Prospective PK study	Patients with renal impairment and	30	20-80 (64.6±NR)	97	CrCl 50-80, >80: 500mg;	Aims: To confirm the practice of dose adjusting LEV according to European guidelines in Japanese patients with renal impairment.	NR

Table 2. Summary of the studies included in this review

Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
		healthy volunteers				CrCl 30-50, <30: 250mg ESRD: 500mg + 250mg post HD All as single doses	Main Results: LEV renal clearance decreased linearly with decreasing CrCl. Non-renal clearance was consistent among the groups. LEV clearance decreased by 50% in severe renal impairment (CrCl <30 ml/min).	
Bahte et al, 2014 (38)	Case report	Peritoneal dialysis (Focal with secondary generalization)	1	73	M	500mg BID x 89 weeks	Aims: To describe a case of LEV toxicity in a 73-year-old patient requiring peritoneal dialysis (PD). Main results: Stupor, fatigue, drowsiness, GCS 10 resolved 5 days after discontinuing LEV 500mg PO BID. LEV level 29.8mg/L 24 hours after discontinuing. Elimination half-life of 18.4 hours upon LEV challenge.	12-46 mg/L
Brockmöller et al, 2005 (42)	Prospective open label PK study	Patients with hepatic impairment and healthy volunteers	21	36-58 (45±9 Healthy; 50±8 CPA; 53±5 CPB; 51±6 CPC)	100	1000 mg single dose	Aims: To determine the impact of varying degrees of liver impairment (Child-Pugh CP A, B, C) on LEV PK. Main results: LEV PK was not altered among health volunteers and patients with CPA and B indicating metabolism of LEV is not dependent on liver function. Clearance was significantly lower in the Child-Pugh C group. CL decrease was attributed to the decreased renal function in those patients.	NR
Nei et al, 2015 (39)	Case report	Renal Impairment RRT (SAH)	1	67	M	2000mg loading dose 1000mg q12h	Aims: To describe the use of LEV for new-onset seizure activity in a critically ill 67-year-old patient requiring CVVH and ECMO. Main results: Elimination half-life was similar to that observed in patients with normal renal function and ranged from 8.72-10.1 hours.	12-46 mg/L
New et al, 2016 (40)	Case report	Renal Impairment RRT (Focal seizures)	1	59	M	1000mg BID	Aims: To describe the use of LEV to treat focal seizures in a 59-year-old patient with acute multiorgan dysfunction, including acute liver dysfunction, requiring CVVH.	12-46 mg/L

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
							Main results: LEV PK in this patient requiring CVVH was similar to that seen with normal renal function.	
Louie et al, 2015 (41)	Case report	Renal Impairment RRT (ICH)	1	51	F	500mg once then 1000mg Q12h	Aims: To describe the use of LEV for seizures due to ICH in a 51-year-old woman requiring CRRT. Main results: Administration of CRRT resulted in marked reductions in LEV concentrations from 60 mg/ml to 19 mg/L.	12-46 mg/L
Critically Ill								
Spencer et al, 2011 (43)	Prospective open label PK study	Critically Ill (SAH, Stroke, TBI)	12	40-68 (54±14)	42	500mg Q12h then 1000mg Q8h then 1500mg Q8h	Aims: To characterize the steady-state PK of IV LEV in neurocritical care patients and to determine which dosing regimen is more likely to achieve trough serum concentrations of 6-20 mg/L. Main results: The terminal half-life was shorter in these neurocritical care patients compared to healthy adults and the systemic clearance was faster. A dosage 1000mg q8h had the highest probability of achieving a trough concentration between 6-20 mg/L (57.1%).	6-20 mg/L
Klein et al, 2012 (44)	Phase II open label PK	Critically Ill (TBI, ICH)	41	6-87 (NR)	NR	55 mg/kg/d	Aims: To evaluate the safety and tolerability of treatment with LEV and to report on the trough levels in patients with TBI. Main results: AUC was similar in these TBI patients as that seen in healthy patients, including population trends such as a higher AUC in elderly (602.1 h.mg/L) and a lower AUC in children (352.6 h.mg/L), compared to adults (448.3 h.mg/L).	NR
Uges et al, 2009 (45)	Prospective open label PK study	Critically Ill (SE, Generalized,	11	44-75 (58.7±NR)	64	2500mg IV over 5 mins	Aims: To assess the feasibility, safety and PK of IV LEV added to the standard therapeutic regimen in adults with status epilepticus (SE).	NR

