Safety profile of Lamotrigine in overdose

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Summary

Background Lamotrigine is an anticonvulsant as well as a mood stabiliser. Apart from its established use in the treatment of epilepsy, there has been an expansion of its use in the treatment of mental disorders. Patients with epilepsy as well as those with mental disorders are at increased risk of deliberate drug overdoses. An evidence base for the safety profile of lamotrigine in overdose is an essential tool for prescribers.

Objective To carry out a narrative synthesis of the existing evidence for the safety profile of lamotrigine in overdose.

Methods A systematic search was conducted of EMBASE (1974- December, 2015), MEDLINE (1946-December, 2015), PsycINFO (1806-December, 2015) and CINAHL (1981-December, 2015) databases. Studies were included in which there was a deliberate or accidental single drug overdose of lamotrigine, with its toxic effects described. Studies that did not involve an overdose were excluded. A narrative synthesis of the described toxic effects was carried out.

Results Out of 562 articles identified, 26 studies were included, mainly in the form of case reports and series. The most commonly described toxic effects of lamotrigine were on the central nervous system, specifically seizures, movement disorders and reduced consciousness. Other toxic effects included QTc interval and QRS complex prolongations, hypersensitivity reactions, serotonin syndrome as well as rhabdomyolysis possibly due to seizures and/or agitation. Deaths were recorded in 2 studies, with cardiovascular and neurological toxic effects described.

Conclusions Even though lamotrigine has been reported to be well tolerated, there is a risk of toxic effects which can be life threatening in overdose. This needs to be borne in mind when prescribing to patients at an increased risk of deliberate drug overdose.

Key words: Lamotrigine, overdose, safety, toxicity, death

Introduction

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] a phenyltriazine derivative inhibits high voltage activated-calcium channels [Stefani *et al.*, 1996] and voltage-sensitive sodium channels as well as reduces neuronal glutamate release. [Biton, 2006] Lamotrigine has effects on the serotonergic pathway with re-uptake inhibition, [Sagud *et al.*, 2008] which may explain its antidepressant property.

In terms of pharmacokinetic properties, lamotrigine has 98% bioavailability, with peak concentrations (C_{max}) reached within 1-3 hours after ingestion. It is 55% protein bound, with an apparent volume of distribution (Vd) reported to be 0.9-1.2L/Kg in healthy volunteers and 1.28-1.36L/Kg in patients who have epilepsy and are on concomitant therapy. It undergoes hepatic glucuronidation with a conversion to the inactive 2N-glucuronide metabolite, which is excreted via the kidneys. A half-life of 24-30 hours has been reported for lamotrigine when it is used as monotherapy, but with multiple dosing it can induce its own metabolism reducing its half-life by 25%, [Splinter, 2005] possibly through a weak induction of some phase II enzymes (uridine diphosphate glucuronosyltransferases). [Benedetti, 2000]

The toxic effects of lamotrigine on the central nervous and cardiovascular systems can be explained via its action on voltage gated sodium channels, which are responsible for the initiation and propagation of action potential in excitable cells such as nerve and muscle cells. [Catterall *et al.*, 2005] By virtue of its serotonin re-uptake inhibition property, there is a risk of serotonin syndrome especially when it is ingested along with other substances that may potentiate this effect. [Kotwal *et al.*, 2015] As central nervous system features of serotonin syndrome include: an altered mental state which could range from agitation to coma; neuromuscular hyperactivity which can present with a variety of features including hyperreflexia, ataxia and nystagmus; and generalized tonic-clonic seizures (in severe cases), [Iqbal *et al.*, 2012] the toxic effects of lamotrigine on the central nervous system may also occur through excess serotonin.

An anticonvulsant hypersensitivity syndrome, which consists of a triad of fever, skin eruption and internal organ involvement, [Knowles *et al.*, 1999] has been associated with lamotrigine, despite its having a different structure to the aromatic anticonvulsants (phenytoin, phenobarbitone and carbamazepine), which have been more commonly associated with the anticonvulsant hypersensitivity syndrome. The exact mechanism for the hypersensitivity syndrome associated with lamotrigine is not clear, but it has been reported even with normal doses (100mg) of lamotrigine (although in this case, the patient was also receiving valproic acid 1000mg/day as treatment). [Chang *et al.*, 2006]

Lamotrigine has an established role as an anticonvulsant in the treatment of partial, primary generalized tonic-clonic seizures and generalized seizures of Lennox-Gestalt syndrome in patients aged 2 years or older.[Goldenberg, 2010] In the treatment of mental disorders, benefits of lamotrigine have been demonstrated in bipolar depression [Calabrese *et al.*, 1999], as well as in the prophylaxis of rapid cycling bipolar disorder. [Calabrese *et al.*, 2000] There is increasing evidence of its possible benefits in the control of affective instability and impulsivity [Reich *et al.*, 2009] in patients with borderline personality disorder, as well as its benefits in managing aggression amongst this group of patients. [Leiberich *et al.*, 2008]

