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de Oliveira MM, Conti C, Prado GF.

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Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD006685.

DOI: 10.1002/14651858.CD006685.pub4.

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[Intervention Review]

Pharmacological treatment for Kleine-Levin syndrome

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Editorial group: Cochrane Epilepsy Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 5, 2016.

Review content assessed as up-to-date: 7 April 2016.

Citation: de Oliveira MM, Conti C, Prado GF. Pharmacological treatment for Kleine-Levin syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD006685. DOI: 10.1002/14651858.CD006685.pub4.

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ABSTRACT

Background

This is an updated version of the original Cochrane review, published in 2009, Issue 2.

Kleine-Levin syndrome (KLS) is a rare disorder that mainly affects adolescent men. It is characterised by recurrent episodes of hypersomnia, usually accompanied by hyperphagia, cognitive and mood disturbances, abnormal behaviour, such as hypersexuality, and signs of dysautonomia.

In 1990, the diagnostic criteria for Kleine-Levin syndrome were modified in the International Classification of Sleep Disorders, where KLS was defined as a syndrome comprised of recurring episodes of undue sleepiness lasting some days, which may or may not be associated with hyperphagia and abnormal behaviour. According to the International Classification of Sleepiness Disorders, 3rd version (ICSD-3), revised in 2014, the Kleine-Levin syndrome is a disorder characterized by recurrent episodes of hypersomnia that last from two days to four weeks, with at least annual recurrence, and hyperphagia (rapid consumption of a large amount of food), usually with onset in early adolescence in males but occasionally in later life and in women. A monosymptomatic form of the disorder with hypersomnia only can occur without binge eating or hypersexuality.

The cause of Kleine-Levin syndrome remains unknown, and several treatment strategies have been used. Some medications have been reported to provide benefit in the treatment of patients with KLS, but because of the rarity of the condition, no long-term follow-up therapies have yet been described.

Objectives

This review aimed to evaluate:

1. whether pharmacological treatment for Kleine Levin syndrome was effective and safe.
2. which drug or category of drugs was effective and safe.

Search methods

For the latest update, we searched the following sources: the Cochrane Epilepsy Group Specialized Register (7 April 2016); the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online CRSO (7 April 2016); MEDLINE (1946 to April 2016); LILACS (7 April 2016); ClinicalTrials.gov (7 April 2016); WHO International Clinical Trials Registry Platform ICTRP (7 April 2016); reference lists of sleep medicine textbooks; review articles and reference lists of articles identified by the search strategies.

Selection criteria

All randomised controlled trials (RCTs) and quasi-randomised controlled trials looking at pharmacological interventions for Kleine-Levin syndrome were eligible. We had planned to include both parallel-group and cross-over studies.

Data collection and analysis

Two review authors (MMO and CC) had planned to extract the data reported in the original articles.

Main results

No studies met the inclusion criteria for this systematic review.

Authors' conclusions

Therapeutic trials of pharmacological treatment for Kleine-Levin syndrome with a double-blind, placebo-controlled design are needed.

PLAIN LANGUAGE SUMMARY

Pharmacological treatment for Kleine-Levin syndrome

Background

Kleine-Levin syndrome (KLS) is a rare disorder that mainly affects adolescent men. It is characterised by recurrent episodes of hypersomnia (excessive sleepiness), hyperphagia (overeating), and abnormal behaviour. The frequency and nature of the attacks can disrupt the individual's social, professional, and family life. The cause of KLS is not known. Several treatments have been used, including stimulant, anti-epileptic, anti-depressant, and anti-psychotic drugs, with some benefit reported, but because of the rarity of the condition, long-term follow-up of participants is difficult.

Objectives

The authors of this review aimed to identify and evaluate randomised controlled trials (RCTs) studying the effectiveness of pharmacological treatment for Kleine-Levin syndrome.

Results

We were not able to find any RCTs. Good-quality evidence is therefore lacking, and therapeutic trials with a double-blind, placebo-controlled design are needed.

The evidence was current to 7 April 2016.

