



A systematic review and meta-analysis assessing safety and tolerability of nicergoline

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID: | bmjopen-2014-005090 |
| Article Type: | Research |
| Date Submitted by the Author: | 20-Feb-2014 |
| Complete List of Authors: | Fioravanti, Mario; University Hospital, Umberto I, Clinical Psychology Nakashima, Taku; Hiroshima University Hospital, Dept. of Molecular & Internal Medicine Xu, Jun; Jiangsu Province Geriatric Hospital, Geriatrics Garg, Amit; Physician |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Evidence based practice, Mental health |
| Keywords: | Meta-analysis, Nicergoline, ergot derivatives, fibrosis, ergotism |
| | |

SCHOLARONE™
Manuscripts

Peer Review Only

1
2
3
4 Title of the article:
5

6
7 **A systematic review and meta-analysis assessing safety and tolerability of nicergoline**
8
9

10 Corresponding author:
11

12 Dr. Amit Garg, M.D.

13 Physician
14

15 A Wing- 304, Aparna Towers
16

17 Kondapur, Kothaguda,
18

19 Hyderabad-500084
20

21 Email: amitgarg.pharm@gmail.com
22

23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Tele: +918790902800

30 Authors:
31

32
33 Mario Fioravanti¹, Taku Nakashima², Jun Xu³, Amit Garg⁴
34
35

36 Affiliations:
37

38
39 1. Prof. Mario Fioravanti, M.D.
40

41 Director of the Clinical Psychology Service
42

43 University Hospital, Umberto I
44

45 Professor of Clinical Psychology
46

47 Department of Neurology and Psychiatry
48

49 University of Rome, Sapienza, Italy
50

51 E-mail: mario.fioravanti@uniroma1.it
52
53
54

55 2. Taku Nakashima, MD, PhD.
56

57 Dept. of Molecular & Internal Medicine,
58
59
60

1
2
3 Hiroshima University Hospital

4
5 1-2-3 Kasumi, Minami-ku Hiroshima, 734-8551 Japan

6
7 E-mail: tnaka@hiroshima-u.ac.jp/tnaka@eos.ocn.ne.jp

8
9
10 3. Prof. Jun Xu

11 Hospital: Jiangsu Province Geriatric Hospital, China

12
13 Email: 13611572068@126.com ; neurojun@126.com

14
15
16 4. Dr. Amit Garg, M.D.

17 Physician, A-Wing- 304, Aparna Towers

18
19 Kondapur, Kothaguda, Hyderabad-500084. India

20
21 Email: amitgarg.pharm@gmail.com

22
23
24
25
26
27
28
29 Keywords:

30
31
32 Meta-analysis, nicergoline, ergot derivatives, fibrosis, ergotism

33
34
35 Word Count:

36
37 2649 words

Abstract

Objective: To evaluate the safety profile of nicergoline compared to placebo and other active agents from published randomised controlled trials.

Design: Systematic review and meta-analysis of nicergoline compared to placebo and other active agents across various indications.

Data sources: Medline, Medline-in-process, Cochrane, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register (CMR) for all the randomized controlled trials, open-label or blinded, in adults treated with nicergoline. Studies published till August 2013 were included.

Review method: Twenty nine studies were included for data extraction. The studies included in this review were majorly from European countries and mostly in cerebrovascular disease (n=15) and dementia (n=8).

Results: The treatment withdrawals were comparatively lower in nicergoline group as compared to placebo group (RR: 0.92; 95%CI: 0.7, 1.21) and other active comparators (RR: 0.45; 95%CI: 0.10, 1.95) but the difference was non-significant. Incidence of any adverse events was slightly higher (RR: 1.05; 95%CI: 0.93, 1.2) while incidence of serious adverse events was lower (RR: 0.85; 95%CI: 0.50, 1.45) in nicergoline compared to placebo group. Frequency of anxiety was significantly lower in Nicergoline as compared to placebo (p=0.01). Other AEs including diarrhoea, gastric upset, dizziness and drowsiness were less frequent in Nicergoline group compared to placebo/active drugs but the difference was non-significant. Frequency of hypotension and hot flushes was slightly higher in nicergoline group but the difference was non-

1
2
3 significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline
4
5 treatment.
6

7 **Conclusions:** Nicergoline is an ergot derivatives but the safety profile is better than other ergot
8
9 derivatives like ergotamine and ergotamine. This systematic review and meta-analysis suggest
10
11 that nicergoline has a good safety profile. None of the studies included in this systematic review
12
13 reported any incidence of fibrosis or ergotism with nicergoline.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Article Summary:

Article focus:

- Currently not many options are available for management of cognitive impairment including pre-dementia and dementia.
- Despite no known association of nicergoline with ergotism, regulators have limited the use of same
- This meta-analysis is in effort to find the exact side effect profile and benefit to risk evaluation

Key messages:

- No evidence was found to suggest any incidence of fibrosis and ergotism with nicergoline
- Nicergoline is found to be a very safe alternative in a disease (cognitive impairment) with lean pipeline

Strengths and limitations of this study:

- First meta-analysis on nicergoline to understand the adverse clinical profile
- Critical in wake of recent EMEA view of blanket limitation on use of all ergot derivatives
- Limited by the availability of long term (more than 2 years) and high dose studies for cognitive impairment

Title:**A systematic review and meta-analysis assessing safety and tolerability of nicergoline****Background**

Nicergoline is a semi synthetic ergot derivative which has been registered in over fifty countries and has been used for more than four decades for the treatment of cognitive, affective, and behavioural disorders of older people.¹ During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Although cholinergic deficits are the major current targets for pharmacological intervention in Alzheimer's dementia, a wide variety of other neurotransmitter changes can be identified in the disease.

Nicergoline has been demonstrated to increase the availability of acetylcholine both through an increased release from cholinergic terminals and a selective inhibition of acetyl cholinesterase.²

Nicergoline may also enhance noradrenalin and dopamine turnover in some areas of the brain.³

Nicergoline has a positive effect on the signal transduction system stimulating the phosphoinositide pathway which is specifically impaired in Alzheimer's dementia.⁴ Other useful actions of Nicergoline in dementia are an increase of phosphoinosiphosphoinositide-PKC translocation which helps in combating beta-amyloid deposition and in retarding the reduction in nerve-growth factor (NGF) which may help in preventing the loss of cholinergic neurons.⁴

The side effects of Nicergoline are usually limited to nausea, hot flushes, mild gastric upset, hypotension and dizziness. At high dosages bradycardia, increased appetite, agitation, diarrhoea and perspiration have been known to occur. Nicergoline has a better safety profile compared to ergot derivates which are associated with increased risk of fibrosis (formation of excess

connective tissue that can damage organs and body structures) and ergotism (symptoms of ergot poisoning, such as spasms and obstructed blood circulation) with these medicines.

Nicergoline is not associated with either fibrosis or ergotism however; concerns about its safety have been raised, especially after the European Medicines Agency's (EMA) restriction on nicergoline because it is an ergot derivative.⁵ Most of the available literature suggests that the adverse events with nicergoline are mild and transient. Hence, a systematic review of literature and meta-analysis was conducted to compare the safety profile of nicergoline with placebo and other active comparators.

Methods

Search strategy

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. The following databases were examined since inception up to 16th August 2013; Medline, Medline-in-process, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register. This review was not restricted to studies conducted in English language and hence studies published in other languages were also included and translated for data extraction.

Selection criteria

To be included in the analysis, a trial had to fulfill the following criteria: 1) randomized trials which could be open-label, single-blind, or double-blind, parallel group studies; 2) use of nicergoline for Alzheimer's disease, dementia or cognitive disorders; 3) use of nicergoline as one of the interventions; 3) Studies comparing nicergoline with ergot derivatives, placebo, or other active agents were included; 4) Studies should report safety and tolerability data for nicergoline.

1
2
3 Studies were excluded if: 1) presented data for children only; 2) study design was not of interest;
4
5 3) disease was other than of interest; 4) study was not presenting safety and tolerability
6
7 outcomes; 5) full-text could not be sourced.
8
9

10 **Data extraction**

11
12
13 Bibliographic details and abstracts of all citations retrieved by the literature search were
14
15 downloaded into Endnotes version X3. Cochrane methodology was used to conduct this
16
17 systematic review. All studies were screened by two independent reviewers with discrepancies
18
19 resolved by a third reviewer.
20
21
22

23 **Outcomes assessed**

24
25
26 The outcomes assessed included total withdrawals, withdrawals due to AEs, incidence rates for
27
28 any AEs, SAEs, and specific AEs including anxiety, constipation, diarrhoea, hot flushes, itching,
29
30 gastric upset, hypotension, headache, dizziness, insomnia, drowsiness and fatigue.
31
32
33

34 **Statistical analysis**

35
36
37 Comparison of safety and tolerability outcomes were made between interventions by pooling
38
39 data from studies using standard meta-analytic techniques. Review Manager (RevMan v 5.1)
40
41 software was used for meta-analysis of the available data. Dichotomous outcomes were
42
43 summarised as risk (relative) ratios.
44
45
46

47 **Results**

48 **Study selection**

49
50
51
52
53
54 A trial flow of the review process (as per PRISMA statement) is presented along with
55
56 manuscript. The search of the literature yielded 437 separate references. Due to the overlap of
57
58
59
60

1
2
3 coverage between the databases, 96 of the references were found to be duplicates. A total of 341
4 citations were reviewed for abstract screening (first pass). Following the first pass of the
5 citations, 56 potentially relevant references were identified. Full-text reports of these citations
6 were obtained for more detailed evaluation. Following detailed examination of the reports, 26
7 citations were excluded. Thirty studies met inclusion criteria however one of them was a
8 secondary publications which was linked to its primary publication. Finally, a total of 29
9 references reporting trials were extracted. Table 1 presents an overview of the study methods in
10 included studies.
11
12
13
14
15
16
17
18
19
20

21 **Baseline Characteristics**

22
23
24 Most of the included studies were in cerebrovascular disease (n=15), followed by Dementia (n=8). Two
25 studies were for Alzheimer's disease and four were in other disease areas. The mean age of included
26 patients ranged from 48 years (Dubreuil 1986) to 81 years (Saletu 1995) across the studies. The
27 % of male patients ranged from 17.9% (Saletu 1995) to 76.7% (Nakashima 2011) in Nicergoline
28 group and was comparable with control group in all studies). The number of patients randomized in
29 these studies ranged from 16 (Ronchi 1982) to 346 (Winblad 2001). The treatment/study duration
30 ranged from 6 days (Ronchi 1982) to 24 months (Bes 1999) across included studies with most
31 studies with duration ≥ 3 months (n=17). The daily dose of nicergoline used was ≤ 30 mg/day in
32 16 studies and was reported to be 60 mg/daily in 12 studies.
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Critical Appraisal**

48
49 Included studies were critically appraised using the Jadad scale which is a standard scale used for
50 evaluating quality of randomised trials in systematic reviews. Method used to generate random
51 allocation sequence was reported in only nine of the included studies and were judged as
52 adequate. None of the study reported the method used for concealment of allocation sequence.
53
54
55
56
57
58 The Jadad score was ≥ 3 in 20 studies and less than 3 in nine studies. Majority of the studies were
59
60

1
2
3 good quality studies as per Jadad scale. All of included studies reported comparable baseline
4
5 characteristics between treatment groups being studied.
6
7

8 **Withdrawals**

9
10
11 Total withdrawals with nicergoline ranged from 0% (Kugler 1985, Materna 1985) to 22.2% (Bes
12
13 1999) and from 0%- 27.8% with other comparator drugs/placebo. Six studies reported lower
14
15 number of patient withdrawals from nicergoline group as compared to other comparator/placebo
16
17 groups. Withdrawals due to AE were similar in nicergoline group as compared to other groups
18
19 across the studies. Figure 1.
20
21

22
23 The meta-analyzed risk ratios between nicergoline and the other comparators and their
24
25 corresponding 95% confidence intervals for study withdrawals are shown in Tables 2. Results of
26
27 meta-analysis showed a non-significant lower rate of withdrawals from nicergoline compared to
28
29 placebo ($p=0.57$) and other active agents ($p=0.28$). For withdrawals due to AE, the withdrawal
30
31 rate was slightly higher with nicergoline when compared to placebo but the difference was only
32
33 apparent and non-significant ($p=0.7$).
34
35

36 **Adverse Events**

37
38
39 There was adequate data to perform meta-analysis for safety outcomes including any AE, any
40
41 serious AE, diarrhoea, hot flushes, gastric upset, itching, hypertension, headache, dizziness,
42
43 anxiety, insomnia, drowsiness and fatigue. However, there was no reference to cases with
44
45 fibrosis and/or ergotism.
46
47
48

49
50
51 The meta-analyzed risk ratios between nicergoline and the other comparators and their
52
53 corresponding 95% confidence intervals for study withdrawals and safety outcomes are shown in
54
55 Tables 3, and 4, respectively. Results of meta-analysis showed a non-significant lower rate of
56
57 withdrawals from nicergoline compared to placebo ($p=0.57$) and other active agents ($p=0.28$).
58
59
60

1
2
3 For withdrawals due to AE, the withdrawal rate was slightly higher with nicergoline when
4 compared to placebo but again the difference was non-significant ($p=0.7$).
5
6

7
8 The risk of any adverse event was similar with nicergoline compared to placebo (10 studies),
9 ergot derivatives and other active comparators, all comparisons being non-significant. Risk of
10 any serious adverse event was slightly lower in the nicergoline group compared to placebo but
11 was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline
12 as compared to placebo ($p=0.01$). Nicergoline was associated with lower risk of diarrhoea as
13 compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence
14 of dizziness was similar in nicergoline group as compared to placebo or other active agents. A
15 comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but
16 the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo
17 group.
18
19
20
21
22
23
24
25
26
27
28
29

30
31 Higher risk of fatigue was associated with nicergoline compared to active comparators including
32 ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported
33 with nicergoline compared to other comparators. Risk of headache and hypotension was higher
34 with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with
35 nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any
36 significant difference was observed compared to the other intervention or placebo. Figure 2.
37
38
39
40
41
42
43
44

45
46 Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in
47 eight studies during the entire study duration, while remaining studies reported excellent or good
48 tolerability in nicergoline treated patients. None of these studies reported any incidence of
49 ergotism or fibrosis with nicergoline.
50
51
52
53
54
55
56
57
58
59
60

Discussion

Nicergoline is a potent and selective alpha-1A adrenergic receptor antagonist.³⁵ Nicergoline is reported to enhance catecholaminergic turnover,³ stimulate cholinergic neuro-transmission,⁴ stimulate phosphoinositide pathway,³ promote cerebral metabolic activity,³⁶ and has neuroprotective and antioxidant properties.³⁷ Nicergoline is used clinically to improve the apathy and affective disorders caused by cerebral infarction (such as reduced mental alertness, inattention, impairment of recent memory, hypobulia, depression, etc.). It is useful in the treatment of acute and chronic peripheral circulation disorders (such as obliterative vascular disease of the limbs, Raynaud's syndrome and other peripheral circulation dysfunction symptoms). Nicergoline has also been prescribed for the treatment of vascular dementia, especially for the improvement in cognitive dysfunction and memory, and to reduce the severity of this disease.

