Pharmacological treatment for Kleine-Levin Syndrome (Review)

Oliveira MM, Conti C, Saconato H, Prado GF

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Pharmacological treatment for Kleine-Levin Syndrome

Marcio M Oliveira¹, Cristiane Conti², Humberto Saconato³, Gilmar F Prado⁴

¹UNIFESP, São Paulo, Brazil. ²Universidade Federal de São Paulo, São Paulo, Brazil. ³Department of Medicine, Santa Casa de Campo Mourão, Campo Mourão, Brazil. ⁴Department of Neurology, Federal University of São Paulo, São Paulo - SP, Brazil

Contact address: Marcio M de Oliveira, Universidade Federal de São Paulo, São Paulo, 04039-001, Brazil. docmmo@uol.com.br

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ABSTRACT

Background

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

Kleine-Levin Syndrome (KLS) is a rare disorder which mainly affects adolescent men. It is characterized by recurrent episodes of hypersomnia, usually accompanied by hyperphagia, cognitive and mood disturbances, abnormal behavior 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 it was defined as a syndrome composed of recurring episodes of undue sleepiness lasting some days, which may or may not be associated with hyperphagia and abnormal behavior.

The etiology of Kleine-Levin Syndrome remains unknown and several treatment strategies have been used. Some medications have been reported to provide some benefit for the treatment of Kleine-Levin Syndrome patients, 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 is effective and safe; and
2. which drug or category of drugs is effective and safe.

Search methods

We obtained relevant trials from the following sources: the Cochrane Epilepsy Group Specialized Register (24 October 2011); the Cochrane Central Register of Controlled Trials (CENTRAL Issue 4 of 4, The Cochrane Library 2011); MEDLINE (1948 to October week 2, 2011); LILACS (24 October 2011); reference lists of sleep medicine textbooks; review articles and reference lists of articles identified by the search strategies.

Selection criteria

All randomized controlled trials (RCTs) and quasi-randomized controlled trials looking at pharmacological interventions for Kleine-Levin Syndrome. We included both parallel group and cross-over studies.
Data collection and analysis

Two review authors (MO and CC) extracted 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

Kleine-Levin Syndrome (KLS) is a rare disorder which mainly affects adolescent men. It is characterized by recurrent episodes of hypersomnia (excessive sleepiness), hyperphagia (over eating) and abnormal behavior. The frequency and nature of the attacks can disrupt the individual's social, professional and family life. The cause of Kleine-Levin Syndrome is not known. Several treatments have been used, including stimulant, antiepileptic, antidepressant and antipsychotic drugs, with some benefit reported, but due to the rarity of the condition, long-term follow up of patients is difficult.

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

Background

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 2, 2009) on 'Pharmacological treatment for Kleine-Levin Syndrome'.

Kleine-Levin Syndrome (KLS) is a rare disorder which mainly affects adolescent men. It is characterized by recurrent episodes of hypersomnia, usually accompanied by hyperphagia, cognitive and mood disturbances, abnormal behavior such as hypersexuality, and signs of dysautonomia (ICSD 1990; Kleine 1925; Levin 1936).

In 1815 Satterley presented the case of a 16-year old male with hypersomnia and hyperphagia after a short period of fever and headache. Kleine-Levin Syndrome was first described by Kleine in 1925 (Kleine 1925) and elaborated on by Levin in 1936 (Levin 1936), but it was only named Kleine-Levin Syndrome in 1942 by Crichtley and Hoffman (Crichtley 1942). Kleine-Levin Syndrome was further defined by Crichtley in 1962 (Crichtley 1962) and Schmidt in 1990, who established the following diagnostic criteria:

- predominance in adolescent males;
- onset in adolescence;
- periodic hypersomnia;
- hyper/mega/polyphagia;
- associated behavioral 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 Kleine-Levin Syndrome were modified in the International Classification of Sleep Disorders, where it was defined as a syndrome composed of recurring episodes of undue sleepiness lasting some days, which may or may not be associated with hyperphagia and abnormal behavior (ICSD 1990).

The etiology of Kleine-Levin Syndrome remains unknown. Numerous atypical or incomplete causes have been hypothesized.

- Diencephalic-hypothalamic dysfunction, reported with hypothalamic and third ventricle tumors, 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 neuropathologic 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 Kleine-Levin Syndrome (Russel 1992).

Due to the frequency and nature of the attacks a person can suffer with Kleine-Levin Syndrome, the individual can 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.);
- antiepileptic drugs (valproic acid, carbamazepine, amobarbital, phenobarbital, phenytoin, etc.);
- antidepressants (imipramine, MAOI, moclobemide, clomipramine, amineptine, fluoxetine, fluvoxamine, sertraline, methylsergide, trazodone, etc.);
- antipsychotic drugs (haloperidol, chlorpromazine, levomepromazine, trifluoperazine, thioridazine, clozapine, risperidone, etc.);
- antivirals (acyclovir);
- lithium;
- hydrocortisone;
- melatonin;
- benzodiaepines;
- levodopa-benserazide.