BACKGROUND

This review is an update of a previously published review in the *Cochrane Database of Systematic Reviews* (2009. Issue 2) on 'Pharmacological treatment for Kleine-Levin syndrome' (Oliveira 2013).

Kleine-Levin syndrome (KLS) is a rare disorder with an estimated prevalence of one to five cases per million population (ISCD-3 2014) that mainly affects adolescent men. It is characterised by recurrent episodes of hypersomnia, usually accompanied by hy-

perphagia, cognitive and mood disturbances, abnormal behaviour, such as hypersexuality, and signs of dysautonomia (ICSD 1990; Kleine 1925; Levin 1936; ISCD-3 2014).

In 1815, Satterley presented the case of a 16-year old male with hypersomnia and hyperphagia following a short period of fever and headache. Kleine-Levin syndrome was first described by Kleine in 1925 (Kleine 1925); this description was elaborated on by Levin in 1936 (Levin 1936), but it was not named Kleine-Levin syndrome until 1942, by Crichtley and Hoffman (Crichtley 1942). Kleine-Levin syndrome was further defined by Crichtley in 1962

(Critchley 1962), and by Schmidt in 1990, who established the following diagnostic criteria:

- Predominance in adolescent males;
- Onset in adolescence;
- Periodic hypersomnia;
- Hyper/mega/polyphagia;
- Association with behavioural and psychological changes;
- Benign clinical course with spontaneous disappearance of clinical symptoms;
- Lack of other neurological or psychiatric disease.

In 1990, the diagnostic criteria for KLS were modified in the International Classification of Sleep Disorders, where it was defined as a syndrome comprised of recurring episodes of undue sleepiness lasting some days, which may, or may not, be associated with hyperphagia and abnormal behaviour (ICSD 1990). According to the International Classification of Sleepiness Disorders, 3rd version (ICSD-3), revised in 2014, Kleine-Levin syndrome is a rare sleep disorder characterized by recurrent episodes of severe hypersomnia associated with cognitive and behavioral disturbances such as confusion, derealization, apathy, compulsive eating, and hypersexuality. Episodes last a few days to several weeks and are separated by weeks or months of normal sleep and behavior. KLS is categorized as a central disorder of hypersomnolence (ICSD-3 2014).

The cause of KLS remains unknown, although numerous atypical or incomplete causes have been hypothesised:

- Diencephalic-hypothalamic dysfunction, reported with hypothalamic and third ventricle tumours, has similar symptoms, suggesting hypothalamic or circadian dysfunction as a cause (Fulton 1929; Haugh 1983).
- Abnormalities in serotonin and dopamine metabolism have been reported, suggesting a neurotransmitter imbalance in the serotonergic or dopaminergic pathway (Chesson 1991; Koerber 1984).
- Inflammatory lesions in the thalamus, diencephalon and midbrain have been described in postmortem neuropathological case reports, suggesting a viral infection (Fenzi 1993; Merriam 1986; Salter 1993).
- Stress status, sleep deprivation, and alcohol abuse have also been suggested as triggers of KLS (Russel 1992).
- A genetic basis for the disorder has been suggested by the preponderance of cases in the Ashkenazi Jewish population, suggesting a founder effect, as well as numerous reports of

familial cases. To date, however, no specific genes have been identified (ICSD-3 2014).

Because of the frequency and the nature of the attacks a person can suffer with KLS, individuals often experience disruption to their social, family, and professional life.

Several treatment strategies have been used:

- Stimulant drugs (methylphenidate, modafinil, pemoline-piracetam-meclofenoxate, D-amphetamine, ephedrine, meta-amphetamine, amphetamine, etc.);
- Anti-epileptic drugs (valproic acid, carbamazepine, amobarbital, phenobarbital, phenytoin, etc.);
- Anti-depressants (imipramine, monoamine oxidase inhibitors (MAOIs), moclobemide, clomipramine, amineptine, fluoxetine, fluvoxamine, sertraline, methysergide, trazodone, etc.);
- Anti-psychotic drugs (haloperidol, chlorpromazine, levomepromazine, trifluoperazine, thioridazine, clozapine, risperidone, etc.);
- Anti-virals (acyclovir);
- Lithium;
- Hydrocortisone;
- Melatonin;
- Benzodiazepines;
- Levodopa-benserazide.