In addition, studies have been reported showing the usefulness of nicergoline in conditions such as post-hemodialysis pruritus, tinnitus and vertigo, ocular conditions such as arterial obstructions, venous thrombosis, diabetic retinopathies, senile macular degenerations, papilla ischaemic oedema and central serous chorioretinopathies. Dosages for known conditions are usually administered at 5–10 mg three times a day, however anti-aging preventative purposes may limit this to 5 mg once or twice a day. Higher doses of up to 60 mg/day have also been prescribed in clinical practice but have been associated with increased risk of adverse events.⁴

The EMEA's Committee for Medicinal Products for Human Use (CHMP) in its recommendations has suggested that ergot containing medicines, including nicergoline, should no longer be used to treat conditions involving blood circulation problems (such as peripheral artery disease, Raynaud's syndrome and retinopathies of vascular origin), memory and sensation problems and migraine headaches. This recommendation has been supported by the EMEA

1
2
3 citing that these ergot derivatives have a high likelihood of causing serious adverse events such
4 as fibrosis and ergotism.⁵ However, in this recommendation, the EMEA suggests that healthcare
5 professionals can continue prescribing nicergoline and other ergot derivatives in dementia
6 (including Alzheimer's disease) and acute migraine.
7
8
9

10
11
12 Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-
13 infarct dementia.^{1,31} Also, nicergoline has shown efficacy in conditions like post-hemodialysis
14 pruritus,³⁸ tinnitus and vertigo.³⁹ Nicergoline has a positive effect on cognition and behaviour in
15 addition to an effect on clinical global impression in older patients with mild to moderate
16 cognitive and behavioural impairment of various clinical origins including chronic
17 cerebrovascular disorders and Alzheimer's dementia.¹
18
19
20
21
22
23
24

25
26
27 Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep
28 disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and
29 increased appetite.^{7,21} Cardiovascular events like temporary rise in BP, syncope, bradycardia, and
30 hypotension have been reported with nicergoline by few studies.^{17,40}
31
32
33
34
35
36

37
38 Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and
39 abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have
40 reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure,
41 and interstitial nephritis.^{41,42}
42
43
44
45

46
47 Results of this meta-analysis showed comparable safety profile of nicergoline with other active
48 agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to
49 adverse events were similar with nicergoline compared to placebo & active agents. Incidence of
50 any adverse event when compared to placebo and ergot derivatives was slightly higher in the
51 nicergoline group but the difference was non-significant. Significantly lower rates of anxiety
52 were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like
53
54
55
56
57
58
59
60

1
2
3 diarrhoea, dizziness, drowsiness, gastric upset and fatigue were slightly lower with nicergoline as
4
5 compared to placebo but the difference was non-significant for all comparisons.
6
7

8 Nicergoline was associated with higher rates of hot flushes, headache, hypotension, insomnia
9
10 and itching. None of the comparisons showed a significant difference but some of these adverse
11
12 events are probably because of the vasodilation action of nicergoline. Higher doses of
13
14 nicergoline (60 mg/day) were associated with higher rates of adverse events compared to the 30
15
16 mg/day dosing but the difference was not significant. None of the studies included in this meta-
17
18 analysis reported any incidence of fibrosis or ergotism with nicergoline.
19
20
21

22
23 In its current recommendation, the EMEA has overlooked the efficacy and safety profile of
24
25 nicergoline and has cautioned against its use in conditions with blood circulation problems,
26
27 memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban
28
29 on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA
30
31 has probably considered the safety profile of all ergot derivatives as similar. The CHMP review
32
33 has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest
34
35 incidence of these AEs with other ergot derivatives as well.
36
37
38

39 EMEA has suggested that echocardiography should be done within 3–6 months of starting
40
41 treatment with ergot derivatives and subsequently at 6–12-month interval.⁴³ In the current meta-
42
43 analysis, most of the included studies were >3 months and up to 24 months in duration and none
44
45 of the included studies reported any incidence of fibrosis or ergotism with nicergoline. There is
46
47 no evidence in literature to suggest any incidence of fibrosis and ergotism with nicergoline.
48
49
50

51 The strengths of this systematic review include the clear definition of the research question,
52
53 adherence to an explicit research protocol that was developed prior to the analysis, the
54
55 comprehensive nature of the data search (employing both electronic databases and manual
56
57 bibliography searches resulting in the inclusion of all relevant publications), consensus between
58
59
60

1
2
3 two reviewers of all data elements prior to entry into the database and the quality control review
4
5 of every element of this report. In addition, the quality of the studies and manuscripts used to
6
7 provide data were relatively high. Only RCTs were included in this systematic review/meta-
8
9 analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to
10
11 compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this
12
13 review could be the publication timeframe of the included studies. Most of the studies were
14
15 published in 1980s and 1990s. There were hardly any trials published in recent years on safety
16
17 evaluation for nicergoline.
18
19

20 21 22 **Conclusions**

23
24
25 This systematic review & meta-analysis has included the evidence to date with regards to
26
27 tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is
28
29 categorized under ergot derivatives. However, the adverse events with nicergoline are mild and
30
31 transient unlike other ergot derivatives (ergotamine & ergotamine) which have been associated
32
33 with fibrosis and ergotism.
34
35

36
37 The results from this systematic review/meta-analysis suggest that nicergoline has a comparable
38
39 safety profile as placebo and other active comparators. None of the studies included in this
40
41 systematic review reported any incidence of fibrosis or ergotism with nicergoline. The evidence
42
43 generated by this review suggests that despite being an ergot derivative, nicergoline is a safe and
44
45 well-tolerated drug. This systematic review/meta-analysis concludes that nicergoline is a safe
46
47 option for therapeutic management in patients with dementia and cerebrovascular disorders.
48
49

50 51 52 **List of abbreviations**

53
54 AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA:
55
56 European Medicines Agency; SAEs: serious adverse event
57
58
59
60

Tables

Table 1: Study methods for included RCTs

| Study Name | Study duration | Country | Blinding | Intervention | Comparator |
|---------------------------------|----------------|-----------|--------------|--------------|--------------------|
| Arrigo 1982 ⁶ | 14 weeks | Italy | Double-blind | Nicergoline | Placebo |
| Battaglia 1989 ⁷ | 6 months | Italy | Double-blind | Nicergoline | Placebo |
| Battaglia 1990 ⁸ | 6 months | Italy | Double-blind | Nicergoline | Ergot mesylates |
| Battaglia 1995 ⁹ | 12 months | Italy | Double-blind | Nicergoline | Placebo |
| Bes 1999 ¹⁰ | 24 months | France | Double-blind | Nicergoline | Placebo |
| Boss 1985 ¹¹ | - | Italy | Double-blind | Nicergoline | Buflomedil |
| Brola 1997 ¹² | 1 month | Poland | Single-blind | Nicergoline | Pentoxifylline |
| Cascone 1978 ¹³ | 1 month | Italy | Double-blind | Nicergoline | Placebo |
| Colombeau 1987 ¹⁴ | 15 days | France | Double-blind | Nicergoline | Placebo |
| Crook 1997 ¹⁵ | 6 months | USA | Double-blind | Nicergoline | Placebo |
| Dubreuil 1986 ¹⁶ | 1 month | France | Double-blind | Nicergoline | GBE |
| Felisati 2002 ¹⁷ | 3 months | Italy | Double-blind | Nicergoline | Placebo |
| Forette 1980 ¹⁸ | 3 weeks | France | Double-blind | Nicergoline | Placebo |
| Gessner 1985 ¹⁹ | 12 weeks | Germany | Double-blind | Nicergoline | GBE |
| Herrmann 1997 ²⁰ | 6 months | Germany | Double-blind | Nicergoline | Placebo |
| Kugler 1985 ²¹ | 6 months | Germany | Double-blind | Nicergoline | Dihydro-ergotamine |
| Lu 2001 ²² | 12 weeks | China | Double-blind | Nicergoline | Aniracetam |
| Marolda 1978 ²³ | 20 days | Italy | Double-blind | Nicergoline | Eburnamonine |
| Materna 1985 ²⁴ | 12 weeks | Germany | Double-blind | Nicergoline | Flunarizine |
| Nakashima 2011 ²⁵ | 6 months | Japan | Double-blind | Nicergoline | Imidapril |
| Nappi 1997 ²⁶ | 12 months | Italy | Double-blind | Nicergoline | Placebo |
| Nishiyama 2010 ²⁷ | 4 weeks | Japan | Open-label | Nicergoline | Placebo |
| Pilkowska 2002 ²⁸ | 3 months | Poland | Double-blind | Nicergoline | Placebo |
| Pogliani 1979 ²⁹ | 3 months | Germany | Double-blind | Nicergoline | Placebo |
| Ronchi 1982 ³⁰ | 6 Days | Italy | Double-blind | Nicergoline | Placebo |
| Saletu 1995 ³¹ | 8 weeks | Austria | Double-blind | Nicergoline | Placebo |
| Setyopranoto 2009 ³² | - | Indonesia | Double-blind | Nicergoline | Placebo |
| Winblad 2001 ³³ | 6 months | Europe | Double-blind | Nicergoline | Placebo |
| Zucconi 1974 ³⁴ | 1 month | Italy | Double-blind | Nicergoline | Dihydro-ergotoxine |

Table 2: Meta analysis of withdrawal rate across included studies

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|-----------------------|--------------|---------------|---------|------|-------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Total withdrawals | Nicergoline | Placebo | 8 | 1234 | 0.92 (0.70, 1.21) | 0.57 | 0% |
| | Nicergoline | Active agents | 3 | 201 | 0.45 (0.10, 1.95) | 0.28 | 18% |
| Withdrawals due to AE | Nicergoline | Placebo | 3 | 565 | 1.13 (0.61, 2.09) | 0.7 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Table 3: Meta analysis of overall adverse events

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|---------------|--------------|-------------------|---------|------|--------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Any AE | Nicergoline | Placebo | 10 | 1448 | 1.05 (0.93, 1.20) | 0.42 | 0% |
| Any AE | Nicergoline | Active agents | 4 | 292 | 1.19 (0.71, 2.01) | 0.51 | 5% |
| Any AE | Nicergoline | Ergot derivatives | 2 | 200 | 1.22 (0.63, 2.34) | 0.56 | 19% |
| Any SAE | Nicergoline | Placebo | 2 | 482 | 0.85 (0.50, 1.45) | 0.54 | 35% |
| Anxiety | Nicergoline | Placebo | 2 | 482 | 0.59 (0.39, 0.88) | 0.01 | 0% |
| Diarrhoea | Nicergoline | Placebo | 2 | 188 | 0.85 (0.24, 3.05) | 0.8 | 0% |
| Diarrhoea | Nicergoline | Ergot derivatives | 2 | 200 | 0.99 (0.14, 6.92) | 0.99 | 0% |
| Dizziness | Nicergoline | Placebo | 3 | 260 | 0.63 (0.15, 2.57) | 0.51 | 0% |
| Dizziness | Nicergoline | Active agents | 2 | 116 | 1.00 [0.18, 5.58] | 1.0 | 0% |
| Drowsiness | Nicergoline | Placebo | 2 | 442 | 0.34 (0.05, 2.12) | 0.24 | 0% |
| Fatigue | Nicergoline | Placebo | 2 | 378 | 0.71 (0.14, 3.53) | 0.68 | 18% |
| Fatigue | Nicergoline | Active agents | 3 | 260 | 1.24 (0.35, 4.47) | 0.74 | 0% |
| Fatigue | Nicergoline | Ergot derivatives | 2 | 200 | 1.79 (0.40, 7.98) | 0.45 | 0% |
| Gastric upset | Nicergoline | Placebo | 6 | 1037 | 0.94 (0.58, 1.52) | 0.8 | 0% |
| Hot Flushes | Nicergoline | All comparisons | 3 | 470 | 3.65 (0.61, 21.93) | 0.16 | 0% |
| Headache | Nicergoline | Placebo | 5 | 1004 | 1.28 (0.63, 2.60) | 0.24 | 0% |
| Hypotension | Nicergoline | Placebo | 2 | 378 | 1.49 (0.26, 8.72) | 0.66 | 0% |
| Insomnia | Nicergoline | Placebo | 3 | 498 | 1.81 (0.39, 8.29) | 0.45 | 0% |
| Itching | Nicergoline | All comparisons | 2 | 108 | 3.23 (0.35, 30.08) | 0.3 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Contributorship Statement: AG carried out the searches in various databases. AG and JX carried out the filtration of citation. AG and JX carried out the data extraction, MF and TN helped to draft the manuscript and reviewed it. All authors read and approved the final manuscript.

Competing Interests: None

Data Sharing Statement: In addition to the manuscript, the corresponding author also has initial results of publication analysis. That explains the reason for inclusion and exclusion of individual studies.

References

1. Fioravanti M, Flicker L. Efficacy of nicergoline in dementia and other age associated forms of cognitive impairment. *Cochrane Database Syst Rev* 2001:CD003159.
2. Carfagna N, Di Clemente A, Cavanus S, Damiani D, Gerna M, Salmoiraghi P, Cattaneo B, Post C. Modulation of hippocampal ACh release by chronic nicergoline treatment in freely moving young and aged rats. *Neurosci Lett* 1995;197:195-8.
3. Carfagna N, Rossi A. Nicergoline: biochemical studies on neuronal metabolism. *Funct Neurol* 1989;4:177-85

- 1
2
3 4. Winblad B, Fioravanti M, Dolezal T, Logina I, Milanov IG, Popescu DC, Solomon A.
4
5 Therapeutic use of nicergoline. *Clin Drug Investig* 2008;28:533-52.
6
- 7
8 5. New restrictions on use of medicines containing ergot derivatives.
9
10 [http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC50014
11 4861.pdf.]
12
- 13
14 6. Arrigo A, Moglia A, Borsotti L. A double-blind, placebo-controlled, crossover trial with
15
16 nicergoline in patients with senile dementia. *International Journal of Clinical Pharmacology*
17
18 *Research* 1982;2:33-41.
19
- 20
21 7. Battaglia A, Bruni G, Ardia A, Sacchetti G. Nicergoline in mild to moderate dementia. A
22
23 multicenter, double-blind, placebo-controlled study. *J Am Geriatr Soc* 1989;37:295-302.
24
- 25
26 8. Battaglia A, Bruni G, Sacchetti G, Pamparana F (Nicergoline Cooperative Study Group). A
27
28 double-blind randomized study of two ergot derivatives in mild to moderate dementia. *Curr*
29
30 *Therap Res* 1990;48:597-612.
31
- 32
33 9. Battaglia A, Annoni K, Pamparana F, DePaolis C, Bonura ML, Stekke W. Nicergoline in the
34
35 Long Term Treatment of Mild or Moderate Senile Dementia. A Multicenter Double-blind,
36
37 Randomized, Placebo- controlled Trial. In 8th European College of
38
39 Neuropsychopharmacology Congress: 30th September - 4th October 1995; Venice.
40
- 41
42 10. Bes A, Orgogozo JM, Poncet M, Rancurel G, Weber M, Bertholom N, Calvez R, Stehle B,
43
44 Destee A, Latinville D. A 24-month, double-blind, placebo-controlled multicentre pilot study
45
46 of the efficacy and safety of nicergoline 60 mg per day in elderly hypertensive patients with
47
48 leukoaraiosis. *European Journal of Neurology* 1999;6:313-22.
49
- 50
51 11. Bossi L. Buflomedil and nicergolin in the treatment of acute cerebral ischaemia. A double-
52
53 blind, randomized comparative study. *Minerva Medica* 1985;76:1005-18.
54
- 55
56 12. Broła W. Evaluation of treatment outcome after nicergoline and pentoxifylline in patients
57
58 with ischemic stroke. *Przegląd lekarski* 1997;54:79-82.
59
60

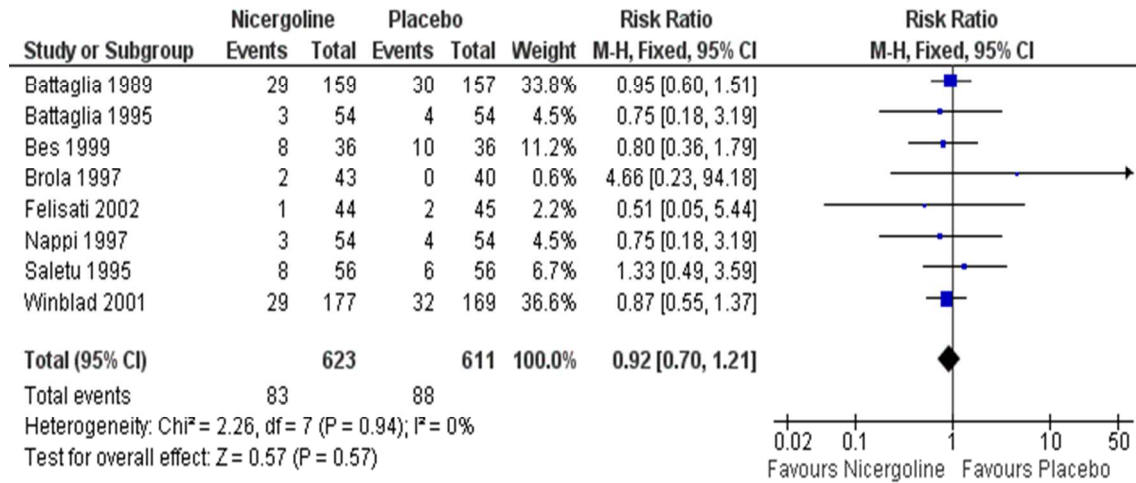
- 1
2
3 13. Cascone A, Liverta C, Pollini C. A double-blind trial of nicergolin and placebo in cerebral
4
5 and peripheral cerebrovascular disturbance in the aged. *Minerva Cardioangiologica* 1978;
6
7 26:95-100.
8
- 9
10 14. Colombeau P, Ballanger P. Results of the double-blind use of an alpha blockader,
11
12 nicergoline, in cervico-prostatic dysfunctions. *Journal d'urologie* 1987;93:533-5.
13
- 14 15. Crook TH. Nicergoline in the treatment of probable Alzheimer's disease Preliminary results
15
16 of a double-blind, randomized, placebo-controlled study. *J Neurol Sci* 1997:S18.
17
- 18 16. Dubreuil C. Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo
19
20 biloba extract and nicergoline. *Presse médicale (Paris, France : 1983)* 1986;15:1559-61.
21
22
- 23 17. Felisati G, Battaglia A, Papini MG, Rossini BM, Pignataro O. Nicergoline in balance
24
25 alterations in adult and elderly patients: A double-blind, placebo-controlled study. *Clinical*
26
27 *Drug Investigation* 2002;22:731-40.
28
- 29 18. Forette F, Varin D, Henry JF, Hervy MP. Treatment of arterial hypertension in the elderly
30
31 with an alpha-blocker: nicergoline (author's transl). *La Nouvelle presse médicale* 1980,
32
33 9:3685-8.
34
35
- 36 19. Gessner B, Voelp A, Klasser M. Study of the long-term action of a Ginkgo biloba extract on
37
38 vigilance and mental performance as determined by means of quantitative pharmaco-EEG
39
40 and psychometric measurements. *Arzneimittel-Forschung/Drug Research* 1985;35:1459-65.
41
42
- 43 20. Herrmann WM. A multicenter randomized double-blind study on the efficacy and safety of
44
45 nicergoline in patients with multi-infarct dementia. *Dementia and Geriatric Cognitive*
46
47 *Disorders* 1997;8:9-17.
48
- 49 21. Kugler JE, Meurer-Krull BC. Electroencephalography and psychometric measurements
50
51 during the treatment of cerebral insufficiency with nicergoline and dihydroergotamine
52
53 mesylate. *Arzneimittelforschung* 1985;35:1865-70.
54
55
56
57
58
59
60