These medications have been reported to provide some benefit in the treatment of Kleine-Levin Syndrome patients, 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 is effective and safe; and 2) which drug or category of drugs is effective and safe.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomized controlled trials (RCTs) of pharmacological treatment for Kleine-Levin Syndrome. We also planned to include quasi-randomized 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 included both parallel group and cross-over studies.

**Types of participants**

**Inclusion criteria**

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

1. Recurring episodes of undue sleepiness lasting some days.
2. Hyperphagia (not obligatory).
3. Abnormal behavior (not obligatory).
4. Periodic hypersomnia.
5. Associated behavioral and psychological changes.
7. Lack of other neurological or psychiatric disease.

**Exclusion criteria**

We excluded studies predominantly recruiting subjects with narcolepsy, obstructive sleep apnea, schizophrenia, bipolar affective disorder, obsessive-compulsive disorder, frontal brain tumor, third ventricle tumor, drug/alcohol abuse, encephalopathies, bulimia, atypical depression disease and delayed sleep maturation.

**Types of interventions**

We included all drugs used for the treatment of Kleine-Levin Syndrome.
Pharmacological interventions

- Stimulant drugs (methylphenidate, modafinil, pemoline-
-piracetam-meclofenoxate, D-amphetamine, ephedrine, meta-
amphetamine, amphetamine, etc.)
- Antiepileptic drugs (valproic acid, carbamazepine, amobarbital, phenobarbital, phenytoin, etc.)
- Antidepressants (imipramine, MAOI, moclobemide, clomipramine, amineptine, fluoxetine, fluvoxamine, sertraline, methylsergide, trazodone, etc.)
- Antipsychotic drugs (haloperidol, chlorpromazine, levomepromazine, trifluoperazine, thioridazine, clozapine, risperidone, etc.)
- Antiviral (acyclovir)
- Lithium
- Hydrocortisone
- Melatonin
- Benzodiazepines
- Levodopa-benserazide

Comparison groups

- Placebo
- No intervention
- Other drug treatments

Types of outcome measures

Primary outcomes
Relief of Kleine-Levin Syndrome symptoms (hypersomnia, hyperphagia, abnormal behavior) measured by any objective or subjective validated scale.

Secondary outcomes
1. Subjective sleep quality (any description of sleep quality; Epworth scale).
2. Sleep quality measured by night polysomnography (measured by sleep efficiency, total sleep time, arousal index).
3. Quality of life measured by a validated scale such as SF-36; visual analogue scale.
4. Adverse events associated with the treatments (to be described in terms of the (i) numbers withdrawing due to adverse events; and (ii) numbers of patients relating any side effect associated with the interventions).

Search methods for identification of studies
The search strategies for the original version of this review are recorded in Appendix 1. For the most recent update of this review we searched the Cochrane Epilepsy Group Specialized Register (24 October 2011). We also searched the following databases:
2. MEDLINE (Ovid, 1948 to October week 2, 2011) using the search strategy outlined in Appendix 3.
3. LILACS (The Latin American and Caribbean Literature on Health Sciences Database) (24 October 2011) using the search strategy outlined in Appendix 4.

We also searched the reference lists of sleep medicine textbooks, review articles and the reference lists of articles identified by the above search strategies.

Data collection and analysis

Selection of studies
Two review authors (MO and CC) undertook the review. We used the broad search strategy described above to obtain the titles and abstracts of studies pertaining to Kleine-Levin Syndrome of any cause. MO and CC 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 did not find any studies which met the eligibility criteria for inclusion. If studies which meet the inclusion criteria are identified for future updates of this review, we will apply the following criteria:

The same two authors will independently carry out data extraction using standard data extraction forms. The two review authors will then independently enter the data into the Review Manager software (RevMan 2008). We will translate studies reported in non-English language journals before assessment. Where more than one publication of a trial exists, we will group the papers together 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 author (GP).

Study quality
MO and CC will independently assess the quality of studies to be included, without blinding to authorship or journal, using the checklist developed by the Cochrane Epilepsy Group. We will resolve discrepancies by discussion with GP. The quality items to
be assessed are allocation concealment, intention-to-treat analysis, completeness of follow up and blinding of investigators, participants and outcome assessors.

**Quality checklist**

1. **Allocation concealment**
   - 'A' adequate - randomization method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
   - 'B' unclear - randomization stated but no information on method used is available.
   - 'C' inadequate - method of randomization such as alternate medical record numbers or unsealed envelopes used; any information in the study that indicated that investigators or participants could influence intervention group.

2. **Blinding**
   - Blinding of investigators: yes/no/not stated.
   - Blinding of participants: yes/no/not stated.
   - Blinding of outcome assessor: yes/no/not stated.
   - Blinding of data analysis: yes/no/not stated.

3. **Intention-to-treat analysis**
   - Yes - specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
   - Yes - not specifically stated but confirmed upon study assessment.
   - No - not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomized were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
   - No - stated but not confirmed upon study assessment.
   - Not stated.

4. **Completeness of follow up**
   - Percentage of participants lost to follow up.