Lamotrigine is reported to be generally well tolerated, with commonly reported adverse effects being dizziness, somnolence, nausea, asthenia and headaches in 8 to 20% of patients. [Sabers *et al.*, 2000] Rash as a side effect has been reported to develop in about 12% of patients, [Sabers *et al.*, 2000] with the incidence of serious rashes in bipolar studies reported to be around 0.1%. [Goldsmith *et al.*, 2003] Stevens-Johnson syndrome, a severe rash characterized by cutaneous erythema with blister formation and mucosal lesions as well as fever, [Mockenhaupt, 2011] has been described to occur in 1/1000 lamotrigine treated adults and 1/100 treated children. [Varghese *et al.*, 2006] The exact mechanism by which Stevens-Johnson syndrome occurs in some patients treated with lamotrigine, is not clear. A molecular target analysis of drugs associated with Stevens-Johnson syndrome using a bio-informatics approach, reported the sodium channel alpha 2 (Nav1.2) as a target highly associated with Stevens-Johnson. [Burkhart *et al.*, 2015] This voltage gated channel has been found to be expressed in keratinocytes present in skin biopsied from patients with painful skin conditions such as complex regional pain syndrome type 1. [Zhao *et al.*, 2008] It may play a role in the development of Stevens-Johnson syndrome in patients treated with lamotrigine, in view of the action of lamotrigine on voltage-gated channels.

Other relatively less common adverse events, which were reported from 12 controlled bipolar clinical trials include: dry mouth (6.3%), diarrhea (6.2%) and tremor (3.9%). Data from the bipolar clinical trials showed the serious adverse events of mania, hypomania and mixed mania occurred in 2.5% of 1256 patients treated with lamotrigine, although this was felt to be comparable to the level found in patients treated with placebo (2.2% of 1094 patients) and lithium (2.5% of 280 patients). A 0.5% incidence of these adverse events were felt to be related to lamotrigine in the studies [Seo *et al.*, 2011]

Generally, mental disorders are associated with a relatively increased risk of suicidal behaviour, of which self-poisoning has been identified as a common method, accounting for 20.2% (N ≈ 1259) and 38.2% (N≈ 2381) of female and male suicides respectively, in the United Kingdom in the year 2013. [Statistics, 2015] A risk of suicide has also been associated with epilepsy, [Christensen *et al.*, 2007] even in the absence of a mental disorder. Hence patients prescribed lamotrigine may be at higher risk of deliberate drug overdose.

The evidence regarding toxic effects of lamotrigine in overdose is mainly in the form of specific case reports, most of which concentrate on a number of specific features related to the case in question. In view of the established and increasing use of lamotrigine in groups of patients who are at an increased risk of drug overdoses, prescribers are in need of evidence on its safety profile in overdose in assessing the risks and benefits of its use. Hence we carried out a review of the literature in order to synthesise the available evidence for the safety profile of lamotrigine in overdose.

Objectives

1) To conduct a systematic literature search of the toxic effects of lamotrigine in overdose

2) To carry out a narrative synthesis of the existing evidence.

Method

Search strategy and selection criteria

We searched the databases EMBASE (1974-December, 2015), MEDLINE (1946-December, 2015), PsycINFO (1806-December, 2015) and CINAHL (1981-December, 2015) for relevant studies in which the toxic effects of lamotrigine were described in accidental or deliberate overdose.

We defined lamotrigine overdose using any of the criteria below:

1. For patients who were prescribed lamotrigine: lamotrigine taken accidentally or deliberately in doses higher than what they were prescribed or intended to take by their prescriber.

2. For individuals not prescribed lamotrigine: lamotrigine taken accidentally or deliberately at doses which are above the British National Formulary (BNF) recommended (adult equivalent) maximum doses for monotherapy (400mg daily for bipolar disorder and up to 500mg daily for seizures).

We did not apply any age or language restrictions to our search. A manual search of the references of the obtained articles was also carried out for relevant studies.

We included studies in which there was a deliberate or accidental overdose of lamotrigine, with the toxic effects attributable to the drug described.

We excluded studies in which:

1. Lamotrigine was taken at prescribed doses with features of toxicity described.

2. Lamotrigine was taken at prescribed doses, but its toxicity was precipitated by other co-prescribed medications.

3. There were co-ingestants along with lamotrigine.

Included studies were mainly case reports and case series and hence an assessment of risk of bias was not possible. A preliminary search carried out by our team had revealed observational studies as the level of evidence available to address the study objectives, with case reports and case series the main evidence found, hence a narrative synthesis was planned given the lack of appropriate data to conduct meta-analysis.

Results

The search revealed a total of 562 records, out of which 26 eligible articles were included in the narrative review. Figure 1 shows the study selection process. Of these 26 articles which represented 543 individual cases, 21 were case reports, 4 were case series and 1 study had a case control design. One of the case series [Lofton *et al.*, 2004] utilised data from 493 single-substance exposures to lamotrigine reported to the American association of poison control centers toxic exposure surveillance system. Another case series [Moore *et al.*, 2013] utilised data from 9 patients admitted to an inpatient toxicology centre with lamotrigine only overdoses. Whilst only one case in each of the other 2 case series, was judged to have met the inclusion criteria and included.

Table 1 shows the characteristics of the included studies.