- 1
2
3 22. Lu JH. Nicergoline in treatment of vascular dementia: a consecutive, multicenter, double-
4 blind clinical trial. *Chinese J Neurol* 2001;88-91.
5
6
7 23. Marolda M, Fragassi N, Buscaino GA. Clinical evaluation of (-)eburnamonine in comparison
8 with nicergoline in patients suffering from chronic brain ischemia. *European Neurology*
9 1978, 17:159-66.
10
11
12 24. Materna F. Leading symptom vertigo: Comparative study with flunarizine and nicergoline.
13 *Medizinische Klinik* 1985, 80:292-5.
14
15
16 25. Nakashima T, Hattori N, Okimoto M, Yanagida J, Kohno N. Nicergoline improves
17 dysphagia by upregulating substance p in the elderly. *Medicine* 2011;90:279-83.
18
19
20 26. Nappi G, Bono G, Merlo P, Borromei A, Caltagirone C, Lomeo C, Martucci N, Fabbrini G,
21 Annoni K, Battaglia A. Long-term nicergoline treatment of mild to moderate senile
22 dementia. Results of a multicentre, double-blind, placebo-controlled study. *Clinical Drug*
23 *Investigation* 1997;13:308-16.
24
25
26 27. Nishiyama Y, Abe A, Ueda M, Katsura KI, Katayama Y. Nicergoline increases serum
27 substance P levels in patients with an ischaemic stroke. *Cerebrovascular Diseases*
28 2010;29:194-8.
29
30
31 28. Pilkowska E, Jakubowska T, Witkowska K, Kulczycki J. Nicergoline in the treatment of
32 patients after a mild ischemic stroke. *Neurologia i neurochirurgia polska* 2002;36:1075-85.
33
34
35 29. Pogliani E, Della Volpe A, Ferrari R. Inhibition of human platelet aggregation by oral
36 administration of nicergoline. A double blind study. *Farmaco, Edizione Pratica* 1975;30:630-
37 40.
38
39
40 30. Ronchi F, Margonato A, Ceccardi R. Symptomatic treatment of benign prostatic obstruction
41 with nicergoline: A placebo controlled clinical study and urodynamic evaluation. *Urological*
42 *Research* 1982;10:131-34.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

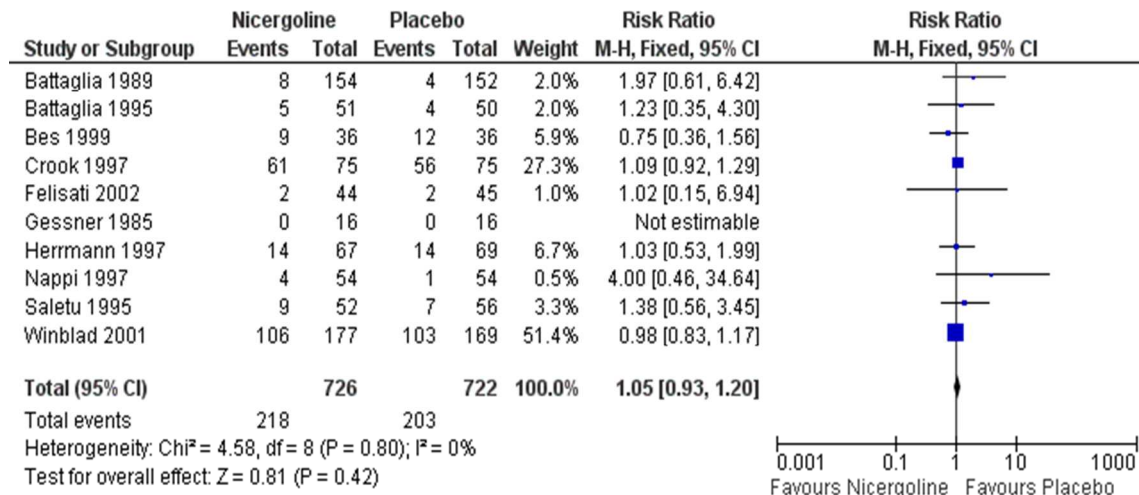
- 1
2
3 31. Saletu B, Paulus E, Linzmayer L, Anderer P, Semlitsch HV, Grunberger J, Wicke L,
4
5 Neuhold A. Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: A
6
7 double blind, placebo controlled, clinical and EEG/ERP mapping study.
8
9
10 Psychopharmacology 1995;117:385-95.
11
12 32. Setyopranoto ISP. Role of nicergoline 60 miligram per oral for improvement of the patients
13
14 with acute ischemic stroke. Journal of the Neurological Sciences 2009;285:S221-S222.
15
16 33. Winblad B, Bonura ML, Rossini BM, Battaglia A. Nicergoline in the treatment of mild-to-
17
18 moderate Alzheimer's disease: A European multicentre trial. Clinical Drug Investigation
19
20 2001;21:621-32.
21
22 34. Zucconi V, Terzi Bolaffio M. Results with nicergolin and dihydroergotoxine in 30
23
24 hemiplegics in the postacute phase. Minerva Medica 1974;65:936-45.
25
26 35. Alvarez-Guerra M, Bertholom N, Garay RP. Selective blockade by nicergoline of vascular
27
28 responses elicited by stimulation of alpha 1A-adrenoceptor subtype in the rat. conam Clin
29
30 Pharmacol 1999;13:50-8.
31
32 36. Shintomi K, Yoshimoto K, Ogawa Y, Itakura T, Fukushima T, Matsumoto M, Matsuoka Y,
33
34 Ishida R. Effects of nicergoline on cerebral energy metabolism in normal mice. Yakugaku
35
36 Zasshi 1986;106:90-4.
37
38 37. Sortino MA, Battaglia A, Pamparana F, Carfagna N, Post C, Canonico PL. Neuroprotective
39
40 effects of nicergoline in immortalized neurons. Eur J Pharmacol 1999;368:285-90.
41
42 38. Bousquet J, Rivory JP, Maheut M, Michel FB, Mion C. Double-blind, placebo-controlled
43
44 study of nicergoline in the treatment of pruritus in patients receiving maintenance
45
46 hemodialysis. J Allergy Clin Immunol 1989;83:825-28.
47
48 39. Akisada T, Orita Y, Sato Y, Handa T, Yada K, Kawai A, Takemoto T, Oku M. Effect of
49
50 nicergoline on vertigo and tinnitus. Practica Otologica 1994;87:845-55.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 40. Boismare F, Lefrancois J. Haemodynamic effects of nicergoline in man at rest and during
4 exercise. Clin Exp Pharmacol Physiol 1980;7:105-12.
5
6
7 41. Gallego J, Forner V, Jimenez F, Martinez E. Nicergoline in the treatment of neuropathic
8 bladder dysfunction: a preliminary report. Paraplegia 1984;22:216-24.
9
10
11 42. Kim MJ, Chang JH, Lee SK, Park JH, Choi YJ, Yang CW, Kim YS, Park SH, Bang BK.
12 Acute interstitial nephritis due to nicergoline (Sermion). Nephron 2002;92:676-79.
13
14
15 43. Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses.
16
17 <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087807>
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

All Withdrawals: Nicergoline vs. Placebo



Any Adverse Event: Nicergoline vs. Placebo



Peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

BMJ Open

A systematic review and meta-analysis assessing safety and tolerability of nicergoline

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID: | bmjopen-2014-005090.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 24-May-2014 |
| Complete List of Authors: | Fioravanti, Mario; University Hospital, Umberto I, Clinical Psychology Nakashima, Taku; Hiroshima University Hospital, Dept. of Molecular & Internal Medicine Xu, Jun; Jiangsu Province Geriatric Hospital, Geriatrics Garg, Amit; Physician |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Evidence based practice, Mental health |
| Keywords: | Meta-analysis, Nicergoline, Ergot derivatives, Fibrosis, Ergotism |
| | |

SCHOLARONE™
Manuscripts

Peer Review Only

1
2
3
4 Title of the article:
5

6
7 **A systematic review and meta-analysis assessing safety and tolerability of nicergoline**
8
9

10 Corresponding author:
11

12 Dr. Amit Garg, M.D.

13 Physician
14

15 A Wing- 304, Aparna Towers
16

17 Kondapur, Kothaguda,
18

19 Hyderabad-500084
20

21 Email: amitgarg.pharm@gmail.com
22

23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Tele: +918790902800

31 Authors:
32

33 Mario Fioravanti¹, Taku Nakashima², Jun Xu³, Amit Garg⁴
34
35

36 Affiliations:
37
38

39 1. Prof. Mario Fioravanti, M.D.

40
41 Director of the Clinical Psychology Service
42

43 University Hospital, Umberto I
44

45 Professor of Clinical Psychology
46

47 Department of Neurology and Psychiatry
48

49 University of Rome, Sapienza, Italy
50

51 E-mail: mario.fioravanti@uniroma1.it
52
53
54

55 2. Taku Nakashima, MD, PhD.

56
57 Dept. of Molecular & Internal Medicine,
58
59
60

1
2
3 Hiroshima University Hospital

4
5 1-2-3 Kasumi, Minami-ku Hiroshima, 734-8551 Japan

6
7 E-mail: tnaka@hiroshima-u.ac.jp/tnaka@eos.ocn.ne.jp

8
9
10 3. Prof. Jun Xu

11 Hospital: Jiangsu Province Geriatric Hospital, China

12
13 Email: 13611572068@126.com ; neurojun@126.com

14
15
16 4. Dr. Amit Garg, M.D.

17 Physician, A-Wing- 304, Aparna Towers

18
19 Kondapur, Kothaguda, Hyderabad-500084. India

20
21 Email: amitgarg.pharm@gmail.com

22
23
24
25
26
27
28
29 Keywords:

30
31
32 Meta-analysis, nicergoline, ergot derivatives, fibrosis, ergotism

33
34
35 Word Count:

36
37 2649 words

Abstract

Objective: To evaluate the safety profile of nicergoline compared to placebo and other active agents from published randomised controlled trials.

Design: Systematic review and meta-analysis of nicergoline compared to placebo and other active agents across various indications.

Data sources: Medline, Medline-in-process, Cochrane, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register (CMR) for all the randomized controlled trials, open-label or blinded, in adults treated with nicergoline. Studies published till August 2013 were included.

Review method: Twenty nine studies were included for data extraction. The studies included in this review were majorly from European countries and mostly in cerebrovascular disease (n=15) and dementia (n=8).

Results: The treatment withdrawals were comparatively lower in nicergoline group as compared to placebo group (RR: 0.92; 95%CI: 0.7, 1.21) and other active comparators (RR: 0.45; 95%CI: 0.10, 1.95) but the difference was non-significant. Incidence of any adverse events was slightly higher (RR: 1.05; 95%CI: 0.93, 1.2) while incidence of serious adverse events was lower (RR: 0.85; 95%CI: 0.50, 1.45) in nicergoline compared to placebo group. Frequency of anxiety was significantly lower in Nicergoline as compared to placebo (p=0.01). Other AEs including diarrhoea, gastric upset, dizziness and drowsiness were less frequent in Nicergoline group compared to placebo/active drugs but the difference was non-significant. Frequency of hypotension and hot flushes was slightly higher in nicergoline group but the difference was non-

1
2
3 significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline
4
5 treatment.
6

7 **Conclusions:** Nicergoline is an ergot derivatives but the safety profile is better than other ergot
8
9 derivatives like ergotamine and ergotamine. This systematic review and meta-analysis suggest
10
11 that nicergoline has a good safety profile. None of the studies included in this systematic review
12
13 reported any incidence of fibrosis or ergotism with nicergoline.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Article Summary:

Article focus:

- Currently not many options are available for management of cognitive impairment including pre-dementia and dementia.
- Despite no known association of nicergoline with ergotism, regulators have limited the use of same
- This meta-analysis is in effort to find the exact side effect profile and benefit to risk evaluation

Key messages:

- No evidence was found to suggest any incidence of fibrosis and ergotism with nicergoline
- Nicergoline is found to be a very safe alternative in a disease (cognitive impairment) with lean pipeline

Strengths and limitations of this study:

- First meta-analysis on nicergoline to understand the adverse clinical profile
- Critical in wake of recent EMEA view of blanket limitation on use of all ergot derivatives
- Limited by the availability of long term (more than 2 years) and high dose studies for cognitive impairment

Title:**A systematic review and meta-analysis assessing safety and tolerability of nicergoline****Background**

Nicergoline is a semi synthetic ergot derivative which has been registered in over fifty countries and has been used for more than four decades for the treatment of cognitive, affective, and behavioural disorders of older people.¹ During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Although cholinergic deficits are the major current targets for pharmacological intervention in Alzheimer's dementia, a wide variety of other neurotransmitter changes can be identified in the disease.

Nicergoline has been demonstrated to increase the availability of acetylcholine both through an increased release from cholinergic terminals and a selective inhibition of acetyl cholinesterase.²

Nicergoline may also enhance noradrenalin and dopamine turnover in some areas of the brain.³

Nicergoline has a positive effect on the signal transduction system stimulating the phosphoinositide pathway which is specifically impaired in Alzheimer's dementia.⁴ Other useful actions of Nicergoline in dementia are an increase of phosphoinosiphosphoinositide-PKC translocation which helps in combating beta-amyloid deposition and in retarding the reduction in nerve-growth factor (NGF) which may help in preventing the loss of cholinergic neurons.⁴

The side effects of Nicergoline are usually limited to nausea, hot flushes, mild gastric upset, hypotension and dizziness. At high dosages bradycardia, increased appetite, agitation, diarrhoea and perspiration have been known to occur. Nicergoline has a better safety profile compared to ergot derivates which are associated with increased risk of fibrosis (formation of excess

connective tissue that can damage organs and body structures) and ergotism (symptoms of ergot poisoning, such as spasms and obstructed blood circulation) with these medicines.

Nicergoline is not associated with either fibrosis or ergotism however; concerns about its safety have been raised, especially after the European Medicines Agency's (EMA) restriction on nicergoline because it is an ergot derivative.⁵ Most of the available literature suggests that the adverse events with nicergoline are mild and transient. Hence, a systematic review of literature and meta-analysis was conducted to compare the safety profile of nicergoline with placebo and other active comparators.

Methods

Search strategy

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. The following databases were examined since inception up to 16th August 2013; Medline, Medline-in-process, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register. Medical subject headings (MeSH terms) and free keywords like "randomised controlled trial", "Nicergoline", "Adverse effects", "toxicity" and "side effects" were used. This review was not restricted to studies conducted in English language and hence studies published in other languages were also included and translated for data extraction.