These medications have been reported to provide some benefit in the treatment of patients with KLS, but because of the rarity of the condition, no long-term follow-up therapies have yet been described.

OBJECTIVES

This review aimed to evaluate:

- (1) whether pharmacological treatment for Kleine-Levin syndrome was effective and safe;
- (2) which drug or category of drugs was effective and safe.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of pharmacological treatment for Kleine-Levin syndrome. We also had planned to include quasi-randomised controlled trials (using inadequate allocation assignment such as date of birth, day of the week or month of the year, medical record number or alternate allocation). We had planned to include both parallel-group and cross-over studies.

Types of participants

Inclusion criteria

We considered children and adults who met the established clinical criteria for KLS (Critchley 1962; ICSD 1990):

ICSD 1990:

- Recurring episodes of undue sleepiness lasting some days;
- Hyperphagia (not obligatory);
- Abnormal behaviour (not obligatory).

Critchley 1962:

- Predominance in adolescent males;
- Onset in adolescence;
- Periodic hypersomnia;
- Hyper/mega/polyphagia;
- Associated behavioural and psychological changes;
- Benign clinical course with spontaneous disappearance of clinical symptoms;
- Lack of other neurological or psychiatric disease.

Exclusion criteria

We excluded studies that predominantly recruited participants with narcolepsy, obstructive sleep apnoea, schizophrenia, bipolar affective disorder, obsessive-compulsive disorder, frontal brain tumour, third ventricle tumour, drug or alcohol abuse, encephalopathies, bulimia, atypical depressive disease, and delayed sleep maturation.

Types of interventions

We included all drugs used for the treatment of KLS.

Pharmacological interventions

- Stimulant drugs (methylphenidate, modafinil, pemoline-piracetam-meclofenoxate, D-amphetamine, ephedrine, meta-amphetamine, amphetamine, etc.);
- Anti-epileptic drugs (valproic acid, carbamazepine, amobarbital, phenobarbital, phenytoin, etc.);
- Anti-depressants (imipramine, MAOIs, moclobemide, clomipramine, amineptine, fluoxetine, fluvoxamine, sertraline, methylsergide, trazodone, etc.);

- Anti-psychotic drugs (haloperidol, chlorpromazine, levomepromazine, trifluoperazine, thioridazine, clozapine, risperidone, etc.);
- Anti-viral (acyclovir);
- Lithium;
- Hydrocortisone;
- Melatonin;
- Benzodiazepines;
- Levodopa-benserazide.

Comparison groups

- Placebo;
- No intervention;
- Other drug treatments.

Types of outcome measures

Primary outcomes

- Relief of KLS symptoms (hypersomnia, hyperphagia, abnormal behaviour) as measured by any objective or subjective validated scale.

Secondary outcomes

- Subjective sleep quality (any description of sleep quality; Epworth scale).
- Sleep quality, as measured by night polysomnography (measured by sleep efficiency, total sleep time, arousal index).
- Quality of life, as measured by a validated scale such as Short-Form Health Survey (SF-36), or a visual analogue scale.
- Adverse events associated with treatments (to be described in terms of (i) numbers of participants withdrawing because of adverse events; and (ii) numbers of participants describing any side effect associated with the interventions).

Search methods for identification of studies

The search strategies used for the original version of this review are recorded in [Appendix 1](#). For the most recent update of this review, we searched the following databases:

- The Cochrane Epilepsy Group Specialized Register (7 April 2016), using the search strategy set out in [Appendix 2](#);
- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online CRSO (7 April 2016), using the search strategy set out in [Appendix 3](#);
- MEDLINE (Ovid, 1946 to 7 April 2016), using the search strategy outlined in [Appendix 4](#);
- LILACS (The Latin American and Caribbean Literature on Health Sciences Database; 7 April 2016), using the search strategy outlined in [Appendix 5](#);

- [ClinicalTrials.gov](#) (7 April 2016), using the search term: “Kleine-Levin” OR “Kleine Levin”;
- [WHO International Clinical Trials Registry Platform ICTRP](#) (7 April 2016), using the search term: Kleine-Levin OR Kleine Levin in the Condition.