<u>Frequency of toxic effects</u>

The study by Lofton and colleagues [Lofton *et al.*, 2004] provided useful information on the frequencies of the observed toxic effects of lamotrigine in overdose. In this study of 493 patients, the frequencies of the following effects were mentioned: drowsiness/lethargy (20.9%); vomiting (11%); nausea (5.1%); ataxia (4.9%); dizziness/vertigo (4.5%); tachycardia (4.3%); confusion (2.2%); agitation (2.0%); rash (1.8%); slurred speech (1.8%); tremor (1.8%); nystagmus (1.6%); blurred vision (1.4%) and coma (1.2%). Seizure as a toxic effect was reported in 8 people (1.6%), with 3 events of multiple seizures and 2 individuals with seizures of a status pattern. Respiratory depression was reported in 3 patients, whilst cardiac conduction disturbances were reported in 2 patients.

Described toxic effects of lamotrigine in deliberate overdose

Central Nervous Effects

In the studies included in this review, central nervous toxic effects appear to be the most commonly associated effect of lamotrigine in overdose. There were 249 individual reports of associated central nervous toxic effects in the form of 20 case reports and 4 case series.

Lamotrigine in overdose was associated with a wide range of central nervous system effects, such as: oculogyric crisis, [Veerapandiyan *et al.*, 2011] dystonia, [Eleftheriou *et al.*, 2009] , nystagmus, ataxia, [Buckley *et al.*, 1993, Briassoulis *et al.*, 1998, Daana *et al.*, 2007, Abesamis *et al.*, 2010, Lapoint *et al.*, 2010, Strimel *et al.*, 2010, Hajiali *et al.*, 2015] slurred speech [Hajiali *et al.*, 2015] and hypertonia. [Buckley *et al.*, 1993] Abnormal movements with intermittent jerking, choreo-athetoid movements, [Chiew *et al.*, 2013] and choreiform dyskinesia [Miller *et al.*, 2008] have been described in case reports.

Paradoxically, lamotrigine which is an anticonvulsant has been associated with seizures in overdose. [Waring, 2009, French *et al.*, 2011] The seizures associated with lamotrigine have occurred in patients without a documented prior history of seizures [Lapoint *et al.*, 2010, French *et al.*, 2011] and in patients with a history of seizures. [Dinnerstein *et al.*, 2007, Waring, 2009, Algahtani *et al.*, 2014] The seizures have been described as generalized, [Thundiyil *et al.*, 2007] with specific seizure types reported with single drug overdoses of Lamotrigine being: tonic-clonic seizures [Briassoulis *et al.*, 1998, Daana *et al.*, 2007, Dinnerstein *et al.*, 2007, Willis *et al.*, 2007, Waring, 2009, Abesamis *et al.*, 2010, Lapoint *et al.*, 2010, French *et al.*, 2011, Nogar *et al.*, 2011, Hajiali *et al.*, 2015] and myoclonic seizures. [Lapoint *et al.*, 2010]. The tonic-clonic seizures were reported along with the clinical findings of clonus and hyperreflexia [Nogar *et al.*, 2011] in a case, and status *epilepticus* developing in another case. [Chavez *et al.*, 2015]) The myoclonic seizures were described as a generalized myoclonic status *epilepticus* [Algahtani *et al.*, 2014] in a report.

Reduced levels of consciousness (without an associated description of seizures) have been reported in single drug overdoses of Lamotrigine. [Zidd *et al.*, 2004, Castanares-Zapatero *et al.*, 2012]

An encephalopathic picture which included an agitated delirium, mutism, nystagmus, upper motor neurone features as well as catatonia was described in a 40-year-old woman, with a previous history of glioblastoma multiforme and seizures, who took thirty 200mg tablets (6000mg) of the extended-release (XR) preparation of lamotrigine. [Hernandez *et al.*, 2010]

Two patients in a case series from an inpatient toxicology centre [Moore *et al.*, 2013] were reported to have met the Hunter criteria [Dunkley *et al.*, 2003] for serotonin syndrome. One of these patients

was a 1year old child with a serum lamotrigine level of 18mg/l (taken at 8hours), who had presented with agitation, diaphoresis and an inducible clonus. All 9 patients in this case series were reported have had altered mental states: with 4 patients having a depressed mental state; 5 patients having an agitated mental state and 3 patients having both depressed and agitated mental states. 5 of the patients in the series had hyperreflexia and intermittent myoclonus.

Cardiac Effects

There were 36 individual reports of associated cardiac toxic effects; these were in the form of 6 case reports, 2 case series and 1 case control study.

Widening of the QRS complexes in association with lamotrigine overdose, has been reported in a patient who had a normal heart rate of 88b/min, but with a Left Bundle branch block ECG pattern. [Castanares-Zapatero *et al.*, 2012] A widening of the QRS complex of up to 210ms has also being associated with a tachycardia, with outcomes of this being complete heart block [French *et al.*, 2011] and a pulseless ventricular tachycardia. [Nogar *et al.*, 2011]. Sinus tachycardia as a nonspecific finding without a description of QRS complex widening, has also been reported.[Thundiyil *et al.*, 2007]

Chavez and colleagues [Chavez *et al.*, 2015] described a male patient who developed a new onset right bundle branch block, with the prolongation of QRS interval (up to 128ms) and QTc intervals (up to 458ms). Much longer QTc prolongations (up to 586ms) were described in a case series study. [Moore *et al.*, 2013] Prolongation of QTc intervals as a toxic effect of lamotrigine in overdose was examined further in a case control study; [Hodson *et al.*, 2009] even though the QTc interval was found to be longer in the lamotrigine overdose group compared to the control group, the difference between the groups was not statistically significant (P=0.137). However this was a small study with 18 cases.