Selection criteria

To meet the study objective, we pre-decided on inclusion criteria which include RCTs reporting adverse events in patients undergoing nicergoline treatment for psychiatric disorders. To be included in the analysis, a trial had to fulfill the following criteria: 1) randomized trials which could be open-label, single-blind, or double-blind, parallel group studies; 2) use of nicergoline

1
2
3 for Alzheimer's disease, dementia or cognitive disorders; 3) use of nicergoline as one of the
4 interventions; 3) Studies comparing nicergoline with ergot derivatives, placebo, or other active
5 agents were included; 4) Studies should report safety and tolerability data for nicergoline.
6
7
8

9
10 Studies were excluded if: 1) presented data for children only; 2) study design was not of interest;
11 3) disease was other than of interest; 4) study was not presenting safety and tolerability
12 outcomes; 5) full-text could not be sourced.
13
14
15
16

17 18 **Data extraction**

19
20 Bibliographic details and abstracts of all citations retrieved by the literature search were
21 downloaded into Endnotes version X3. Cochrane methodology was used to conduct this
22 systematic review. All studies were screened by two independent reviewers with discrepancies
23 resolved by a third reviewer.
24
25
26
27
28
29
30

31 32 **Outcomes assessed**

33
34 In most of the included studies, safety evaluation included monitoring of adverse events, vital
35 signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at
36 baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-
37 emergent adverse events (elicited or observed); physical examination including ECG recording;
38 vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to
39 adverse event were reported.
40
41
42
43
44
45
46
47

48
49 The data from these studies were pooled for total withdrawals, withdrawals due to AEs,
50 incidence rates for any AEs, SAEs, and specific AEs including anxiety, constipation, diarrhoea,
51 hot flushes, itching, gastric upset, hypotension, headache, dizziness, insomnia, drowsiness and
52 fatigue. Only studies which presented data for same comparators were included in direct meta-
53 analysis for each outcome.
54
55
56
57
58
59
60

Statistical analysis

Comparison of safety and tolerability outcomes were made between interventions by pooling data from studies using direct meta-analysis technique. Only head-to-head comparisons between interventions were included for meta-analysis. Review Manager (RevMan v 5.1) software was used for meta-analysis of the available data. Dichotomous outcomes were summarised as risk (relative) ratios.

Results

Study selection

A trial flow of the review process (as per PRISMA statement) is presented along with manuscript. The search of the literature yielded 437 separate references. Due to the overlap of coverage between the databases, 96 of the references were found to be duplicates. A total of 341 citations were reviewed for abstract screening (first pass). Following the first pass of the citations, 56 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports, 26 citations were excluded. Thirty studies met inclusion criteria however one of them was a secondary publication which was linked to its primary publication. Finally, a total of 29 references reporting trials were extracted. Table 1 presents an overview of the study methods in included studies. Fifteen studies were not included in meta-analysis as data from these could not be pooled. These were studies reporting standalone adverse events, or for standalone comparators.

Baseline Characteristics

Most of the included studies were in cerebrovascular disease (n=15), followed by Dementia (n=8). Two studies were for Alzheimer's disease and four were in other disease areas. The mean

1
2
3 age of included patients ranged from 48 years (Dubreuil 1986) to 81 years (Saletu 1995) across
4
5 the studies. The % of male patients ranged from 17.9% (Saletu 1995) to 76.7% (Nakashima
6
7 2011) in Nicergoline group and was comparable with control group in all studies). The number
8
9 of patients randomized in these studies ranged from 16 (Ronchi 1982) to 346 (Winblad
10
11 2001). The treatment/study duration ranged from 6 days (Ronchi 1982) to 24 months (Bes 1999)
12
13 across included studies with most studies with duration ≥ 3 months (n=17). The daily dose of
14
15 nicergoline used was ≤ 30 mg/day in 16 studies and was reported to be 60 mg/daily in 12 studies.
16
17
18
19

20 21 22 **Critical Appraisal**

23
24 Included studies were critically appraised using the Jadad scale which is a standard scale used for
25
26 evaluating quality of randomised trials in systematic reviews. Method used to generate random
27
28 allocation sequence was reported in only nine of the included studies and were judged as
29
30 adequate. None of the study reported the method used for concealment of allocation sequence.
31
32 The Jadad score was ≥ 3 in 20 studies and less than 3 in nine studies. Majority of the studies were
33
34 good quality studies as per Jadad scale. All of included studies reported comparable baseline
35
36 characteristics between treatment groups being studied.
37
38
39
40
41
42

43 44 **Withdrawals**

45
46 Total withdrawals with nicergoline ranged from 0% (Kugler 1985, Materna 1985) to 22.2% (Bes
47
48 1999) and from 0%- 27.8% with other comparator drugs/placebo. Six studies reported lower
49
50 number of patient withdrawals from nicergoline group as compared to other comparator/placebo
51
52 groups. Withdrawals due to AE were similar in nicergoline group as compared to other groups
53
54 across the studies, Figure 1.
55
56
57
58
59
60

1
2
3 The meta-analyzed risk ratios between nicergoline and the other comparators and their
4
5 corresponding 95% confidence intervals for study withdrawals are shown in Tables 2. Results of
6
7 meta-analysis showed a non-significant lower rate of withdrawals from nicergoline compared to
8
9 placebo ($p=0.57$) and other active agents ($p=0.28$). For withdrawals due to AE, the withdrawal
10
11 rate was slightly higher with nicergoline when compared to placebo but the difference was only
12
13 apparent and non-significant ($p=0.7$).
14
15

16 17 **Adverse Events**

18
19
20 There was adequate data to perform meta-analysis for safety outcomes including any AE, any
21
22 serious AE, diarrhoea, hot flushes, gastric upset, itching, hypertension, headache, dizziness,
23
24 anxiety, insomnia, drowsiness and fatigue (Supplementary Table 1). However, there was no
25
26 reference to cases with fibrosis and/or ergotism.
27
28

29
30 The meta-analyzed risk ratios between nicergoline and the other comparators and their
31
32 corresponding 95% confidence intervals for study withdrawals and safety outcomes are shown in
33
34 Tables 2, and 3, respectively. Results of meta-analysis showed a non-significant lower rate of
35
36 withdrawals from nicergoline compared to placebo ($p=0.57$) and other active agents ($p=0.28$).
37
38 For withdrawals due to AE, the withdrawal rate was slightly higher with nicergoline when
39
40 compared to placebo but again the difference was non-significant ($p=0.7$).
41
42
43

44
45 The risk of any adverse event was similar with nicergoline compared to placebo (10 studies),
46
47 ergot derivatives and other active comparators, all comparisons being non-significant. Risk of
48
49 any serious adverse event was slightly lower in the nicergoline group compared to placebo but
50
51 was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline
52
53 as compared to placebo ($p=0.01$). Nicergoline was associated with lower risk of diarrhoea as
54
55 compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence
56
57 of dizziness was similar in nicergoline group as compared to placebo or other active agents. A
58
59
60

1
2
3 comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but
4
5 the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo
6
7 group.
8
9

10
11 Higher risk of fatigue was associated with nicergoline compared to active comparators including
12
13 ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported
14
15 with nicergoline compared to other comparators. Risk of headache and hypotension was higher
16
17 with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with
18
19 nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any
20
21 significant difference was observed compared to the other intervention or placebo, Figure 2.
22
23

24
25 Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in
26
27 eight studies during the entire study duration, while remaining studies reported excellent or good
28
29 tolerability in nicergoline treated patients. None of these studies reported any incidence of
30
31 ergotism or fibrosis with nicergoline.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Discussion

Nicergoline is a potent and selective alpha-1A adrenergic receptor antagonist.³⁵ Nicergoline is reported to enhance catecholaminergic turnover,³ stimulate cholinergic neuro-transmission,⁴ stimulate phosphoinositide pathway,³ promote cerebral metabolic activity,³⁶ and has neuroprotective and antioxidant properties.³⁷ Nicergoline is used clinically to improve the apathy and affective disorders caused by cerebral infarction (such as reduced mental alertness, inattention, impairment of recent memory, hypobulia, depression, etc.). It is useful in the treatment of acute and chronic peripheral circulation disorders (such as obliterative vascular disease of the limbs, Raynaud's syndrome and other peripheral circulation dysfunction symptoms). Nicergoline has also been prescribed for the treatment of vascular dementia, especially for the improvement in cognitive dysfunction and memory, and to reduce the severity of this disease.

In addition, studies have been reported showing the usefulness of nicergoline in conditions such as post-hemodialysis pruritus, tinnitus and vertigo, ocular conditions such as arterial obstructions, venous thrombosis, diabetic retinopathies, senile macular degenerations, papilla ischaemic oedema and central serous chorioretinopathies. Dosages for known conditions are usually administered at 5–10 mg three times a day, however anti-aging preventative purposes may limit this to 5 mg once or twice a day. Higher doses of up to 60 mg/day have also been prescribed in clinical practice but have been associated with increased risk of adverse events.⁴

The EMEA's Committee for Medicinal Products for Human Use (CHMP) in its recommendations has suggested that ergot containing medicines, including nicergoline, should no longer be used to treat conditions involving blood circulation problems (such as peripheral artery disease, Raynaud's syndrome and retinopathies of vascular origin), memory and sensation problems and migraine headaches. This recommendation has been supported by the EMEA

1
2
3 citing that these ergot derivatives have a high likelihood of causing serious adverse events such
4 as fibrosis and ergotism.⁵ However, in this recommendation, the EMEA suggests that healthcare
5 professionals can continue prescribing nicergoline and other ergot derivatives in dementia
6 (including Alzheimer's disease) and acute migraine.
7
8
9
10

11
12 Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-
13 infarct dementia.^{1,31} Also, nicergoline has shown efficacy in conditions like post-hemodialysis
14 pruritus,³⁸ tinnitus and vertigo.³⁹ Nicergoline has a positive effect on cognition and behaviour in
15 addition to an effect on clinical global impression in older patients with mild to moderate
16 cognitive and behavioural impairment of various clinical origins including chronic
17 cerebrovascular disorders and Alzheimer's dementia.¹
18
19
20
21
22
23
24

25
26 Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep
27 disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and
28 increased appetite.^{7,21} Cardiovascular events like temporary rise in BP, syncope, bradycardia, and
29 hypotension have been reported with nicergoline by few studies.^{17,40}
30
31
32
33
34
35
36

37 Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and
38 abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have
39 reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure,
40 and interstitial nephritis.^{41,42}
41
42
43
44
45

46
47 Results of this meta-analysis showed comparable safety profile of nicergoline with other active
48 agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to
49 adverse events were similar with nicergoline compared to placebo & active agents. Incidence of
50 any adverse event when compared to placebo and ergot derivatives was slightly higher in the
51 nicergoline group but the difference was non-significant. Significantly lower rates of anxiety
52 were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like
53
54
55
56
57
58
59
60

1
2
3 diarrhoea, dizziness, drowsiness, gastric upset and fatigue were slightly lower with nicergoline as
4
5 compared to placebo but the difference was non-significant for all comparisons.
6
7

8 Nicergoline was associated with higher rates of hot flushes, headache, hypotension, insomnia
9
10 and itching. None of the comparisons showed a significant difference but some of these adverse
11
12 events are probably because of the vasodilation action of nicergoline. Higher doses of
13
14 nicergoline (60 mg/day) were associated with higher rates of adverse events compared to the 30
15
16 mg/day dosing but the difference was not significant. None of the studies included in this meta-
17
18 analysis reported any incidence of fibrosis or ergotism with nicergoline.
19
20
21

22
23 In its current recommendation, the EMEA has overlooked the efficacy and safety profile of
24
25 nicergoline and has cautioned against its use in conditions with blood circulation problems,
26
27 memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban
28
29 on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA
30
31 has probably considered the safety profile of all ergot derivatives as similar. The CHMP review
32
33 has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest
34
35 incidence of these AEs with other ergot derivatives as well.
36
37
38

39 EMEA has suggested that echocardiography should be done within 3–6 months of starting
40
41 treatment with ergot derivatives and subsequently at 6–12-month interval.⁴³ In the current meta-
42
43 analysis, most of the included studies were >3 months and up to 24 months in duration and none
44
45 of the included studies reported any incidence of fibrosis or ergotism with nicergoline. There is
46
47 no evidence in literature to suggest any incidence of fibrosis and ergotism with nicergoline.
48
49
50

51 The strengths of this systematic review include the clear definition of the research question,
52
53 adherence to an explicit research protocol that was developed prior to the analysis, the
54
55 comprehensive nature of the data search (employing both electronic databases and manual
56
57 bibliography searches resulting in the inclusion of all relevant publications), consensus between
58
59
60

1
2
3 two reviewers of all data elements prior to entry into the database and the quality control review
4
5 of every element of this report. In addition, the quality of the studies and manuscripts used to
6
7 provide data were relatively high. Only RCTs were included in this systematic review/meta-
8
9 analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to
10
11 compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this
12
13 review could be the publication timeframe of the included studies. Most of the studies were
14
15 published in 1980s and 1990s. There were hardly any trials published in recent years on safety
16
17 evaluation for nicergoline.
18
19

20 21 22 **Conclusions**

23
24
25 This systematic review & meta-analysis has included the evidence to date with regards to
26
27 tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is
28
29 categorized under ergot derivatives. However, the adverse events with nicergoline are mild and
30
31 transient unlike other ergot derivatives (ergotamine & ergotamine) which have been associated
32
33 with fibrosis and ergotism.
34
35

36
37 The results from this systematic review/meta-analysis suggest that nicergoline has a comparable
38
39 safety profile as placebo and other active comparators. None of the studies included in this
40
41 systematic review reported any incidence of fibrosis or ergotism with nicergoline. The evidence
42
43 generated by this review suggests that despite being an ergot derivative, nicergoline is a safe and
44
45 well-tolerated drug. This systematic review/meta-analysis concludes that nicergoline is a safe
46
47 option for therapeutic management in patients with dementia and cerebrovascular disorders.
48
49

50 51 52 **List of abbreviations**

53
54 AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA:
55
56 European Medicines Agency; SAEs: serious adverse event
57
58
59
60

Tables

Table 1: Study methods for included RCTs

| Study Name | Study duration | Country | Blinding | Intervention | Comparator | Daily Dose of Nicergoline |
|---------------------------------|----------------|-----------|--------------|--------------|--------------------|---------------------------|
| Arrigo 1982 ⁶ | 14 weeks | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1989 ⁷ | 6 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1990 ⁸ | 6 months | Italy | Double-blind | Nicergoline | Ergot mesylate | 60mg |
| Battaglia 1995 ⁹ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Bes 1999 ¹⁰ | 24 months | France | Double-blind | Nicergoline | Placebo | 60mg |
| Boss 1985 ¹¹ | - | Italy | Double-blind | Nicergoline | Buflomedil | 8mg |
| Brola 1997 ¹² | 1 month | Poland | Single-blind | Nicergoline | Pentoxifylline | 30mg |
| Cascone 1978 ¹³ | 1 month | Italy | Double-blind | Nicergoline | Placebo | 15mg |
| Colombeau 1987 ¹⁴ | 15 days | France | Double-blind | Nicergoline | Placebo | 40mg |
| Crook 1997 ¹⁵ | 6 months | USA | Double-blind | Nicergoline | Placebo | 60mg |
| Dubreuil 1986 ¹⁶ | 1 month | France | Double-blind | Nicergoline | GBE | NR |
| Felisati 2002 ¹⁷ | 3 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Forette 1980 ¹⁸ | 3 weeks | France | Double-blind | Nicergoline | Placebo | 30mg |
| Gessner 1985 ¹⁹ | 12 weeks | Germany | Double-blind | Nicergoline | GBE | 15mg |
| Herrmann 1997 ²⁰ | 6 months | Germany | Double-blind | Nicergoline | Placebo | 60mg |
| Kugler 1985 ²¹ | 6 months | Germany | Double-blind | Nicergoline | Dihydro-ergotamine | 30mg |
| Lu 2001 ²² | 12 weeks | China | Double-blind | Nicergoline | Aniracetam | 60mg |
| Marolda 1978 ²³ | 20 days | Italy | Double-blind | Nicergoline | Eburnamonine | 15-20mg |
| Materna 1985 ²⁴ | 12 weeks | Germany | Double-blind | Nicergoline | Flunarizine | 10-30mg |
| Nakashima 2011 ²⁵ | 6 months | Japan | Double-blind | Nicergoline | Imidapril | 15mg |
| Nappi 1997 ²⁶ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Nishiyama 2010 ²⁷ | 4 weeks | Japan | Open-label | Nicergoline | Placebo | 45mg |
| Pilkowska 2002 ²⁸ | 3 months | Poland | Double-blind | Nicergoline | Placebo | 60mg |
| Pogliani 1979 ²⁹ | 3 months | Germany | Double-blind | Nicergoline | Placebo | 15mg |
| Ronchi 1982 ³⁰ | 6 Days | Italy | Double-blind | Nicergoline | Placebo | |
| Saletu 1995 ³¹ | 8 weeks | Austria | Double-blind | Nicergoline | Placebo | 30-60mg |
| Setyopranoto 2009 ³² | - | Indonesia | Double-blind | Nicergoline | Placebo | 60mg |
| Winblad 2001 ³³ | 6 months | Europe | Double-blind | Nicergoline | Placebo | 60mg |
| Zucconi 1974 ³⁴ | 1 month | Italy | Double-blind | Nicergoline | Dihydro-ergotoxine | 2mg i.m. |

Table 2: Meta analysis of withdrawal rate across included studies

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|-----------------------|--------------|---------------|---------|------|-------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Total withdrawals | Nicergoline | Placebo | 8 | 1234 | 0.92 (0.70, 1.21) | 0.57 | 0% |
| | Nicergoline | Active agents | 3 | 201 | 0.45 (0.10, 1.95) | 0.28 | 18% |
| Withdrawals due to AE | Nicergoline | Placebo | 3 | 565 | 1.13 (0.61, 2.09) | 0.7 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Table 3: Meta analysis of overall adverse events