Previously, we searched SCOPUS as an alternative to EMBASE, using the search strategy outlined in [Appendix 6](#), but this is no longer necessary, because randomised and quasi-randomised controlled trials in EMBASE are now included in CENTRAL. We also searched the reference lists of sleep medicine textbooks, review articles, and the reference lists of articles identified by the search strategies described here.

Data collection and analysis

Selection of studies

Two review authors (MMO and CC) undertook the review. We used the broad search strategy already described to obtain the titles and abstracts of studies pertaining to KLS of any cause. The same two review authors independently screened the titles and abstracts, and discarded studies that were not applicable; however, they initially retained studies and reviews that might have included relevant data or information on trials. The same two review authors independently assessed the retrieved abstracts, and if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

We found no studies that met the eligibility criteria for inclusion. If studies that meet the inclusion criteria are identified for future updates of this review, we will apply the following methodology.

Data extraction and management

The same two review authors will independently carry out data extraction using standard data extraction forms, and then independently enter the data into the Review Manager software ([RevMan 2012](#)). We will translate studies reported in non-English language journals before assessment. When more than one publication of a trial exists, we will group the articles, and for each available outcome, we will extract results from the publication with the most complete data. We will request any further information required from the original author by written correspondence, and will include any relevant information obtained in this manner in the review. We will resolve disagreements in consultation with a third review when necessary.

Assessment of risk of bias in included studies

The two review authors will independently assess the risk of bias of the studies to be included, without blinding to authorship or

journal, using the new Cochrane ‘Risk of bias’ tool ([Higgins 2011](#)). We will resolve discrepancies by discussion with GFP. ‘Risk of bias’ factors to be assessed include: randomisation, allocation concealment, blinding of investigators, participants and outcomes assessors, completeness of follow-up, selective reporting,

Measures of treatment effect

Dichotomous outcomes

For dichotomous outcomes (such as frequency of adverse reactions requiring withdrawal), we will express results as relative risk (RR) with 95% confidence interval (CI). We will pool data using the random-effects model but will also analyse the fixed-effect model to ensure the robustness of the model chosen and susceptibility to outliers.

Continuous outcomes

When continuous scales of measurement are used to assess the effects of treatment (such as various of KLS symptoms or effects on quality of life), we will use the mean difference (MD), or the standardised mean difference (SMD) if different scales have been used.

Dealing with missing data

If possible, we will perform all analyses according to the intention-to-treat method, using the last reported observed response (‘carry forward’) and including all participants regardless of compliance or follow-up.

Assessment of heterogeneity

We will analyse heterogeneity using the Q statistic, a Chi² test on N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance. We will also quantify inconsistency with the I² statistic, calculated by $[(Q - df)/Q \times 100\%]$, which describes the percentage of variability in effect estimates caused by heterogeneity rather than by sampling error. A value greater than 50% will be considered to signify substantial heterogeneity ([Higgins 2011](#)). When sufficient data are available, we will pool study findings according to subcategory to explore possible sources of heterogeneity. We will divide the studies according to the following:

- Age of participants;
- Severity of the disorder;
- Type of medication given;
- Methodological quality of the study (allocation concealment, blinding, intention-to-treat analysis).

Sensitivity analysis

We will perform 'a worst case scenario' analysis and will consider participants with missing data as treatment failures.

RESULTS

Description of studies

We initially identified 257 studies using the search strategy.

(1) Excluded studies

The search identified 36 potentially eligible studies from the sources previously described. Of these, none were ultimately included in the review. All 36 studies were excluded because of study design: all were case reports or reviews. See the table of 'Characteristics of excluded studies' for details.

(2) Ongoing studies

The review authors know of no ongoing studies.

(3) Included studies

No studies met the eligibility criteria for inclusion.