A brugada-like ECG pattern has been described in an adult patient who had a serum lamotrigine level of 20.4mg/l. [Strimel *et al.*, 2010]

Other described toxic effects

A range of other features of toxicity have been described in the course of a lamotrigine overdose, including nausea, vomiting, vertigo, lethargy, respiratory depression. [Lofton *et al.*, 2004] Headaches, diplopia, dizziness, sweating and abdominal pain [Hajiali *et al.*, 2015] were other described features which appeared to have preceded the onset of a tonic-clonic seizure in a patient.

Abnormal vital sign readings were stated in some of the reports, these included: tachypnea with recorded respiratory rates of up to 32 breaths per minute; [Hajiali *et al.*, 2015] tachycardia with heart rates up to 131 beats/min ; [Nogar *et al.*, 2011] elevated blood pressure readings of up to 185/95mmHg [Hajiali *et al.*, 2015] and pyrexia with a temperature above 38^{o}C. [Moore *et al.*, 2013]

Rhabdomyolysis has been reported in the context of lamotrigine overdose, although this might have been the consequence of the associated seizure [French *et al.*, 2011]or agitation.

Mylonakis and colleagues [Mylonakis *et al.*, 1999] described a hypersensitivity-like syndrome with low grade pyrexia, erythema and oedema involving the periorbital region, leucocytosis, elevated

phosphokinase (7222 units/L), elevated alanine aminotransferase (76units/l), elevated aspartate aminotransferase (154units/l) and a raised creatinine (24mg/l) in a 49-year-old man, who inadvertently received 4 daily doses of 2700mg of lamotrigine.

Hajiali and colleague [Hajiali *et al.*, 2015] described menorrhagia of a 2 day duration observed in a 26 year old who was reported to have taken up to 40grams of Lamotrigine. The patient was reported to have had a normal gynaecological examination at the time. Her menstrual periods were reported to have been normal prior to this. Apart from the drop in the patient's haemoglobin levels, investigations carried out in this patient were reported to be normal, although no specific mention was made of whether the investigations involved coagulation tests.

Rash, a common and important adverse reaction in normal doses, has also been described in two case reports of lamotrigine overdose. A flat, lacy, reticular blanching rash occurred along with a transient mild derangement of liver function tests in a 3-year-old who accidentally ingested up to 1150mg of lamotrigine. [Zidd *et al.*, 2004] A diffuse, discrete confluent, branching red maculo-papular rash without mucosal involvement was described in the context of lamotrigine overdose presenting with a hypersensitivity like syndrome. [Mylonakis *et al.*, 1999]

Death

Death occurring in the course of lamotrigine overdose was well described in 2 separate case reports.

French and colleagues [French *et al.*, 2011] described a case of a 19-year-old patient who took 4000mg of lamotrigine. Events following the overdose had involved the development of seizures and a cardiac arrest. The patient subsequently developed a respiratory and metabolic acidosis as well as cardiac arrhythmias including complete heart block. He developed an acute renal failure, which was felt to be due to rhabdomyolysis with a recorded CK of over 23000 U/L. A bacterial pneumonia infection (with Staphylococcus and Klebsiela) and a disseminated intravascular coagulation occurred prior to his death.

Nogar and colleagues [Nogar *et al.*, 2011] described a 48-year-old man who ingested 7500mg of lamotrigine, who developed a tonic-clonic seizure and subsequently developed a broad complex tachycardia which became pulseless, with a resulting anoxic brain injury and death four days later.

Both overdoses were solitary drug overdoses of Lamotrigine.

Discussion

Lamotrigine taken in overdose is not always associated with toxic effects. In the case series of 493 patients [Lofton *et al.*, 2004] who ingested lamotrigine as a single substance overdose, the majority (52.1%) did not experience any toxic effects, and there were no deaths. However, a study using a calculated Shannon information index to compare requirements for interventions in overdoses of newer anticonvulsants, reported lamotrigine as the most toxic in overdose by this definition, [Wills *et al.*, 2014] compared to gabapentin, levetiracetam , pregabalin, tiagabine, topiramate and oxcarbazepine.

In this review, reported single-agent overdoses of lamotrigine with doses of 100-40000mg and serum concentrations of 15.5-74.7mg/l, have been associated with a wide variety of toxic effects on

the central nervous and cardiovascular systems, as well as hypersensitivity like syndrome. Figure 1 shows mechanisms for the toxic actions of lamotrigine on the body. Toxicity has been correlated with increasing serum lamotrigine levels in some [Froscher *et al.*, 2002, Hirsch *et al.*, 2004] but not all studies. [Kilpatrick *et al.*, 1996] In view of the available evidence in this review for the toxic effects of lamotrigine being mainly case reports and case series, it was not possible to calculate a minimum dose or serum concentration associated with toxic effects.