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|---------------|--------------|-------------------|---------|------|--------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Any AE | Nicergoline | Placebo | 10 | 1448 | 1.05 (0.93, 1.20) | 0.42 | 0% |
| Any AE | Nicergoline | Active agents | 4 | 292 | 1.19 (0.71, 2.01) | 0.51 | 5% |
| Any AE | Nicergoline | Ergot derivatives | 2 | 200 | 1.22 (0.63, 2.34) | 0.56 | 19% |
| Any SAE | Nicergoline | Placebo | 2 | 482 | 0.85 (0.50, 1.45) | 0.54 | 35% |
| Anxiety | Nicergoline | Placebo | 2 | 482 | 0.59 (0.39, 0.88) | 0.01 | 0% |
| Diarrhoea | Nicergoline | Placebo | 2 | 188 | 0.85 (0.24, 3.05) | 0.8 | 0% |
| Diarrhoea | Nicergoline | Ergot derivatives | 2 | 200 | 0.99 (0.14, 6.92) | 0.99 | 0% |
| Dizziness | Nicergoline | Placebo | 3 | 260 | 0.63 (0.15, 2.57) | 0.51 | 0% |
| Dizziness | Nicergoline | Active agents | 2 | 116 | 1.00 [0.18, 5.58] | 1.0 | 0% |
| Drowsiness | Nicergoline | Placebo | 2 | 442 | 0.34 (0.05, 2.12) | 0.24 | 0% |
| Fatigue | Nicergoline | Placebo | 2 | 378 | 0.71 (0.14, 3.53) | 0.68 | 18% |
| Fatigue | Nicergoline | Active agents | 3 | 260 | 1.24 (0.35, 4.47) | 0.74 | 0% |
| Fatigue | Nicergoline | Ergot derivatives | 2 | 200 | 1.79 (0.40, 7.98) | 0.45 | 0% |
| Gastric upset | Nicergoline | Placebo | 6 | 1037 | 0.94 (0.58, 1.52) | 0.8 | 0% |
| Hot Flushes | Nicergoline | All comparisons | 3 | 470 | 3.65 (0.61, 21.93) | 0.16 | 0% |
| Headache | Nicergoline | Placebo | 5 | 1004 | 1.28 (0.63, 2.60) | 0.24 | 0% |
| Hypotension | Nicergoline | Placebo | 2 | 378 | 1.49 (0.26, 8.72) | 0.66 | 0% |
| Insomnia | Nicergoline | Placebo | 3 | 498 | 1.81 (0.39, 8.29) | 0.45 | 0% |
| Itching | Nicergoline | All comparisons | 2 | 108 | 3.23 (0.35, 30.08) | 0.3 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

1
2
3 **Contributorship Statement:** AG carried out the searches in various databases. AG and JX
4 carried out the filtration of citation. AG and JX carried out the data extraction, MF and TN
5 helped to draft the manuscript and reviewed it. All authors read and approved the final
6 manuscript.
7
8

9
10 **Competing Interests:** None

11
12 **Funding:** None

13
14 **Data Sharing Statement:** In addition to the manuscript, the corresponding author
15 also has initial results of publication analysis. That explains the reason for inclusion
16 and exclusion of individual studies.
17
18
19

20 21 22 23 **Figure Legends**

24
25 Figure 1: Results of meta-analysis, all withdrawals: Nicergoline vs. Placebo

26
27 Figure 2: Results of meta-analysis, any adverse events: Nicergoline vs. Placebo
28
29
30
31
32
33

34 35 **References**

- 36
37 1. Fioravanti M, Flicker L. Efficacy of nicergoline in dementia and other age associated forms
38 of cognitive impairment. Cochrane Database Syst Rev 2001:CD003159.
39
40 2. Carfagna N, Di Clemente A, Cavanus S, et al. Modulation of hippocampal ACh release by
41 chronic nicergoline treatment in freely moving young and aged rats. Neurosci Lett
42 1995;197:195-8.
43
44 3. Carfagna N, Rossi A. Nicergoline: biochemical studies on neuronal metabolism. Funct
45 Neurol 1989;4:177-85
46
47 4. Winblad B, Fioravanti M, Dolezal T, et al. Therapeutic use of nicergoline. Clin Drug Investig
48 2008;28:533-52.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 5. New restrictions on use of medicines containing ergot derivatives.
4
5 [http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC50014
6
7 4861.pdf.]
8
- 9
10 6. Arrigo A, Moglia A, Borsotti L. A double-blind, placebo-controlled, crossover trial with
11
12 nicergoline in patients with senile dementia. *International Journal of Clinical Pharmacology*
13
14 *Research* 1982;2:33-41.
15
- 16 7. Battaglia A, Bruni G, Ardia A, et al. Nicergoline in mild to moderate dementia. A
17
18 multicenter, double-blind, placebo-controlled study. *J Am Geriatr Soc* 1989;37:295-302.
19
- 20 8. Battaglia A, Bruni G, Sacchetti G, et al. A double-blind randomized study of two ergot
21
22 derivatives in mild to moderate dementia. *Curr Therap Res* 1990;48:597-612.
23
24
- 25 9. Battaglia A, Annoni K, Pamparana F, et al. Nicergoline in the Long Term Treatment of Mild
26
27 or Moderate Senile Dementia. A Multicenter Double-blind, Randomized, Placebo- controlled
28
29 Trial. In 8th European College of Neuropsychopharmacology Congress: 30th September -
30
31 4th October 1995; Venice.
32
33
- 34 10. Bes A, Orgogozo JM, Poncet M, et al. A 24-month, double-blind, placebo-controlled
35
36 multicentre pilot study of the efficacy and safety of nicergoline 60 mg per day in elderly
37
38 hypertensive patients with leukoaraiosis. *European Journal of Neurology* 1999;6:313-22.
39
40
- 41 11. Bossi L. Buflomedil and nicergolin in the treatment of acute cerebral ischaemia. A double-
42
43 blind, randomized comparative study. *Minerva Medica* 1985;76:1005-18.
44
- 45 12. Broła W. Evaluation of treatment outcome after nicergoline and pentoxifylline in patients
46
47 with ischemic stroke. *Przegląd Lekarski* 1997;54:79-82.
48
- 49 13. Cascone A, Liverta C, Pollini C. A double-blind trial of nicergolin and placebo in cerebral
50
51 and peripheral cerebrovascular disturbance in the aged. *Minerva Cardioangiologica* 1978;
52
53 26:95-100.
54
55
56
57
58
59
60

- 1
2
3 14. Colombeau P, Ballanger P. Results of the double-blind use of an alpha blockader,
4
5 nicergoline, in cervico-prostatic dysfunctions. *Journal d'urologie* 1987;93:533-5.
6
- 7
8 15. Crook TH. Nicergoline in the treatment of probable Alzheimer's disease Preliminary results
9
10 of a double-blind, randomized, placebo-controlled study. *J Neurol Sci* 1997:S18.
- 11
12 16. Dubreuil C. Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo
13
14 biloba extract and nicergoline. *Presse médicale (Paris, France : 1983)* 1986;15:1559-61.
15
- 16
17 17. Felisati G, Battaglia A, Papini MG, et al. Nicergoline in balance alterations in adult and
18
19 elderly patients: A double-blind, placebo-controlled study. *Clinical Drug Investigation*
20
21 2002;22:731-40.
22
- 23
24 18. Forette F, Varin D, Henry JF, et al. Treatment of arterial hypertension in the elderly with an
25
26 alpha-blocker: nicergoline (author's transl). *La Nouvelle presse médicale* 1980, 9:3685-8.
- 27
28 19. Gessner B, Voelp A, Klasser M. Study of the long-term action of a Ginkgo biloba extract on
29
30 vigilance and mental performance as determined by means of quantitative pharmaco-EEG
31
32 and psychometric measurements. *Arzneimittel-Forschung/Drug Research* 1985;35:1459-65.
33
- 34
35 20. Herrmann WM. A multicenter randomized double-blind study on the efficacy and safety of
36
37 nicergoline in patients with multi-infarct dementia. *Dementia and Geriatric Cognitive*
38
39 *Disorders* 1997;8:9-17.
40
- 41
42 21. Kugler JE, Meurer-Krull BC. Electroencephalography and psychometric measurements
43
44 during the treatment of cerebral insufficiency with nicergoline and dihydroergotamine
45
46 mesylate. *Arzneimittelforschung* 1985;35:1865-70.
47
- 48
49 22. Lu JH. Nicergoline in treatment of vascular dementia: a consecutive, multicenter, double-
50
51 blind clinical trial. *Chinese J Neurol* 2001:88-91.
- 52
53 23. Marolda M, Fragassi N, Buscaino GA. Clinical evaluation of (-)eburnamonine in comparison
54
55 with nicergoline in patients suffering from chronic brain ischemia. *European Neurology*
56
57 1978, 17:159-66.
58
59
60

- 1
2
3 24. Materna F. Leading symptom vertigo: Comparative study with flunarizine and nicergoline.
4
5 Medizinsische Klinik 1985, 80:292-5.
6
7
8 25. Nakashima T, Hattori N, Okimoto M, et al. Nicergoline improves dysphagia by upregulating
9
10 substance p in the elderly. *Medicine* 2011;90:279-83.
11
12 26. Nappi G, Bono G, Merlo P, et al. Long-term nicergoline treatment of mild to moderate
13
14 senile dementia. Results of a multicentre, double-blind, placebo-controlled study. *Clinical*
15
16 *Drug Investigation* 1997;13:308-16.
17
18 27. Nishiyama Y, Abe A, Ueda M, et al. Nicergoline increases serum substance P levels in
19
20 patients with an ischaemic stroke. *Cerebrovascular Diseases* 2010;29:194-8.
21
22 28. Pilkowska E, Jakubowska T, Witkowska K, et al. Nicergoline in the treatment of patients
23
24 after a mild ischemic stroke. *Neurologia i neurochirurgia polska* 2002;36:1075-85.
25
26 29. Pogliani E, Della Volpe A, Ferrari R. Inhibition of human platelet aggregation by oral
27
28 administration of nicergoline. A double blind study. *Farmaco, Edizione Pratica* 1975;30:630-
29
30 40.
31
32 30. Ronchi F, Margonato A, Ceccardi R. Symptomatic treatment of benign prostatic obstruction
33
34 with nicergoline: A placebo controlled clinical study and urodynamic evaluation. *Urological*
35
36 *Research* 1982;10:131-34.
37
38 31. Saletu B, Paulus E, Linzmayer L, et al. Nicergoline in senile dementia of Alzheimer type
39
40 and multi-infarct dementia: A double blind, placebo controlled, clinical and EEG/ERP
41
42 mapping study. *Psychopharmacology* 1995;117:385-95.
43
44 32. Setyopranoto ISP. Role of nicergoline 60 miligram per oral for improvement of the patients
45
46 with acute ischemic stroke. *Journal of the Neurological Sciences* 2009;285:S221-S222.
47
48 33. Winblad B, Bonura ML, Rossini BM, et al. Nicergoline in the treatment of mild-to-moderate
49
50 Alzheimer's disease: A European multicentre trial. *Clinical Drug Investigation* 2001;21:621-
51
52 32.
53
54
55
56
57
58
59
60

- 1
2
3 34. Zucconi V, Terzi Bolaffio M. Results with nicergolin and dihydroergotoxine in 30
4
5 hemiplegics in the postacute phase. *Minerva Medica* 1974;65:936-45.
6
7
8 35. Alvarez-Guerra M, Bertholom N, Garay RP. Selective blockade by nicergoline of vascular
9
10 responses elicited by stimulation of alpha 1A-adrenoceptor subtype in the rat. *conam Clin*
11
12 *Pharmacol* 1999;13:50-8.
13
14 36. Shintomi K, Yoshimoto K, Ogawa Y, et al. Effects of nicergoline on cerebral energy
15
16 metabolism in normal mice. *Yakugaku Zasshi* 1986;106:90-4.
17
18 37. Sortino MA, Battaglia A, Pamparana F, et al. Neuroprotective effects of nicergoline in
19
20 immortalized neurons. *Eur J Pharmacol* 1999;368:285-90.
21
22
23 38. Bousquet J, Rivory JP, Maheut M, et al. Double-blind, placebo-controlled study of
24
25 nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J*
26
27 *Allergy Clin Immunol* 1989;83:825-28.
28
29 39. Akisada T, Orita Y, Sato Y, et al. Effect of nicergoline on vertigo and tinnitus. *Practica*
30
31 *Otologica* 1994;87:845-55.
32
33
34 40. Boismare F, Lefrancois J. Haemodynamic effects of nicergoline in man at rest and during
35
36 exercise. *Clin Exp Pharmacol Physiol* 1980;7:105-12.
37
38
39 41. Gallego J, Forner V, Jimenez F, et al. Nicergoline in the treatment of neuropathic bladder
40
41 dysfunction: a preliminary report. *Paraplegia* 1984;22:216-24.
42
43 42. Kim MJ, Chang JH, Lee SK, et al. Acute interstitial nephritis due to nicergoline (Sermion).
44
45 *Nephron* 2002;92:676-79.
46
47 43. Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses.

48
49
50 <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087807>
51
52
53
54
55
56
57
58
59
60

1
2
3
4 Title of the article:
5

6
7 **A systematic review and meta-analysis assessing safety and tolerability of nicergoline**
8
9

10 Corresponding author:
11

12 Dr. Amit Garg, M.D.

13 Physician
14

15 A Wing- 304, Aparna Towers
16

17 Kondapur, Kothaguda,
18

19 Hyderabad-500084
20

21 Email: amitgarg.pharm@gmail.com
22

23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Tele: +918790902800

31 Authors:
32

33 Mario Fioravanti¹, Taku Nakashima², Jun Xu³, Amit Garg⁴
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

37 Affiliations:
38

39 1. Prof. Mario Fioravanti, M.D.

40
41 Director of the Clinical Psychology Service
42

43 University Hospital, Umberto I
44

45 Professor of Clinical Psychology
46

47 Department of Neurology and Psychiatry
48

49 University of Rome, Sapienza, Italy
50

51 E-mail: mario.fioravanti@uniroma1.it
52
53
54

55 2. Taku Nakashima, MD, PhD.
56

57 Dept. of Molecular & Internal Medicine,
58
59
60

1
2
3 Hiroshima University Hospital

4
5 1-2-3 Kasumi, Minami-ku Hiroshima, 734-8551 Japan

6
7 E-mail: tnaka@hiroshima-u.ac.jp/tnaka@eos.ocn.ne.jp

8
9
10 3. Prof. Jun Xu

11 Hospital: Jiangsu Province Geriatric Hospital, China

12
13 Email: 13611572068@126.com ; neurojun@126.com

14
15
16 4. Dr. Amit Garg, M.D.

17 Physician, A-Wing- 304, Aparna Towers

18
19 Kondapur, Kothaguda, Hyderabad-500084. India

20
21 Email: amitgarg.pharm@gmail.com

22
23
24
25
26
27
28
29 Keywords:

30
31
32 Meta-analysis, nicergoline, ergot derivatives, fibrosis, ergotism

33
34
35 Word Count:

36
37 2649 words

Abstract

Objective: To evaluate the safety profile of nicergoline compared to placebo and other active agents from published randomised controlled trials.

Design: Systematic review and meta-analysis of nicergoline compared to placebo and other active agents across various indications.

Data sources: Medline, Medline-in-process, Cochrane, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register (CMR) for all the randomized controlled trials, open-label or blinded, in adults treated with nicergoline. Studies published till August 2013 were included.

Review method: Twenty nine studies were included for data extraction. The studies included in this review were majorly from European countries and mostly in cerebrovascular disease (n=15) and dementia (n=8).