Risk of bias in included studies

No studies met the eligibility criteria for inclusion.

Effects of interventions

No studies met the eligibility criteria for inclusion.

DISCUSSION

We found no randomised, placebo-controlled trials of pharmacological treatments for KLS, and no studies could be included in this review. Kleine-Levin syndrome has a benign clinical course with spontaneous disappearance of symptoms; the findings of case reports excluded from this review were unpredictable. However,

some case reports have described improvement in specific symptoms of KLS as follows:

- Stimulant drugs, especially amphetamines, significantly improved sleepiness but did not improve other symptoms (Gallinek 1962).
- Anti-depressant drugs had no effect on preventing relapse, except in one case, in which a monoamine oxidase inhibitor (moclobemide) was used (Chaudhry 1992).
- Anti-epileptic drugs showed, in a single case, improvement in abnormal behaviour when carbamazepine was used (Mukaddes 1999).
- Lithium significantly improved abnormal behaviour and recovery of symptoms (reducing the duration of episodes and decreasing relapses) (Keller 1977; Poppe 2003; Smolik 1988).

Unfortunately, no evidence was available to support the use of these therapies.

It is important to remember that the frequent occurrence of attacks and of severe behavioural disorders incapacitates patients with KLS both professionally and socially. We believe that double-blind, placebo-controlled therapeutical trials of drugs that can prevent or improve all symptoms of KLS are warranted, and that because of the rarity of the condition, these trials should have a multicentre design.

AUTHORS' CONCLUSIONS

Implications for practice

No evidence indicated that pharmacological treatment for Kleine-Levin syndrome was effective and safe.

Implications for research

Therapeutic, double-blind, placebo-controlled drug trials for Kleine-Levin syndrome are needed that use a robust methodology, and in the light of the rarity of this condition, a multicentre design.

ACKNOWLEDGEMENTS

We would like to acknowledge Humberto Saconato who was on the review author team for the original protocol and review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Billiard 1998	Review.
Billiard 2001	Review.
Brouns SH 2012	Case report
Chaudhry 1992	Case report.
Chiles 1976	Case report.
Crumley 1997	Case report.
Crumley 1998	Case report.
Duffy 1968	Case report.
El Otmani H 2013	Case Report
Gallinek 1962	Case report.
Goldberg 1983	Case report.
Hart 1985	Case report.
Kapson B 2014	Case Report
Kellet 1977	Case report.
Kornreich 2000	Case report.
Lenz 1980	Case report.
Mapari 2005	Case report.
Masi 2000	Case report.
Minvielle 2000	Case report.
Mukaddes 1999	Case report.
Muratori 2002	Case report.

(Continued)

Pike 1994	Case report.
Poppe 2003	Case report and review.
Reimao 1998	Case report.
Rezvanian E 2013	Case Report
Roth 1980	Case report.
Savet 1986	Case report.
Smolik 1986	Case report and review.
Smolik 1988	Case report.
Suzuki 1998	Review.
Vlach 1962	Case report.
Wenzel 1976	Case report.
Will 1988	Case report.
Wurthmann 1989	Case report.
Yassa 1978	Case report.
Y. Imaz S 2015	Case report

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Search strategies for original version of this review

We searched the Cochrane Epilepsy Group Specialized Register (1 December 2007) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2007) using the following terms

:#1 KLEINE-LEVIN SYNDROME

#2 (Kleine-Levin* next syndrome*)

#3 (periodic next hypersomnia next sleep*)

#4 (compulsive next eating*)

#5 (hyperphagia or megaphagia or polyphagia*)

#6 (hypersexuality)

#7 (KLS)

#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7)

We also searched the following electronic databases.

- MEDLINE (1966 to December 2007) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of randomized controlled trials (Dickersin 1994).

- EMBASE (1980 to December 2007) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of randomized controlled clinical trials (Lefebvre 1996).

- LILACS (1982 to December 2007) using a search strategy adapted for the identification of randomized controlled clinical trials.