Treatment of lamotrigine toxicity is largely based on the observed clinical effects, and may involve the use of measures to prevent further absorption of the ingested lamotrigine such as use of activated charcoal and gastric lavage.

There has been a recommendation for the use of alkalinisation via sodium bicarbonate when cardiotoxicity due to sodium channel blockade is suspected, [Castanares-Zapatero *et al.*, 2012] which is similar to its suggested use in the management of tricyclic antidepressant toxicity. [Newton, 2015] In view of lamotrigine's lipophilic properties, use of intravenous lipid emulsion has been suggested as a potential treatment strategy in cases of cardiac toxicity in the context of sodium channel blockade, if refractory to alkalinisation therapy. [Castanares-Zapatero *et al.*, 2012] The exact mechanism by which lipid emulsion therapy works is not entirely clear. It has been suggested that lipid emulsion therapy may work by creating a "lipid sink" [Weinberg *et al.*, 1998] in the blood stream, which draws in a lipophilic substance thereby reducing the plasma aqueous concentration of the substance. It may also work by increasing the cardiac energy supply by improving fatty acid metabolism [Picard *et al.*, 2006] or by activation of calcium channels, [Castanares-Zapatero *et al.*, 2012] thereby increasing the inotropic action.[Chavez *et al.*, 2015] In a case report, there was a narrowing of a previously widened QRS complex and a normalisation of conduction interval disturbances, a few minutes after the initial bolus of lipid emulsion therapy was administered to a patient whose ECG had showed no response to sodium bicarbonate therapy. [Castanares-Zapatero *et al.*, 2012] As the toxic effect of lamotrigine on the central nervous system can also be explained via sodium channel blockade [Catterall *et al.*, 2005], the criteria for the use of lipid emulsion therapy would include life- threatening cardiac and/or neurologic toxicity refractory to conventional therapy.

Prompt and effective management of seizures is required, with parenteral benzodiazepines recommended as the first line treatment for drug induced seizures, and barbiturates or propofol recommended as second line anticonvulsants. It is felt propofol may have a synergistic effect when used with benzodiazepines or barbiturates. [Chen *et al.*, 2016] Sedation with benzodiazepines may also play an important role in the management of features that may occur with a serotonin syndrome, Such as: anxiety, agitation, increased muscular activity, tremors, hypertension, tachycardia and pyrexia. [Dvir *et al.*, 2008, Iqbal *et al.*, 2012, Volpi-Abadie *et al.*, 2013]

The Strategies for managing lamotrigine overdose are summarized in Table 1.

The role for haemodialysis in lamotrigine overdose has been considered. Using a 100mg dose of lamotrigine in a study of the pharmacokinetics of lamotrigine in renal impairment, haemodialysis was reported to have shortened the elimination half-life from 59.6 +/- 28.1 hours during the interdialysis period to 12.2 +/- 6.4 hours during the dialysis period, with 17% of the drug extracted by haemodialysis. [Fillastre *et al.*, 1993] Lu and colleagues [Lu *et al.*, 2012] described a reduction in the serum concentration of lamotrigine from 61.2 mg/l to 7.2mg/l over a 62 hour period using blood perfusion which involved haemodialysis and haemoperfusion. Taking into consideration its half- life

and a potential to induce its own metabolism, [Splinter, 2005] it was difficult to assess the role of haemodialysis in this instance. Further studies are required to clarify the role (if any) of haemodialysis in the management of lamotrigine overdose.

In conclusion, even though lamotrigine has been reported to be well tolerated at normal doses (and even in some overdoses), there is evidence of clinically important toxicity in overdose, with variable outcomes; this may be a complete recovery occurring in majority of the cases, but death has been reported. Its toxic profile must be considered when prescribing lamotrigine to patients who are potentially at an increased risk of taking overdoses. This should form part of the risk-benefit analysis particularly in the drug's longer term and increasing use in psychiatric populations, when weighed against alternative mood stabilisers. There is a paucity of systematic observational studies for the toxic effects of lamotrigine in overdose, with only one case control study found and included in this study. Hence frequencies of specific toxic effects could be judged from this single study alone. There remains a need for more systematic evidence for the toxic effects of lamotrigine in overdose, in the form of case control studies as well as retrospective cohort studies, which can help confirm a direct association between the observed toxic effects and the overdose, including the consideration that some of the observed effects may well be indirect effects, with the triggering event being the overdose.

Limitations

Due to the nature of the review, only evidence in the form of observational studies (mainly case reports) was available. We sought to follow the principles of the PRISMA reporting guideline, [Moher *et al.*, 2009] but this was limited by the absence of quantitative studies; for instance there was no risk of bias assessment we could conduct. Although we did not place a language restriction on our search criteria and on the included studies, we were not able to include one of the obtained articles in this review, due to our inability to translate its full text from Farsi to English language.