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
		Focal, non-convulsive)					Main results: Total body clearance (0.79 ml/min/kg) and terminal half-life (5.8-13.9h) of IV LEV was similar in these SE patients compared to healthy adults. No serious side effects were directly related to IV LEV.	
Cook et al, 2013 (46)	Case report	Critically Ill (SAH)	1	22	F	1000mg BID then 1000mg TID, then 4000mg load, then 1500mg Q8h	Aims: To describe a case of ARC in a patient administered LEV for TBI. Main results: Lower than expected LEV levels were reported with standard dosing. A trough of 13 mg/L prompted a 4G IV loading dose, then a 1.5G q8h maintenance dose was associated with a peak level of 34 mg/L.	NR
Pregnancy								
Garrity et al, 2014 (32)	Case report	Pregnancy (Idiopathic localization-related epilepsy)	1	16	F	2000mg XR/d, titrated to 5000mg XR/d	Aims: To describe a case of breakthrough seizures associated with increased LEV clearance in a pregnant patient. Main results: Daily doses of 5000 mg were required in the third trimester to maintain trough levels near 40 mg/L. A trough level of 69.8 mg/L was seen in the post-partum period. Breakthrough seizures occurred in the first and third trimester and post-partum period.	12-46 mg/L
Cappellari et al, 2015 (33)	Case report	Pregnancy (Focal epilepsy)	1	36	F	1750mg/d, titrated to 3375mg/d	Aims: To report on a case of breakthrough nocturnal seizures in a pregnant patient associated with a sub therapeutic trough LEV level. Main results: A breakthrough seizure correlated with a trough level <2.4mg/L. A dose increase from 1750mg to 3375mg/day divided QID maintained desired trough levels and no further seizures occurred.	10-40 mg/L (individual)
Westin et al, 2008 (34)	Prospective observational	Pregnancy (Focal 30%; Focal-generalized 30%;	20	21-38 (29±NR)	F	1000mg-3500mg/d	Aims: To report on pregnancy related alterations in LEV serum concentrations and dose ratios. Main results: In the third trimester, LEV serum concentrations dropped to 50% of baseline levels	NR

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
		Myoclonic 5%; Generalized 10%; None 25%)					on average. There was not a clear correlation between lowered LEV levels and breakthrough seizures.	
Tomson et al, 2007 (35)	Prospective observational	Pregnancy (Unspecified)	14	21-37 (NR)	F	1000-3000mg/d	Aims: To investigate the PK of LEV during pregnancy, peri-partum and post-partum and to report on plasma levels of LEV in neonates following birth. Main results: CL was significantly higher in the third trimester and LEV plasma concentrations dropped to almost 60% of that in first (4.7 mg/L) and second trimesters (11.8mg/L).	NR
López-Fraile et al, 2009 (36)	Prospective observational	Pregnancy (Focal-Generalized 20%; Focal 40%; Focal with secondary generalization 60%)	5	29-40 (NR)	F	2000-3000mg/d	Aims: To determine variations in LEV levels from pre-pregnancy baseline during pregnancy and two and 12 months post-delivery. Main results: Compared to pre-pregnancy baseline levels, a decline in LEV concentrations occurred in the third trimester ranging from 17.6 to 47.8% and an increase of approximately 30% occurred 2 months post-partum.	NR
Other Included Studies								
Johannessen Landmark et al, 2012 (56)	Retrospective PK study	Pediatrics, Adults, Elderly with refractory epilepsy (unspecified)	289	0-9, N=42 10-17, N=60 18-64, N=167 65-86, N=21	NR	NR	Aims: To compare the impact of age and co-medication on PK variability between lamotrigine, levetiracetam, oxcarbazepine and topiramate in patients with refractory epilepsy. Main results: Age had the largest effect on LEV CL and compared with adults (3.88±1.88ml/kg/min), a 60% higher LEV CL was reported in children 0-9 years of age(6.25±3.8ml/kg/min) and a 40% lower LEV CL in elderly patients 65-86 years of age (2.41±1.31mg/kg/min). CL in those 10-17 years	NR

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Author, Year of publication	Study Design	Population Studied (Seizure types)	N	Age, years Range (Average±SD)	Sex Male (%)	LEV dosage range	Study aims and main results	Suggested reference range
							of age was (4.06±2.29ml/kg/min). CL of LEV was increased by approximately 25% by EIAEDs.	
May et al, 2003 (55)	Prospective PK study	Pediatrics, Adults, Elderly with epilepsy (unspeficied)	297	2.2-75.6 <12y – 8.1% >18y – 84.8% >60y – 5.1%	57	4.3-111mg/kg/d	Aims: To determine the influence of age, body weight, gender and co-medication on the LEV serum concentrations in people with epilepsy. Main results: Age, co-medication and dose-per-body weight had a significant influence on serum LEV concentrations. Compared to Adults, children less than 12 years old required larger doses per body weight while patients greater than 65 required lower doses. Co-medication with phenytoin, carbamazepine, oxcarbazepine and methsuximide decreased LEV concentrations by 20-30%.	12-46 mg/L

AE, adverse effects; AEDs, antiepileptic drugs; CL, clearance; CPA, Child-pugh A; CPB, Child-pugh B; CPC, Child-pugh C; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; EIAED, enzyme-inducing antiepileptic drugs; ESRD, end-stage renal disease; GA, gestational age; HD, hemodialysis; HIE, hypoxic-ischemic encephalopathy; HPLC, high performance liquid chromatography; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; LEV, levetiracetam; NA, not applicable; NR, not reported; NCSE, Non-convulsive status epilepticus; OC, oral contraceptives; PK, pharmacokinetics; SAH, subarachnoid hemorrhage; SE, status epilepticus; VPA, valproic acid; XR, extended-release