MEDLINE search strategy (1966 to December 2007)

((kleine[All Fields] AND levin[All Fields]) OR ("kleine-levin syndrome"[MeSH Terms] OR kleine levin syndrome[Text Word])) AND (megaphagia[All Fields] OR ("disorders of excessive somnolence"[TIAB] NOT Medline[SB]) OR "disorders of excessive somnolence"[MeSH Terms] OR hypersomnia[Text Word]) OR hypersexuality[All Fields] OR ("hyperphagia"[MeSH Terms] OR hyperphagia[Text Word]))

EMBASE search strategy (1980 to December 2007)

'kleine levin' AND ('syndrome'/exp OR 'syndrome') AND 'kleine levin' AND ('hyperphagia'/exp OR 'hyperphagia') AND megaphagia AND ('polyphagia'/exp OR 'polyphagia') AND ('hypersomnia'/exp OR 'hypersomnia') AND periodic AND ('hypersomnia'/exp OR 'hypersomnia') AND ('hypersexuality'/exp OR 'hypersexuality') AND kls

LILACS search strategy (1982 to December 2007)

"síndrome de KLEINE-levin" or (tw kleine and tw levin) [Descriptor de assunto]

Appendix 2. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Kleine-Levin Syndrome Explode All
#2 Kleine-Levin* next syndrome*
#3 periodic next hypersomnia next sleep*
#4 compulsive next eating*
#5 hyperphagia or megaphagia or polyphagia*
#6 hypersexuality
#7 KLS
#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7) AND INREGISTER AND >02/05/2013:CRSCREATED

Appendix 3. CENTRAL via CRSO search strategy

#1 MESH DESCRIPTOR Kleine-Levin Syndrome EXPLODE ALL TREES
#2 (Kleine AND Levin):TI,AB,KY
#3 #1 OR #2
#4 31/05/2013 TO 31/07/2015:DL
#5 #3 AND #4

Appendix 4. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in [Lefebvre 2011](#).

1. exp Kleine-Levin Syndrome/
2. (Kleine and Levin).tw.
3. 1 or 2
4. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.
5. clinical trials as topic.sh.
6. trial.ti.
7. 4 or 5 or 6
8. exp animals/ not humans.sh.
9. 7 not 8
10. 3 and 9
11. limit 10 to ed=20130502-20150707

Appendix 5. LILACS search strategy

(tw:(“kleine levin”)) OR (mh:(“kleine-levin syndrome”)) AND (instance:“regional”) AND (type of study:(“case control” OR “cohort”))

Appendix 6. SCOPUS search strategy

(TITLE(“Kleine-Levin”) OR ABS(“Kleine-Levin”)) AND (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR “parallel group” OR crossover OR “cross over” OR cluster OR “head to head”) PRE/2 (trial OR method OR procedure OR study)) OR ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR “parallel group” OR crossover OR “cross over” OR cluster OR “head to head”) PRE/2 (trial OR method OR procedure OR study)))

WHAT'S NEW

Last assessed as up-to-date: 7 April 2016.

Date	Event	Description
7 April 2016	New search has been performed	Searches updated 7 April 2016.
7 April 2016	New citation required but conclusions have not changed	No new studies identified; conclusions are unchanged.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2009

Date	Event	Description
7 May 2013	New citation required but conclusions have not changed	Conclusions unchanged.
2 May 2013	New search has been performed	Searches updated; no new studies identified.
13 March 2012	New search has been performed	Searches updated 24 October 2011; no new studies identified.
5 March 2010	New search has been performed	Searches updated 5 March 2010; no new trials identified.
19 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Marcio M de Oliveira: protocol development, literature searching, study selection, data extraction, statistical analysis, drafting of written submissions, development of final review.

Cristiane Conti: protocol development, literature searching, study selection, data extraction, statistical analysis, development of final review.

Gilmar F Prado: protocol development, literature searching, study selection, data extraction, statistical analysis, development of final review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK, UK.

This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

INDEX TERMS

Medical Subject Headings (MeSH)

Kleine-Levin Syndrome [*drug therapy]; Rare Diseases [*drug therapy]

MeSH check words

Humans