Conflict of interest

The authors declare that there is no conflict of interest

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None received

Associated Effect of lamotrigine overdose	Management
All effects (Central Nervous System Effects Cardiac Effects Nausea Vomiting)	Treatment is based on observed clinical effects and may involve: • Maintenance and support of the airway, breathing and circulation • Measures to prevent further absorption e.g use of activated charcoal use, gastric lavage • Benzodiazepines for seizures, increased muscular activity, tremors, agitation, anxiety, hypertension, tachycardia • Antiemetics if indicated
Life threatening cardiac effect including arrhythmias, widened QRS intervals, QTc interval prolongation	General measures as above and Alkalinisation using Sodium Bicarbonate as an infusion. If symptoms fail to respond to above measures then consider Lipid emulsion therapy
Life threatening neurologic features	General measures as above and Use of phenobarbitone &/ propofol for refractory seizures Alkalinisation using Sodium Bicarbonate as an infusion. If symptoms fail to respond to above measures then consider Lipid emulsion therapy
Hypersensitivity reactions	General measures above as appropriate Use of antihistamines and steroids as appropriate

Table 1: General principles for the management of Associated Effects of lamotrigine Overdose

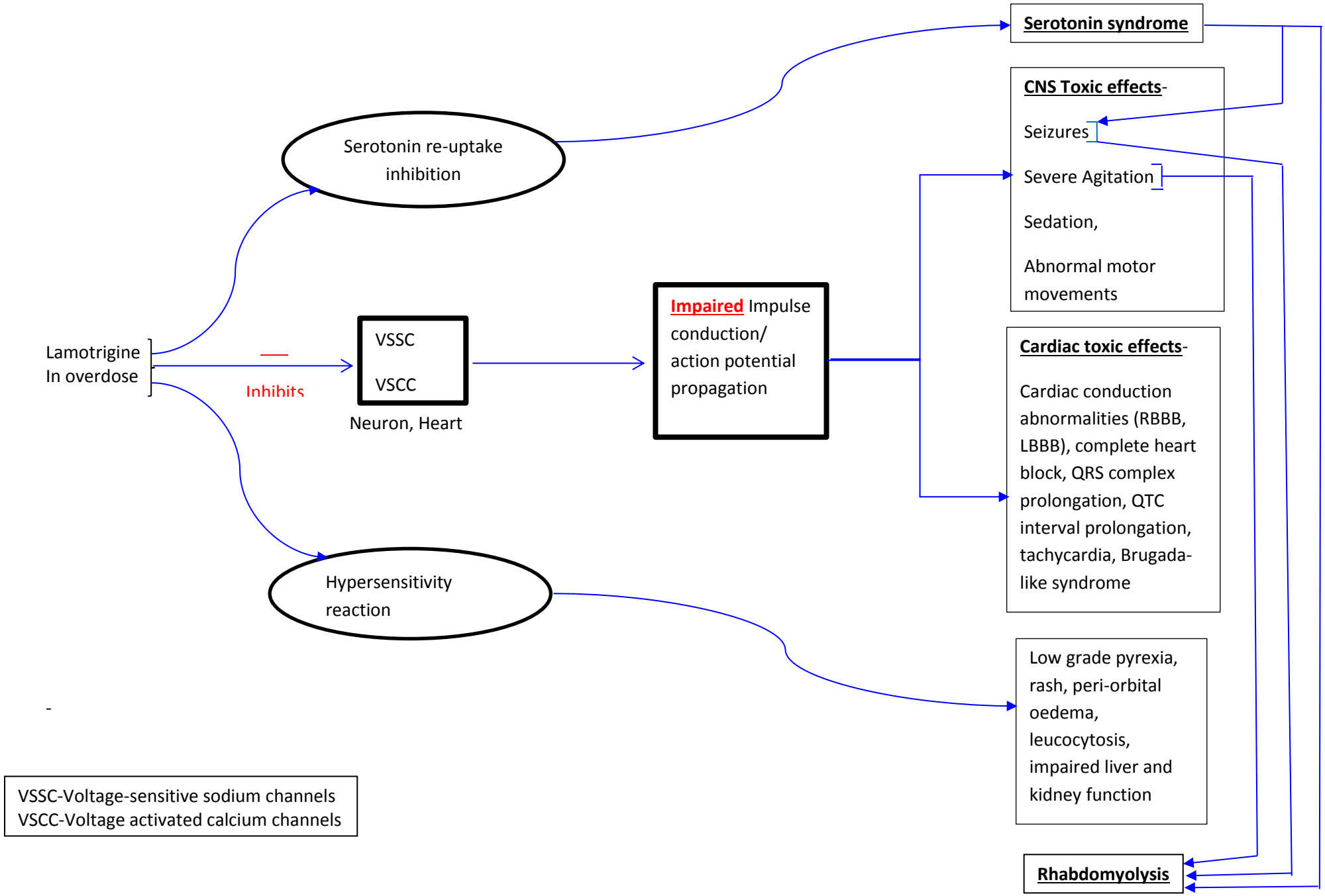

Fig 1 : Mechanisms of the toxic effects of Lamotrigine in overdose, on the human body