Results: The treatment withdrawals were comparatively lower in nicergoline group as compared to placebo group (RR: 0.92; 95%CI: 0.7, 1.21) and other active comparators (RR: 0.45; 95%CI: 0.10, 1.95) but the difference was non-significant. Incidence of any adverse events was slightly higher (RR: 1.05; 95%CI: 0.93, 1.2) while incidence of serious adverse events was lower (RR: 0.85; 95%CI: 0.50, 1.45) in nicergoline compared to placebo group. Frequency of anxiety was significantly lower in Nicergoline as compared to placebo (p=0.01). Other AEs including diarrhoea, gastric upset, dizziness and drowsiness were less frequent in Nicergoline group compared to placebo/active drugs but the difference was non-significant. Frequency of hypotension and hot flushes was slightly higher in nicergoline group but the difference was non-

1
2
3 significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline
4
5 treatment.
6

7 **Conclusions:** Nicergoline is an ergot derivatives but the safety profile is better than other ergot
8
9 derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest
10
11 that nicergoline has a good safety profile. None of the studies included in this systematic review
12
13 reported any incidence of fibrosis or ergotism with nicergoline.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 Article Summary:
5
6

7 **Article focus:**

- 8
9 - Currently not many options are available for management of cognitive
10 impairment including pre-dementia and dementia.
11
12 - Despite no known association of nicergoline with ergotism, regulators have
13 limited the use of same
14
15 - This meta-analysis is in effort to find the exact side effect profile and benefit
16 to risk evaluation
17
18
19
20
21

22 **Key messages:**

- 23
24 - No evidence was found to suggest any incidence of fibrosis and ergotism with
25 nicergoline
26
27
28 - Nicergoline is found to be a very safe alternative in a disease (cognitive
29 impairment) with lean pipeline
30
31
32

33 **Strengths and limitations of this study:**

- 34
35 - First meta-analysis on nicergoline to understand the adverse clinical profile
36
37 - Critical in wake of recent EMEA view of blanket limitation on use of all ergot
38 derivatives
39
40
41 - Limited by the availability of long term (more than 2 years) and high dose
42 studies for cognitive impairment
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Title:**A systematic review and meta-analysis assessing safety and tolerability of nicergoline****Background**

Nicergoline is a semi synthetic ergot derivative which has been registered in over fifty countries and has been used for more than four decades for the treatment of cognitive, affective, and behavioural disorders of older people.¹ During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Although cholinergic deficits are the major current targets for pharmacological intervention in Alzheimer's dementia, a wide variety of other neurotransmitter changes can be identified in the disease.

Nicergoline has been demonstrated to increase the availability of acetylcholine both through an increased release from cholinergic terminals and a selective inhibition of acetyl cholinesterase.²

Nicergoline may also enhance noradrenalin and dopamine turnover in some areas of the brain.³

Nicergoline has a positive effect on the signal transduction system stimulating the phosphoinositide pathway which is specifically impaired in Alzheimer's dementia.⁴ Other useful actions of Nicergoline in dementia are an increase of phosphoinosiphosphoinositide-PKC translocation which helps in combating beta-amyloid deposition and in retarding the reduction in nerve-growth factor (NGF) which may help in preventing the loss of cholinergic neurons.⁴

The side effects of Nicergoline are usually limited to nausea, hot flushes, mild gastric upset, hypotension and dizziness. At high dosages bradycardia, increased appetite, agitation, diarrhoea and perspiration have been known to occur. Nicergoline has a better safety profile compared to ergot derivates which are associated with increased risk of fibrosis (formation of excess

connective tissue that can damage organs and body structures) and ergotism (symptoms of ergot poisoning, such as spasms and obstructed blood circulation) with these medicines.

Nicergoline is not associated with either fibrosis or ergotism however; concerns about its safety have been raised, especially after the European Medicines Agency's (EMA) restriction on nicergoline because it is an ergot derivative.⁵ Most of the available literature suggests that the adverse events with nicergoline are mild and transient. Hence, a systematic review of literature and meta-analysis was conducted to compare the safety profile of nicergoline with placebo and other active comparators.

Methods

Search strategy

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. The following databases were examined since inception up to 16th August 2013; Medline, Medline-in-process, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register. Medical subject headings (MeSH terms) and free keywords like "randomised controlled trial", "Nicergoline", "Adverse effects", "toxicity" and "side effects" were used. This review was not restricted to studies conducted in English language and hence studies published in other languages were also included and translated for data extraction.

Selection criteria

To meet the study objective, we pre-decided on inclusion criteria which include RCTs reporting adverse events in patients undergoing nicergoline treatment for psychiatric disorders. To be included in the analysis, a trial had to fulfill the following criteria: 1) randomized trials which could be open-label, single-blind, or double-blind, parallel group studies; 2) use of nicergoline

1
2
3 for Alzheimer's disease, dementia or cognitive disorders; 3) use of nicergoline as one of the
4 interventions; 3) Studies comparing nicergoline with ergot derivatives, placebo, or other active
5 agents were included; 4) Studies should report safety and tolerability data for nicergoline.
6
7
8

9
10 Studies were excluded if: 1) presented data for children only; 2) study design was not of interest;
11 3) disease was other than of interest; 4) study was not presenting safety and tolerability
12 outcomes; 5) full-text could not be sourced.
13
14
15

16 17 18 **Data extraction**

19
20 Bibliographic details and abstracts of all citations retrieved by the literature search were
21 downloaded into Endnotes version X3. Cochrane methodology was used to conduct this
22 systematic review. All studies were screened by two independent reviewers with discrepancies
23 resolved by a third reviewer.
24
25
26
27
28
29

30 31 **Outcomes assessed**

32
33
34 In most of the included studies, safety evaluation included monitoring of adverse events, vital
35 signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at
36 baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-
37 emergent adverse events (elicited or observed); physical examination including ECG recording;
38 vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to
39 adverse event were reported.
40
41
42
43
44
45
46
47

48
49 The data from these studies were pooled for total withdrawals, withdrawals due to AEs,
50 incidence rates for any AEs, SAEs, and specific AEs including anxiety, constipation, diarrhoea,
51 hot flushes, itching, gastric upset, hypotension, headache, dizziness, insomnia, drowsiness and
52 fatigue. Only studies which presented data for same comparators were included in direct meta-
53 analysis for each outcome.
54
55
56
57
58
59
60

Statistical analysis

Comparison of safety and tolerability outcomes were made between interventions by pooling data from studies using direct meta-analysis technique. Only head-to-head comparisons between interventions were included for meta-analysis. Review Manager (RevMan v 5.1) software was used for meta-analysis of the available data. Dichotomous outcomes were summarised as risk (relative) ratios.

Results

Study selection

A trial flow of the review process (as per PRISMA statement) is presented along with manuscript. The search of the literature yielded 437 separate references. Due to the overlap of coverage between the databases, 96 of the references were found to be duplicates. A total of 341 citations were reviewed for abstract screening (first pass). Following the first pass of the citations, 56 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports, 26 citations were excluded. Thirty studies met inclusion criteria however one of them was a secondary publication which was linked to its primary publication. Finally, a total of 29 references reporting trials were extracted. Table 1 presents an overview of the study methods in included studies. Fifteen studies were not included in meta-analysis as data from these could not be pooled. These were studies reporting standalone adverse events, or for standalone comparators.

Baseline Characteristics

Most of the included studies were in cerebrovascular disease (n=15), followed by Dementia (n=8). Two studies were for Alzheimer's disease and four were in other disease areas. The mean

1
2
3 age of included patients ranged from 48 years (Dubreuil 1986) to 81 years (Saletu 1995) across
4
5 the studies. The % of male patients ranged from 17.9% (Saletu 1995) to 76.7% (Nakashima
6
7 2011) in Nicergoline group and was comparable with control group in all studies). The number
8
9 of patients randomized in these studies ranged from 16 (Ronchi 1982) to 346 (Winblad
10
11 2001).The treatment/study duration ranged from 6 days (Ronchi 1982) to 24 months (Bes 1999)
12
13 across included studies with most studies with duration ≥ 3 months (n=17). The daily dose of
14
15 nicergoline used was ≤ 30 mg/day in 16 studies and was reported to be 60 mg/daily in 12 studies.
16
17
18
19

20 21 22 **Critical Appraisal**

23
24 Included studies were critically appraised using the Jadad scale which is a standard scale used for
25
26 evaluating quality of randomised trials in systematic reviews. Method used to generate random
27
28 allocation sequence was reported in only nine of the included studies and were judged as
29
30 adequate. None of the study reported the method used for concealment of allocation sequence.
31
32 The Jadad score was ≥ 3 in 20 studies and less than 3 in nine studies. Majority of the studies were
33
34 good quality studies as per Jadad scale. All of included studies reported comparable baseline
35
36 characteristics between treatment groups being studied.
37
38
39
40
41
42

43 44 **Withdrawals**

45
46 Total withdrawals with nicergoline ranged from 0% (Kugler 1985, Materna 1985) to 22.2% (Bes
47
48 1999) and from 0%- 27.8% with other comparator drugs/placebo. Six studies reported lower
49
50 number of patient withdrawals from nicergoline group as compared to other comparator/placebo
51
52 groups. Withdrawals due to AE were similar in nicergoline group as compared to other groups
53
54 across the studies, Figure 1.
55
56
57
58
59
60

1
2
3 The meta-analyzed risk ratios between nicergoline and the other comparators and their
4
5 corresponding 95% confidence intervals for study withdrawals are shown in Tables 2. Results of
6
7 meta-analysis showed a non-significant lower rate of withdrawals from nicergoline compared to
8
9 placebo ($p=0.57$) and other active agents ($p=0.28$). For withdrawals due to AE, the withdrawal
10
11 rate was slightly higher with nicergoline when compared to placebo but the difference was only
12
13 apparent and non-significant ($p=0.7$).
14

15 16 17 **Adverse Events**

18
19
20 There was adequate data to perform meta-analysis for safety outcomes including any AE, any
21
22 serious AE, diarrhoea, hot flushes, gastric upset, itching, hypertension, headache, dizziness,
23
24 anxiety, insomnia, drowsiness and fatigue (Supplementary Table 1). However, there was no
25
26 reference to cases with fibrosis and/or ergotism.
27

28
29
30 The meta-analyzed risk ratios between nicergoline and the other comparators and their
31
32 corresponding 95% confidence intervals for study withdrawals and safety outcomes are shown in
33
34 Tables 2, and 3, respectively. Results of meta-analysis showed a non-significant lower rate of
35
36 withdrawals from nicergoline compared to placebo ($p=0.57$) and other active agents ($p=0.28$).
37
38 For withdrawals due to AE, the withdrawal rate was slightly higher with nicergoline when
39
40 compared to placebo but again the difference was non-significant ($p=0.7$).
41
42

43
44 The risk of any adverse event was similar with nicergoline compared to placebo (10 studies),
45
46 ergot derivatives and other active comparators, all comparisons being non-significant. Risk of
47
48 any serious adverse event was slightly lower in the nicergoline group compared to placebo but
49
50 was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline
51
52 as compared to placebo ($p=0.01$). Nicergoline was associated with lower risk of diarrhoea as
53
54 compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence
55
56 of dizziness was similar in nicergoline group as compared to placebo or other active agents. A
57
58
59

1
2
3 comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but
4
5 the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo
6
7 group.
8
9

10
11 Higher risk of fatigue was associated with nicergoline compared to active comparators including
12
13 ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported
14
15 with nicergoline compared to other comparators. Risk of headache and hypotension was higher
16
17 with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with
18
19 nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any
20
21 significant difference was observed compared to the other intervention or placebo, Figure 2.
22
23

24
25 Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in
26
27 eight studies during the entire study duration, while remaining studies reported excellent or good
28
29 tolerability in nicergoline treated patients. None of these studies reported any incidence of
30
31 ergotism or fibrosis with nicergoline.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Discussion

Nicergoline is a potent and selective alpha-1A adrenergic receptor antagonist.³⁵ Nicergoline is reported to enhance catecholaminergic turnover,³ stimulate cholinergic neuro-transmission,⁴ stimulate phosphoinositide pathway,³ promote cerebral metabolic activity,³⁶ and has neuroprotective and antioxidant properties.³⁷ Nicergoline is used clinically to improve the apathy and affective disorders caused by cerebral infarction (such as reduced mental alertness, inattention, impairment of recent memory, hypobulia, depression, etc.). It is useful in the treatment of acute and chronic peripheral circulation disorders (such as obliterative vascular disease of the limbs, Raynaud's syndrome and other peripheral circulation dysfunction symptoms). Nicergoline has also been prescribed for the treatment of vascular dementia, especially for the improvement in cognitive dysfunction and memory, and to reduce the severity of this disease.

In addition, studies have been reported showing the usefulness of nicergoline in conditions such as post-hemodialysis pruritus, tinnitus and vertigo, ocular conditions such as arterial obstructions, venous thrombosis, diabetic retinopathies, senile macular degenerations, papilla ischaemic oedema and central serous chorioretinopathies. Dosages for known conditions are usually administered at 5–10 mg three times a day, however anti-aging preventative purposes may limit this to 5 mg once or twice a day. Higher doses of up to 60 mg/day have also been prescribed in clinical practice but have been associated with increased risk of adverse events.⁴

The EMEA's Committee for Medicinal Products for Human Use (CHMP) in its recommendations has suggested that ergot containing medicines, including nicergoline, should no longer be used to treat conditions involving blood circulation problems (such as peripheral artery disease, Raynaud's syndrome and retinopathies of vascular origin), memory and sensation problems and migraine headaches. This recommendation has been supported by the EMEA

1
2
3 citing that these ergot derivatives have a high likelihood of causing serious adverse events such
4
5 as fibrosis and ergotism.⁵ However, in this recommendation, the EMEA suggests that healthcare
6
7 professionals can continue prescribing nicergoline and other ergot derivatives in dementia
8
9 (including Alzheimer's disease) and acute migraine.
10

11
12 Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-
13
14 infarct dementia.^{1,31} Also, nicergoline has shown efficacy in conditions like post-hemodialysis
15
16 pruritus,³⁸ tinnitus and vertigo.³⁹ Nicergoline has a positive effect on cognition and behaviour in
17
18 addition to an effect on clinical global impression in older patients with mild to moderate
19
20 cognitive and behavioural impairment of various clinical origins including chronic
21
22 cerebrovascular disorders and Alzheimer's dementia.¹
23
24

25
26 Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep
27
28 disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and
29
30 increased appetite.^{7,21} Cardiovascular events like temporary rise in BP, syncope, bradycardia, and
31
32 hypotension have been reported with nicergoline by few studies.^{17,40}
33
34
35

36
37 Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and
38
39 abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have
40
41 reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure,
42
43 and interstitial nephritis.^{41,42}
44
45

46
47 Results of this meta-analysis showed comparable safety profile of nicergoline with other active
48
49 agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to
50
51 adverse events were similar with nicergoline compared to placebo & active agents. Incidence of
52
53 any adverse event when compared to placebo and ergot derivatives was slightly higher in the
54
55 nicergoline group but the difference was non-significant. Significantly lower rates of anxiety
56
57 were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like
58
59
60

1
2
3 diarrhoea, dizziness, drowsiness, gastric upset and fatigue were slightly lower with nicergoline as
4
5 compared to placebo but the difference was non-significant for all comparisons.
6
7

8 Nicergoline was associated with higher rates of hot flushes, headache, hypotension, insomnia
9
10 and itching. None of the comparisons showed a significant difference but some of these adverse
11
12 events are probably because of the vasodilation action of nicergoline. Higher doses of
13
14 nicergoline (60 mg/day) were associated with higher rates of adverse events compared to the 30
15
16 mg/day dosing but the difference was not significant. None of the studies included in this meta-
17
18 analysis reported any incidence of fibrosis or ergotism with nicergoline.
19
20
21

22
23 In its current recommendation, the EMEA has overlooked the efficacy and safety profile of
24
25 nicergoline and has cautioned against its use in conditions with blood circulation problems,
26
27 memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban
28
29 on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA
30
31 has probably considered the safety profile of all ergot derivatives as similar. The CHMP review
32
33 has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest
34
35 incidence of these AEs with other ergot derivatives as well.
36
37
38

39 EMEA has suggested that echocardiography should be done within 3–6 months of starting
40
41 treatment with ergot derivatives and subsequently at 6–12-month interval.⁴³ In the current meta-
42
43 analysis, most of the included studies were >3 months and up to 24 months in duration and none
44
45 of the included studies reported any incidence of fibrosis or ergotism with nicergoline. There is
46
47 no evidence in literature to suggest any incidence of fibrosis and ergotism with nicergoline.
48
49
50

51 The strengths of this systematic review include the clear definition of the research question,
52
53 adherence to an explicit research protocol that was developed prior to the analysis, the
54
55 comprehensive nature of the data search (employing both electronic databases and manual
56
57 bibliography searches resulting in the inclusion of all relevant publications), consensus between
58
59
60

1
2
3 two reviewers of all data elements prior to entry into the database and the quality control review
4
5 of every element of this report. In addition, the quality of the studies and manuscripts used to
6
7 provide data were relatively high. Only RCTs were included in this systematic review/meta-
8
9 analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to
10
11 compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this
12
13 review could be the publication timeframe of the included studies. Most of the studies were
14
15 published in 1980s and 1990s. There were hardly any trials published in recent years on safety
16
17 evaluation for nicergoline.
18
19

20 21 22 **Conclusions**

23
24
25 This systematic review & meta-analysis has included the evidence to date with regards to
26
27 tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is
28
29 categorized under ergot derivatives. However, the adverse events with nicergoline are mild and
30
31 transient unlike other ergot derivatives (ergotamine & ergotamine) which have been associated
32
33 with fibrosis and ergotism.
34
35