**Dichotomous outcomes**

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

**Continuous outcomes**

Where continuous scales of measurement are used to assess the effects of treatment (such as the various of Kleine-Levin symptoms or quality of life), we will use the weighted mean difference (WMD), or the standardized mean difference (SMD) if different scales have been used.

**Heterogeneity analysis**

We will analyze 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 (Higgins 2003), calculated by [Q - df)/Q x 100%], which describes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error. A value greater than 50% will be considered substantial heterogeneity. Where sufficient data are available, we will pool the studies according to subcategory to explore possible sources of heterogeneity. We will divide the studies according to:
1. age;
2. severity;
3. type of medication;
4. methodological quality (allocation concealment, blinding, intention-to-treat analysis).

**R E S U L T S**

**Description of studies**

See: Characteristics of excluded studies.

1. **Excluded studies**

The search identified 31 potentially eligible studies from the sources described above. Of these, none were ultimately included in the review. All 31 studies were excluded due to 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
Two hundred and fifty-seven studies were initially identified using the search strategy. Out of this total only 31 had the potential to be included, however after further examination all these studies had to be excluded as they did not meet the eligibility criteria for inclusion. Only case reports and reviews were found.

DISCUSSION
We found no randomized, placebo-controlled trials of pharmacological treatments for Kleine-Levin Syndrome and no studies could be included in this review. Kleine-Levin Syndrome has a benign clinical course, with spontaneous disappearance of symptoms, and the findings of case reports excluded from this review were unpredictable. However, some case reports have shown improvement of specific symptoms of Kleine-Levin Syndrome as follows.

- Stimulant drugs, especially amphetamines, significantly improved sleepiness but did not improve the other symptoms (Gallinek 1962).

- Antidepressant drugs had no effect on preventing relapses, except for one case using a monoamine oxidase inhibitor (moclobemide) (Chaudhry 1992).

- Antiepileptic drugs showed, in a single case, an improvement in abnormal behavior using carbamazepine (Mukaddes 1999).

- Lithium had significantly improved abnormal behavior and recovery of symptoms (reducing the duration of episodes and decreasing relapses) (Kellet 1977; Poppe 2003; Smolik 1988).

Unfortunately, there is no evidence to support the use of these therapies.

It is important to remember that the frequent occurrence of attacks and severe behavioral disorders incapacitate Kleine-Levin Syndrome patients professionally and socially. We believe that double-blind, placebo-controlled therapeutical trials of drugs able to prevent or to improve all the symptoms of Kleine-Levin Syndrome are warranted, and that because of the rarity of the condition these trials should have a multicenter design.

AUTHORS’ CONCLUSIONS

Implications for practice
There is no evidence that pharmacological treatment for Kleine-Levin Syndrome is effective and safe.

Implications for research
Therapeutic, double-blind, placebo-controlled drug trials for Kleine-Levin Syndrome are needed, with a robust methodology and, in the light of the rarity of the condition, a multicenter design.

REFERENCES

References to studies excluded from this review

Billiard 1998 (published data only)

Billiard 2001 (published data only)

Chaudhry 1992 (published data only)

Chiles 1976 (published data only)

Crumley 1997 (published data only)

Crumley 1998 (published data only)


Additional references

Critchley 1942

Critchley 1962

Dickerson 1994

Fenzi 1993

Fulton 1929

Haugh 1983

Higgins 2003

ICSD 1990

Kleine 1925

Koerber 1984

Lefebvre 1996

Lefebvre 2009

Levin 1936

Merriam 1986

RevMan 2008

Russel 1992

Salter 1993

* Indicates the major publication for the study
# Characteristics of Studies

## Characteristics of excluded studies  
*ordered by study ID*

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DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. 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 KLINE-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)


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)

“sindrome de KLEINE-levin” or (tw kleine and tw levin) [Descritor de assunto]
Appendix 2. CENTRAL search strategy

#1 MeSH descriptor Kleine-Levin Syndrome explode all trees
#2 (Kleine-Levin)
#3 (periodic hypersomnia)
#4 MeSH descriptor Disorders of Excessive Somnolence explode all trees
#5 MeSH descriptor Hyperphagia, this term only
#6 (compulsive eating)
#7 (hyperphagia) or (megaphagia) or (polyphagia)
#8 (hypersexuality)
#9 (KLS)
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2009.
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Kleine-Levin Syndrome/
13. megaphagia.tw.
14. “Disorders of Excessive Somnolence”/
15. hypersonnia.tw.
16. hypersexuality.tw.
17. “Hyperphagia”
18. hyperphagia.tw.
19. KLS.tw.
20. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 10 and 20

Appendix 4. LILACS search strategy

Kleine-Levin [Words] or (kleine-levin syndrome) [Subject descriptor]
WHAT’S NEW

Last assessed as up-to-date: 24 October 2011.

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HISTORY

Review first published: Issue 2, 2009

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CONTRIBUTIONS OF AUTHORS

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

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

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

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

DECLARATIONS OF INTEREST

None known.
INDEX TERMS
Medical Subject Headings (MeSH)
Kleine-Levin Syndrome ["drug therapy"]

MeSH check words
Humans