	Authors	Year of publication	Study design/type	Age of patient	Dose of ingested Lamotrigine if stated	Stated Serum Concentration (No of hours after ingestion)	Feature of toxicity included in narrative synthesis
1	[Lofton *et al.*, 2004]	2004	Case series, with 493 exposures to Lamotrigine identified	40.2% were between 20-59years. 35.4% were less than 4 years old	Variable doses	Not stated	Drowsiness(20.9%), vomiting(11%),nausea(5.1%), ataxia(4.9%), vertigo(4.5%), tachycardia(4.3%), rash(1.8%), tremor(1.8%) and respiratory depression (N=3). 52.1% had no toxic features.
2	[Veerapandiyan *et al.*, 2011]	2011	Case series- Only one report met the inclusion criteria	25 years	1600mg	Not stated, but the mean for the series was 15.5mg/l	Oculogyric crisis.
3	[[Eleftheriou *et al.*, 2009]	2009	Case report	45years	8400mg	40 mg/l (Time after ingestion not stated)	Acute dystonia.
4	[Buckley *et al.*, 1993]	1993	Case report	26 years	1350mg	17.4mg/l (3 hrs)	Hypertonia, nystagmus and ataxia.
5	[Briassoulis *et al.*, 1998]	1998	Case report	2 years old	800mg(weight of child not stated)	3.8mg/l (≈2hrs)	Generalized tonic-clonic seizures, severe ataxia.

	Authors	Year of publication	Study design/type	Age of patient	Dose of ingested Lamotrigine if stated	Stated Serum Concentration (No of hours after ingestion)	Feature of toxicity included in narrative synthesis
6	[Daana *et al.*, 2007]	2007	Case report	2 years (weight 20kg)	500mg (25mg/kg)	Not done	Generalized tonic-clonic seizures.
7	[Abesamis *et al.*, 2010]	2010	Case report	20 months (weight not stated)	1500mg	30.5mg/l (Time after ingestion not stated)	Ataxic gait, tonic-clonic activity.
8	[Lapoint *et al.*, 2010]	2010	Case report	13 months	800mg	31.1mg/l (3 hrs)	Nystagmus, ataxia, tonic-clonic activity, myoclonic seizure.
9	[Strimel *et al.*, 2010]	2010	Case report	22 years	Not clear	20.4mg/l (Time after ingestion not stated)	Brugada-like ECG pattern, mild ataxia.
10	[Hajiali *et al.*, 2015]	2015	Case report	26 years	40000mg	≈73mg/l (2 days-exact number of hours uncertain)	Headaches, diplopia, sweating, ataxia, nystagmus, tonic-clonic seizures. Tachycardia. Menorrhagia.
11	[Chiew *et al.*, 2013]]	2013	Case series(2)-only 1 report included	18 months (9kg)	100mg(11.1mg/kg)	≈30.3mg/l* (Time after ingestion not stated)	Intermittent jerking, choreo-athetoid movements.

	Authors	Year of publication	Study design/type	Age of patient	Dose of ingested Lamotrigine if stated	Stated Serum Concentration (No of hours after ingestion)	Feature of toxicity included in narrative synthesis
12	[Miller *et al.*, 2008]	2008	Case report	23 years	"All his tablets"	63.9mg/l (Time after ingestion not stated)	Choreiform dyskinesia.
13	[Waring, 2009, Moore *et al.*, 2013]	2009	Case report	42 years	Unknown	30mg/l (1.3 hrs)	Tonic-clonic seizure.
14	[French *et al.*, 2011]	2011	Case report	19 years	4000mg	37.5mg/l (19 hrs)	Generalized tonic-clonic seizure, QRS widening (214ms), complete heart block, death.
15	[Dinnerstein *et al.*, 2007]	2007	Case report	42 years	4100mg	47.4mg/l (Time after ingestion not stated)	Secondarily generalized tonic-clonic seizures.
16	[Algahtani *et al.*, 2014]	2014	Case report	46 years	6000mg	≈ 25.6mg/l* (time after ingestion unclear)	Generalized myoclonus status epilepticus.
17	[Thundiyil *et al.*, 2007]	2007	Case report	19 month old	Unknown	20.3mg/l (1 hrs)	Generalized seizures, sinus tachycardia.
18	[Willis *et al.*, 2007]	2007	Case report	12 day old	Unknown	35mg/l (unclear)	Tonic-clonic seizure.

	Authors	Year of publication	Study design/type	Age of patient	Dose of ingested Lamotrigine if stated	Stated Serum Concentration (No of hours after ingestion)	Feature of toxicity included in narrative synthesis
19	[Nogar et al., 2011]	2011	Case report	48 years	7500mg	74.7mg/l (Time after ingestion not stated)	Tonic-clonic seizures. Wide complex tachycardia, which became pulseless. Death.
20	[Chavez *et al.*, 2015]	2015	Case report	36 years	13500mg	78mg/l (2 hrs)	Tonic-clonic seizures, status *epilepticus.*
21	[Zidd *et al.*, 2004]	2004	Case report	3 years (weight = 15mg)	1150mg (76.7mg/kg)	25.3mg/l (1.3hrs)	Rash, transient (mild) derangement of liver function tests, sedation.
22	[Castanares-Zapatero *et al.*, 2012]	2012	Case report	50 years	3500mg	29.7mg/l (6hrs)	Reduced Glasgow coma score (GCS of 6) Left bundle branch ECG pattern.
23	[Hernandez *et al.*, 2010]	2010	Case report	40 years	6000mg	49.5mg/l (5 days-exact number of hours uncertain)	Agitated delirium, mutism and catatonia.
24	[Hodson *et al.*, 2009]	2009	Case control study (with 18 cases)	Median age 39years (range 19-60years)	Median ingested dose= 750mg (range 200-5600mg)	Not stated	Mean difference in QTc between lamotrigine overdose group and controls was 15.3ms (P=0.137).
	Authors	**Year of publication**	**Study design/type**	**Age of**	**Dose of ingested Lamotrigine if**	**Stated Serum Concentration (No of hours after**	**Feature of toxicity included in narrative synthesis**