36
37 The results from this systematic review/meta-analysis suggest that nicergoline has a comparable
38
39 safety profile as placebo and other active comparators. None of the studies included in this
40
41 systematic review reported any incidence of fibrosis or ergotism with nicergoline. The evidence
42
43 generated by this review suggests that despite being an ergot derivative, nicergoline is a safe and
44
45 well-tolerated drug. This systematic review/meta-analysis concludes that nicergoline is a safe
46
47 option for therapeutic management in patients with dementia and cerebrovascular disorders.
48
49

50 51 52 **List of abbreviations**

53
54 AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA:
55
56 European Medicines Agency; SAEs: serious adverse event
57
58
59
60

Tables

Table 1: Study methods for included RCTs

| Study Name | Study duration | Country | Blinding | Intervention | Comparator | Daily Dose of Nicergoline |
|---------------------------------|----------------|-----------|--------------|--------------|--------------------|---------------------------|
| Arrigo 1982 ⁶ | 14 weeks | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1989 ⁷ | 6 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1990 ⁸ | 6 months | Italy | Double-blind | Nicergoline | Ergot mesylate | 60mg |
| Battaglia 1995 ⁹ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Bes 1999 ¹⁰ | 24 months | France | Double-blind | Nicergoline | Placebo | 60mg |
| Boss 1985 ¹¹ | - | Italy | Double-blind | Nicergoline | Buflomedil | 8mg |
| Brola 1997 ¹² | 1 month | Poland | Single-blind | Nicergoline | Pentoxifylline | 30mg |
| Cascone 1978 ¹³ | 1 month | Italy | Double-blind | Nicergoline | Placebo | 15mg |
| Colombeau 1987 ¹⁴ | 15 days | France | Double-blind | Nicergoline | Placebo | 40mg |
| Crook 1997 ¹⁵ | 6 months | USA | Double-blind | Nicergoline | Placebo | 60mg |
| Dubreuil 1986 ¹⁶ | 1 month | France | Double-blind | Nicergoline | GBE | NR |
| Felisati 2002 ¹⁷ | 3 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Forette 1980 ¹⁸ | 3 weeks | France | Double-blind | Nicergoline | Placebo | 30mg |
| Gessner 1985 ¹⁹ | 12 weeks | Germany | Double-blind | Nicergoline | GBE | 15mg |
| Herrmann 1997 ²⁰ | 6 months | Germany | Double-blind | Nicergoline | Placebo | 60mg |
| Kugler 1985 ²¹ | 6 months | Germany | Double-blind | Nicergoline | Dihydro-ergotamine | 30mg |
| Lu 2001 ²² | 12 weeks | China | Double-blind | Nicergoline | Aniracetam | 60mg |
| Marolda 1978 ²³ | 20 days | Italy | Double-blind | Nicergoline | Eburnamonine | 15-20mg |
| Materna 1985 ²⁴ | 12 weeks | Germany | Double-blind | Nicergoline | Flunarizine | 10-30mg |
| Nakashima 2011 ²⁵ | 6 months | Japan | Double-blind | Nicergoline | Imidapril | 15mg |
| Nappi 1997 ²⁶ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Nishiyama 2010 ²⁷ | 4 weeks | Japan | Open-label | Nicergoline | Placebo | 45mg |
| Pilkowska 2002 ²⁸ | 3 months | Poland | Double-blind | Nicergoline | Placebo | 60mg |
| Pogliani 1979 ²⁹ | 3 months | Germany | Double-blind | Nicergoline | Placebo | 15mg |
| Ronchi 1982 ³⁰ | 6 Days | Italy | Double-blind | Nicergoline | Placebo | |
| Saletu 1995 ³¹ | 8 weeks | Austria | Double-blind | Nicergoline | Placebo | 30-60mg |
| Setyopranoto 2009 ³² | - | Indonesia | Double-blind | Nicergoline | Placebo | 60mg |
| Winblad 2001 ³³ | 6 months | Europe | Double-blind | Nicergoline | Placebo | 60mg |
| Zucconi 1974 ³⁴ | 1 month | Italy | Double-blind | Nicergoline | Dihydro-ergotoxine | 2mg i.m. |

Table 2: Meta analysis of withdrawal rate across included studies

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|-----------------------|--------------|---------------|---------|------|-------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Total withdrawals | Nicergoline | Placebo | 8 | 1234 | 0.92 (0.70, 1.21) | 0.57 | 0% |
| | Nicergoline | Active agents | 3 | 201 | 0.45 (0.10, 1.95) | 0.28 | 18% |
| Withdrawals due to AE | Nicergoline | Placebo | 3 | 565 | 1.13 (0.61, 2.09) | 0.7 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Table 3: Meta analysis of overall adverse events

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|---------------|--------------|-------------------|---------|------|--------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Any AE | Nicergoline | Placebo | 10 | 1448 | 1.05 (0.93, 1.20) | 0.42 | 0% |
| Any AE | Nicergoline | Active agents | 4 | 292 | 1.19 (0.71, 2.01) | 0.51 | 5% |
| Any AE | Nicergoline | Ergot derivatives | 2 | 200 | 1.22 (0.63, 2.34) | 0.56 | 19% |
| Any SAE | Nicergoline | Placebo | 2 | 482 | 0.85 (0.50, 1.45) | 0.54 | 35% |
| Anxiety | Nicergoline | Placebo | 2 | 482 | 0.59 (0.39, 0.88) | 0.01 | 0% |
| Diarrhoea | Nicergoline | Placebo | 2 | 188 | 0.85 (0.24, 3.05) | 0.8 | 0% |
| Diarrhoea | Nicergoline | Ergot derivatives | 2 | 200 | 0.99 (0.14, 6.92) | 0.99 | 0% |
| Dizziness | Nicergoline | Placebo | 3 | 260 | 0.63 (0.15, 2.57) | 0.51 | 0% |
| Dizziness | Nicergoline | Active agents | 2 | 116 | 1.00 [0.18, 5.58] | 1.0 | 0% |
| Drowsiness | Nicergoline | Placebo | 2 | 442 | 0.34 (0.05, 2.12) | 0.24 | 0% |
| Fatigue | Nicergoline | Placebo | 2 | 378 | 0.71 (0.14, 3.53) | 0.68 | 18% |
| Fatigue | Nicergoline | Active agents | 3 | 260 | 1.24 (0.35, 4.47) | 0.74 | 0% |
| Fatigue | Nicergoline | Ergot derivatives | 2 | 200 | 1.79 (0.40, 7.98) | 0.45 | 0% |
| Gastric upset | Nicergoline | Placebo | 6 | 1037 | 0.94 (0.58, 1.52) | 0.8 | 0% |
| Hot Flushes | Nicergoline | All comparisons | 3 | 470 | 3.65 (0.61, 21.93) | 0.16 | 0% |
| Headache | Nicergoline | Placebo | 5 | 1004 | 1.28 (0.63, 2.60) | 0.24 | 0% |
| Hypotension | Nicergoline | Placebo | 2 | 378 | 1.49 (0.26, 8.72) | 0.66 | 0% |
| Insomnia | Nicergoline | Placebo | 3 | 498 | 1.81 (0.39, 8.29) | 0.45 | 0% |
| Itching | Nicergoline | All comparisons | 2 | 108 | 3.23 (0.35, 30.08) | 0.3 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

1
2
3 **Contributorship Statement:** AG carried out the searches in various databases. AG and JX
4 carried out the filtration of citation. AG and JX carried out the data extraction, MF and TN
5 helped to draft the manuscript and reviewed it. All authors read and approved the final
6 manuscript.
7
8

9
10 **Competing Interests:** None

11
12 **Funding:** None

13
14 **Data Sharing Statement:** In addition to the manuscript, the corresponding author
15 also has initial results of publication analysis. That explains the reason for inclusion
16 and exclusion of individual studies.
17
18
19

20 21 22 23 **Figure Legends**

24
25 Figure 1: Results of meta-analysis, all withdrawals: Nicergoline vs. Placebo

26
27 Figure 2: Results of meta-analysis, any adverse events: Nicergoline vs. Placebo
28
29
30
31
32
33

34 35 **References**

- 36
37 1. Fioravanti M, Flicker L. Efficacy of nicergoline in dementia and other age associated forms
38 of cognitive impairment. *Cochrane Database Syst Rev* 2001:CD003159.
- 39
40 2. Carfagna N, Di Clemente A, Cavanus S, Damiani D, Gerna M, Salmoiraghi P, Cattaneo B,
41 Post C. Modulation of hippocampal ACh release by chronic nicergoline treatment in freely
42 moving young and aged rats. *Neurosci Lett* 1995;197:195-8.
- 43
44 3. Carfagna N, Rossi A. Nicergoline: biochemical studies on neuronal metabolism. *Funct*
45 *Neurol* 1989;4:177-85
- 46
47 4. Winblad B, Fioravanti M, Dolezal T, Logina I, Milanov IG, Popescu DC, Solomon A.
48
49
50
51
52
53
54
55
56
57
58
59
60
Therapeutic use of nicergoline. *Clin Drug Investig* 2008;28:533-52.

- 1
2
3 5. New restrictions on use of medicines containing ergot derivatives.
4
5 [http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC50014
6
7 4861.pdf.]
8
9
- 10 6. Arrigo A, Moglia A, Borsotti L. A double-blind, placebo-controlled, crossover trial with
11 nicergoline in patients with senile dementia. *International Journal of Clinical Pharmacology*
12 *Research* 1982;2:33-41.
13
14
- 15 7. Battaglia A, Bruni G, Ardia A, Sacchetti G. Nicergoline in mild to moderate dementia. A
16 multicenter, double-blind, placebo-controlled study. *J Am Geriatr Soc* 1989;37:295-302.
17
18
- 19 8. Battaglia A, Bruni G, Sacchetti G, Pamparana F (Nicergoline Cooperative Study Group). A
20 double-blind randomized study of two ergot derivatives in mild to moderate dementia. *Curr*
21 *Therap Res* 1990;48:597-612.
22
23
- 24 9. Battaglia A, Annoni K, Pamparana F, DePaolis C, Bonura ML, Stekke W. Nicergoline in the
25 Long Term Treatment of Mild or Moderate Senile Dementia. A Multicenter Double-blind,
26 Randomized, Placebo- controlled Trial. In 8th European College of
27 Neuropsychopharmacology Congress: 30th September - 4th October 1995; Venice.
28
29
- 30 10. Bes A, Orgogozo JM, Poncet M, Rancurel G, Weber M, Bertholom N, Calvez R, Stehle B,
31 Destee A, Latinville D. A 24-month, double-blind, placebo-controlled multicentre pilot study
32 of the efficacy and safety of nicergoline 60 mg per day in elderly hypertensive patients with
33 leukoaraiosis. *European Journal of Neurology* 1999;6:313-22.
34
35
- 36 11. Bossi L. Buflomedil and nicergolin in the treatment of acute cerebral ischaemia. A double-
37 blind, randomized comparative study. *Minerva Medica* 1985;76:1005-18.
38
39
- 40 12. Brola W. Evaluation of treatment outcome after nicergoline and pentoxifylline in patients
41 with ischemic stroke. *Przegląd lekarski* 1997;54:79-82.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

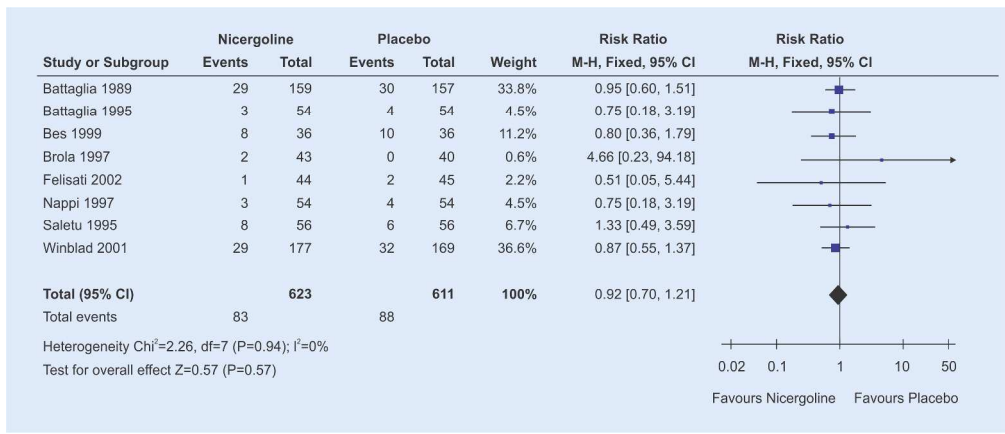
- 1
2
3 13. Cascone A, Liverta C, Pollini C. A double-blind trial of nicergolin and placebo in cerebral
4
5 and peripheral cerebrovascular disturbance in the aged. *Minerva Cardioangiologica* 1978;
6
7 26:95-100.
8
- 9
10 14. Colombeau P, Ballanger P. Results of the double-blind use of an alpha blockader,
11
12 nicergoline, in cervico-prostatic dysfunctions. *Journal d'urologie* 1987;93:533-5.
13
- 14 15. Crook TH. Nicergoline in the treatment of probable Alzheimer's disease Preliminary results
15
16 of a double-blind, randomized, placebo-controlled study. *J Neurol Sci* 1997:S18.
17
- 18 16. Dubreuil C. Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo
19
20 biloba extract and nicergoline. *Presse médicale (Paris, France : 1983)* 1986;15:1559-61.
21
22
- 23 17. Felisati G, Battaglia A, Papini MG, Rossini BM, Pignataro O. Nicergoline in balance
24
25 alterations in adult and elderly patients: A double-blind, placebo-controlled study. *Clinical*
26
27 *Drug Investigation* 2002;22:731-40.
28
- 29 18. Forette F, Varin D, Henry JF, Hervy MP. Treatment of arterial hypertension in the elderly
30
31 with an alpha-blocker: nicergoline (author's transl). *La Nouvelle presse médicale* 1980,
32
33 9:3685-8.
34
35
- 36 19. Gessner B, Voelp A, Klasser M. Study of the long-term action of a Ginkgo biloba extract on
37
38 vigilance and mental performance as determined by means of quantitative pharmaco-EEG
39
40 and psychometric measurements. *Arzneimittel-Forschung/Drug Research* 1985;35:1459-65.
41
42
- 43 20. Herrmann WM. A multicenter randomized double-blind study on the efficacy and safety of
44
45 nicergoline in patients with multi-infarct dementia. *Dementia and Geriatric Cognitive*
46
47 *Disorders* 1997;8:9-17.
48
- 49 21. Kugler JE, Meurer-Krull BC. Electroencephalography and psychometric measurements
50
51 during the treatment of cerebral insufficiency with nicergoline and dihydroergotamine
52
53 mesylate. *Arzneimittelforschung* 1985;35:1865-70.
54
55
56
57
58
59
60