				patient	**stated**	**ingestion)**	
25	[Moore *et al.*, 2013]	2013	Case Series (of 9 patients)	Age ranged from 1year to 57years old	Stated amounts ranged from 400mg(≈35mg/kg) to 13500mg	Stated concentrations Include: 26mg/l (3 hrs) 17.8mg/l (6hrs) 18mg/l (8 hrs) 90mg/l (16.7hrs)	Serotonin syndrome, altered mental states, hyperreflexia, myoclonus, prolonged QTc interval, pyrexia.
26	[Mylonakis *et al.*, 1999]	1999	Case report	49 years	2700mg daily for 4 days	Not stated	Facial oedema, maculo-papular rash, leucocytosis, hepatitis and acute renal failure.
	* 1mg/l = 3.9umol/l [Patsalos P, 2014]						

Table 2: Characteristics of included studies

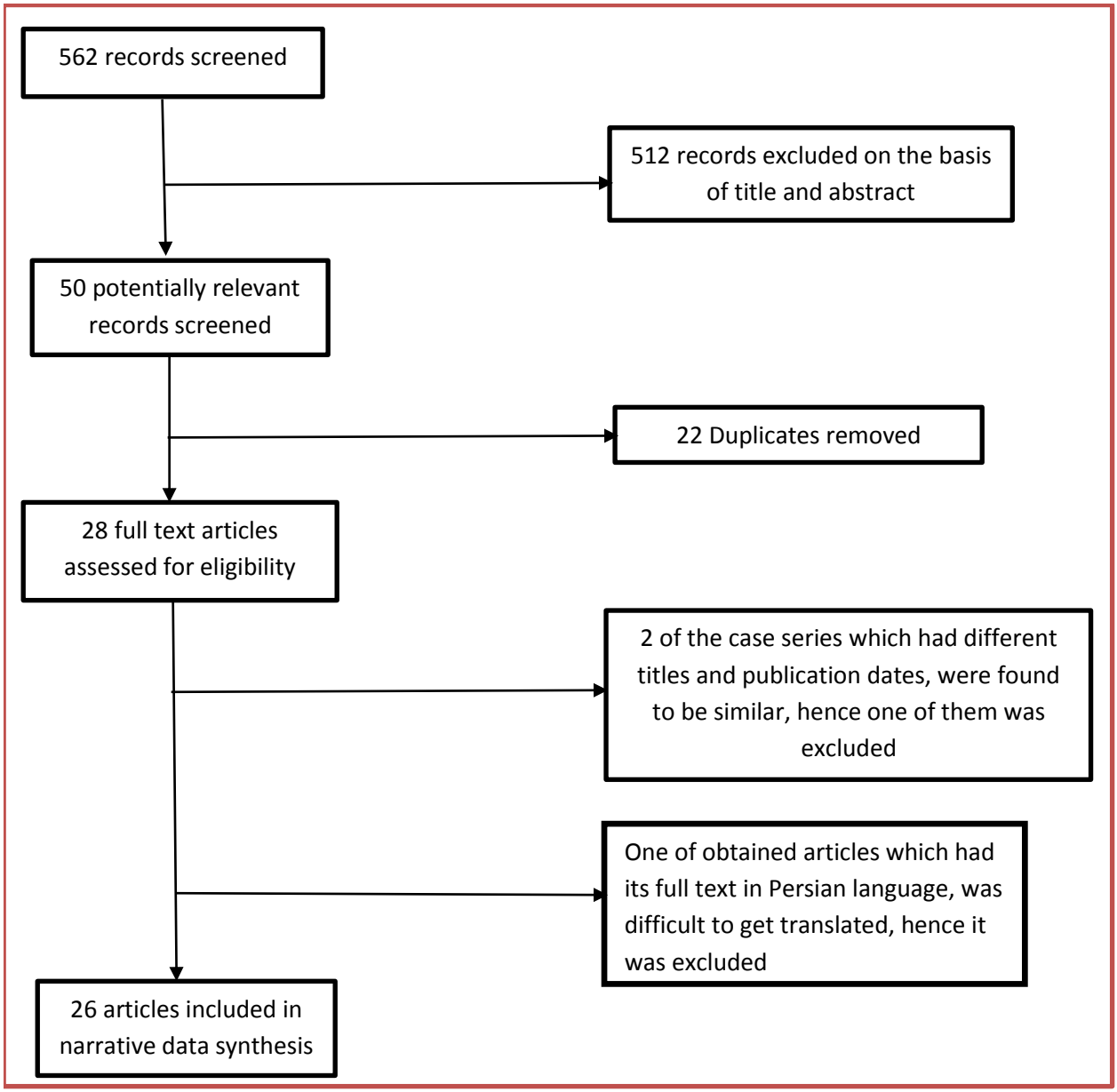

Figure 2: Study selection process

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