- 1
2
3 22. Lu JH. Nicergoline in treatment of vascular dementia: a consecutive, multicenter, double-
4 blind clinical trial. *Chinese J Neurol* 2001;88-91.
5
6
7 23. Marolda M, Fragassi N, Buscaino GA. Clinical evaluation of (-)eburnamonine in comparison
8 with nicergoline in patients suffering from chronic brain ischemia. *European Neurology*
9 1978, 17:159-66.
10
11
12 24. Materna F. Leading symptom vertigo: Comparative study with flunarizine and nicergoline.
13 *Medizinische Klinik* 1985, 80:292-5.
14
15
16 25. Nakashima T, Hattori N, Okimoto M, Yanagida J, Kohno N. Nicergoline improves
17 dysphagia by upregulating substance p in the elderly. *Medicine* 2011;90:279-83.
18
19
20 26. Nappi G, Bono G, Merlo P, Borromei A, Caltagirone C, Lomeo C, Martucci N, Fabbrini G,
21 Annoni K, Battaglia A. Long-term nicergoline treatment of mild to moderate senile
22 dementia. Results of a multicentre, double-blind, placebo-controlled study. *Clinical Drug*
23 *Investigation* 1997;13:308-16.
24
25
26 27. Nishiyama Y, Abe A, Ueda M, Katsura KI, Katayama Y. Nicergoline increases serum
27 substance P levels in patients with an ischaemic stroke. *Cerebrovascular Diseases*
28 2010;29:194-8.
29
30
31 28. Pilkowska E, Jakubowska T, Witkowska K, Kulczycki J. Nicergoline in the treatment of
32 patients after a mild ischemic stroke. *Neurologia i neurochirurgia polska* 2002;36:1075-85.
33
34
35 29. Pogliani E, Della Volpe A, Ferrari R. Inhibition of human platelet aggregation by oral
36 administration of nicergoline. A double blind study. *Farmaco, Edizione Pratica* 1975;30:630-
37 40.
38
39
40 30. Ronchi F, Margonato A, Ceccardi R. Symptomatic treatment of benign prostatic obstruction
41 with nicergoline: A placebo controlled clinical study and urodynamic evaluation. *Urological*
42 *Research* 1982;10:131-34.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 31. Saletu B, Paulus E, Linzmayer L, Anderer P, Semlitsch HV, Grunberger J, Wicke L,
4
5 Neuhold A. Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: A
6
7 double blind, placebo controlled, clinical and EEG/ERP mapping study.
8
9
10 Psychopharmacology 1995;117:385-95.
11
12 32. Setyopranoto ISP. Role of nicergoline 60 miligram per oral for improvement of the patients
13
14 with acute ischemic stroke. Journal of the Neurological Sciences 2009;285:S221-S222.
15
16 33. Winblad B, Bonura ML, Rossini BM, Battaglia A. Nicergoline in the treatment of mild-to-
17
18 moderate Alzheimer's disease: A European multicentre trial. Clinical Drug Investigation
19
20 2001;21:621-32.
21
22 34. Zucconi V, Terzi Bolaffio M. Results with nicergolin and dihydroergotoxine in 30
23
24 hemiplegics in the postacute phase. Minerva Medica 1974;65:936-45.
25
26 35. Alvarez-Guerra M, Bertholom N, Garay RP. Selective blockade by nicergoline of vascular
27
28 responses elicited by stimulation of alpha 1A-adrenoceptor subtype in the rat. conam Clin
29
30 Pharmacol 1999;13:50-8.
31
32 36. Shintomi K, Yoshimoto K, Ogawa Y, Itakura T, Fukushima T, Matsumoto M, Matsuoka Y,
33
34 Ishida R. Effects of nicergoline on cerebral energy metabolism in normal mice. Yakugaku
35
36 Zasshi 1986;106:90-4.
37
38 37. Sortino MA, Battaglia A, Pamparana F, Carfagna N, Post C, Canonico PL. Neuroprotective
39
40 effects of nicergoline in immortalized neurons. Eur J Pharmacol 1999;368:285-90.
41
42 38. Bousquet J, Rivory JP, Maheut M, Michel FB, Mion C. Double-blind, placebo-controlled
43
44 study of nicergoline in the treatment of pruritus in patients receiving maintenance
45
46 hemodialysis. J Allergy Clin Immunol 1989;83:825-28.
47
48 39. Akisada T, Orita Y, Sato Y, Handa T, Yada K, Kawai A, Takemoto T, Oku M. Effect of
49
50 nicergoline on vertigo and tinnitus. Practica Otologica 1994;87:845-55.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 40. Boismare F, Lefrancois J. Haemodynamic effects of nicergoline in man at rest and during
4 exercise. Clin Exp Pharmacol Physiol 1980;7:105-12.
5
6
7 41. Gallego J, Forner V, Jimenez F, Martinez E. Nicergoline in the treatment of neuropathic
8 bladder dysfunction: a preliminary report. Paraplegia 1984;22:216-24.
9
10
11 42. Kim MJ, Chang JH, Lee SK, Park JH, Choi YJ, Yang CW, Kim YS, Park SH, Bang BK.
12 Acute interstitial nephritis due to nicergoline (Sermion). Nephron 2002;92:676-79.
13
14
15 43. Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses.
16
17 <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087807>
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

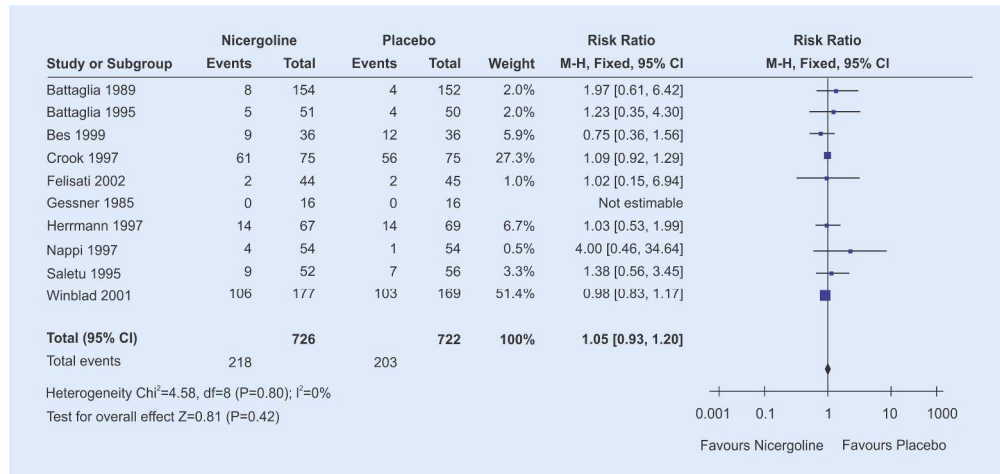
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



289x123mm (300 x 300 DPI)

Peer review only

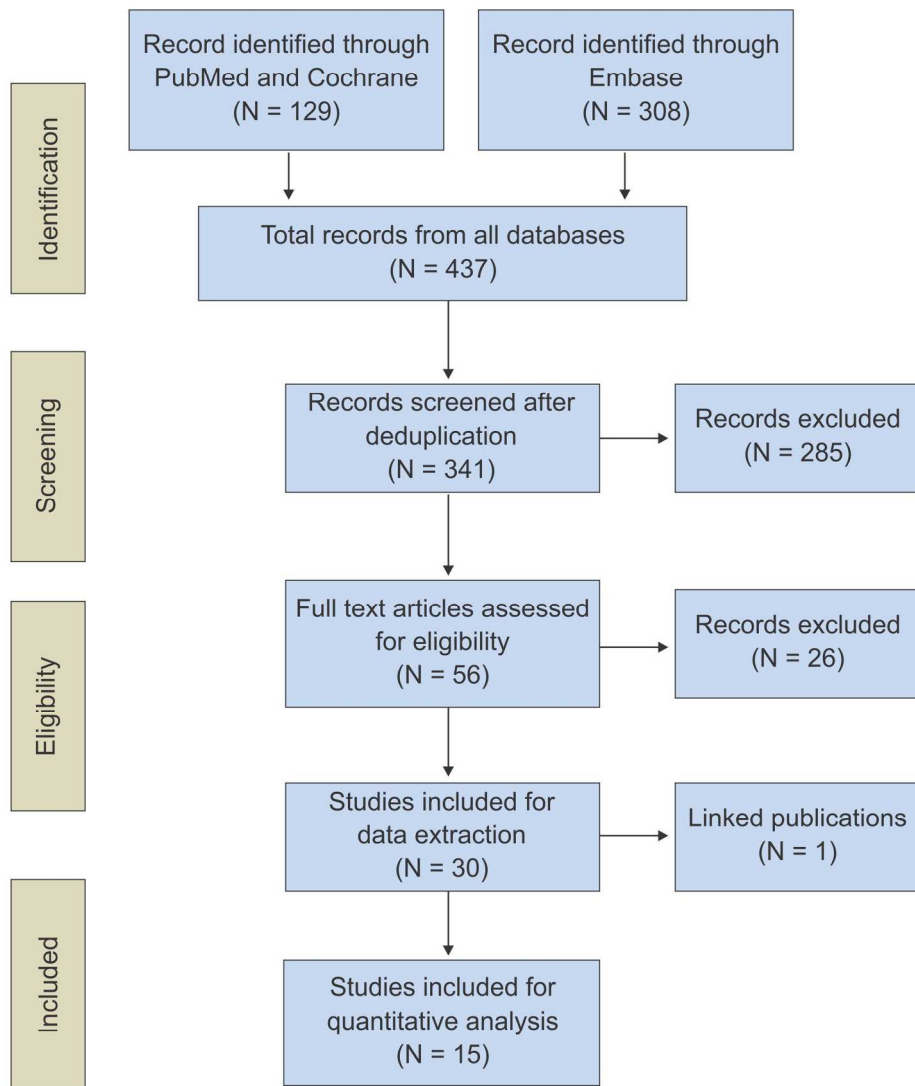
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



294x139mm (300 x 300 DPI)

er review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



168x196mm (300 x 300 DPI)

Supplementary Table 1: Incidence of adverse events with nicergoline and comparators

| Study Name | Intervention | Total Included | Any AEs | Any SAEs | Agitation/anxiety | Diarrhoea | Dizziness | Drowsiness | Fatigue | Gastric upset | Hot Flushes | Headache | Hypotension | Insomnia | Itching |
|-------------------|--------------------|----------------|---------|----------|-------------------|-----------|-----------|------------|---------|---------------|-------------|----------|-------------|----------|---------|
| Batalgia 1989 | Nicergoline | 154 | 8 | - | - | - | - | 1 | 1 | 4 | 2 | 1 | 1 | 1 | - |
| | Placebo | 152 | 4 | - | - | - | - | 2 | 0 | 3 | 0 | 0 | 1 | 1 | - |
| Battalgia 1990 | Nicergoline | 73 | 8 | - | - | 1 | - | - | 1 | 1 | - | 2 | - | - | - |
| | Ergoloid Mesylates | 71 | 4 | - | - | 0 | - | - | 0 | 0 | - | 1 | - | - | - |
| Battalgia 1995 | Nicergoline | 51 | 5 | - | - | - | - | - | - | - | - | - | - | - | - |
| | Placebo | 50 | 4 | - | - | - | - | - | - | - | - | - | - | - | - |
| Bes 1999 | Nicergoline | 36 | 9 | - | - | - | 2 | - | 1 | - | - | - | 2 | - | - |
| | Placebo | 36 | 12 | - | - | - | 2 | - | 3 | - | - | - | 1 | - | - |
| Crook 1997 | Nicergoline | 75 | 61 | - | - | - | - | - | - | - | - | - | - | - | - |
| | Placebo | 75 | 56 | - | - | - | - | - | - | - | - | - | - | - | - |
| Felisati 2002 | Nicergoline | 44 | 2 | - | - | - | - | - | - | 0 | - | - | - | - | - |
| | Placebo | 45 | 2 | - | - | - | - | - | - | 2 | - | - | - | - | - |
| Herrmann 1997 | Nicergoline | 67 | 14 | 0 | 0 | 3 | 0 | 0 | - | 0 | - | 2 | - | 1 | - |
| | Placebo | 69 | 14 | 3 | 1 | 4 | 1 | 2 | - | 1 | - | 2 | - | 0 | - |
| Kugler 1985 | Nicergoline | 28 | 8 | - | - | 0 | 1 | 1 | 3 | - | 1 | - | - | 1 | 1 |
| | Dihydroergotamine | 28 | 9 | - | - | 1 | 2 | 2 | 2 | - | 0 | - | - | 0 | 0 |
| Materna 1985 | Nicergoline | 30 | 8 | - | - | - | 1 | - | 0 | 3 | - | - | - | - | - |
| | Flunarizine | 30 | 8 | - | - | - | 0 | - | 1 | 1 | - | - | - | - | - |
| Nappi 1997 | Nicergoline | 54 | 4 | - | - | - | - | - | - | 1 | 1 | 2 | - | - | - |
| | Placebo | 54 | 1 | - | - | - | - | - | - | 1 | 0 | 0 | - | - | - |
| Saletu 1995 | Nicergoline (SDAT) | 24 | 7 | - | - | 1 | 0 | - | - | 1 | - | 2 | - | - | 1 |
| | Placebo (SDAT) | 28 | 4 | - | - | 1 | 1 | - | - | - | - | - | - | - | 0 |
| | Nicergoline (MID) | 28 | 2 | - | - | - | - | - | - | - | - | - | - | 2 | - |
| | Placebo (MID) | 28 | 3 | - | - | - | - | - | - | - | - | 1 | - | - | - |
| Winblad 2001 | Nicergoline | 177 | 106 | 22 | 30 | - | - | - | - | 22 | - | 9 | - | - | - |
| | Placebo | 169 | 103 | 22 | 48 | - | - | - | - | 22 | - | 9 | - | 14 | - |

BMJ Open

A systematic review and meta-analysis assessing adverse event profile and tolerability of nicergoline

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID: | bmjopen-2014-005090.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 05-Jun-2014 |
| Complete List of Authors: | Fioravanti, Mario; University Hospital, Umberto I, Clinical Psychology Nakashima, Taku; Hiroshima University Hospital, Dept. of Molecular & Internal Medicine Xu, Jun; Jiangsu Province Geriatric Hospital, Geriatrics Garg, Amit; Physician |
| Primary Subject Heading: | Neurology |
| Secondary Subject Heading: | Evidence based practice, Mental health |
| Keywords: | Meta-analysis, Nicergoline, Ergot derivatives, Fibrosis, Ergotism |
| | |

SCHOLARONE™
Manuscripts

Peer Review Only

1
2
3
4 Title of the article:
5

6 **A systematic review and meta-analysis assessing adverse event profile and tolerability of**
7
8 **nicergoline**
9

10
11
12 Corresponding author:
13

14 Dr. Amit Garg, M.D.

15 Physician

16 A Wing- 304, Aparna Towers

17 Kondapur, Kothaguda,

18 Hyderabad-500084

19 Email: amitgarg.pharm@gmail.com

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Tele: +918790902800

Authors:

Mario Fioravanti¹, Taku Nakashima², Jun Xu³, Amit Garg⁴

Affiliations:

1. Prof. Mario Fioravanti, M.D.

Director of the Clinical Psychology Service

University Hospital, Umberto I

Professor of Clinical Psychology

Department of Neurology and Psychiatry

University of Rome, Sapienza, Italy

E-mail: mario.fioravanti@uniroma1.it

2. Taku Nakashima, MD, PhD.

1
2
3 Dept. of Molecular & Internal Medicine,
4
5 Hiroshima University Hospital
6
7 1-2-3 Kasumi, Minami-ku Hiroshima, 734-8551 Japan
8
9
10 E-mail: tnaka@hiroshima-u.ac.jp/tnaka@eos.ocn.ne.jp

11
12 3. Prof. Jun Xu

13
14 Hospital: Jiangsu Province Geriatric Hospital, China
15
16 Email: 13611572068@126.com ; neurojun@126.com

17
18
19 4. Dr. Amit Garg, M.D.

20
21 Physician, A-Wing- 304, Aparna Towers
22
23 Kondapur, Kothaguda, Hyderabad-500084. India
24
25 Email: amitgarg.pharm@gmail.com
26
27
28
29
30

31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords:

Meta-analysis, nicergoline, ergot derivatives, fibrosis, ergotism

Word Count:

2649 words

Abstract

Objective: To evaluate the safety profile of nicergoline compared to placebo and other active agents from published randomised controlled trials.

Design: Systematic review and meta-analysis of nicergoline compared to placebo and other active agents across various indications.

Data sources: Medline, Medline-in-process, Cochrane, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register (CMR) for all the randomized controlled trials, open-label or blinded, in adults treated with nicergoline. Studies published till August 2013 were included.

Review method: Twenty nine studies were included for data extraction. The studies included in this review were majorly from European countries and mostly in cerebrovascular disease (n=15) and dementia (n=8).

Results: The treatment withdrawals were comparatively lower in nicergoline group as compared to placebo group (RR: 0.92; 95%CI: 0.7, 1.21) and other active comparators (RR: 0.45; 95%CI: 0.10, 1.95) but the difference was non-significant. Incidence of any adverse events was slightly higher (RR: 1.05; 95%CI: 0.93, 1.2) while incidence of serious adverse events was lower (RR: 0.85; 95%CI: 0.50, 1.45) in nicergoline compared to placebo group. Frequency of anxiety was significantly lower in Nicergoline as compared to placebo (p=0.01). Other AEs including diarrhoea, gastric upset, dizziness and drowsiness were less frequent in Nicergoline group compared to placebo/active drugs but the difference was non-significant. Frequency of hypotension and hot flushes was slightly higher in nicergoline group but the difference was non-

1
2
3 significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline
4
5 treatment.
6

7 **Conclusions:** Nicergoline is an ergot derivatives but the safety profile is better than other ergot
8
9 derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest
10
11 that nicergoline has a good safety profile. None of the studies included in this systematic review
12
13 reported any incidence of fibrosis or ergotism with nicergoline.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Article Summary:

Article focus:

- Currently not many options are available for management of cognitive impairment including pre-dementia and dementia.
- Despite no known association of nicergoline with ergotism, regulators have limited the use of same
- This meta-analysis is in effort to find the exact side effect profile and benefit to risk evaluation

Key messages:

- No evidence was found to suggest any incidence of fibrosis and ergotism with nicergoline
- Nicergoline is found to be a very safe alternative in a disease (cognitive impairment) with lean pipeline

Strengths and limitations of this study:

- First meta-analysis on nicergoline to understand the adverse clinical profile
- Critical in wake of recent EMEA view of blanket limitation on use of all ergot derivatives
- Limited by the availability of long term (more than 2 years) and high dose studies for cognitive impairment

Title:**A systematic review and meta-analysis assessing safety and tolerability of nicergoline****Background**

Nicergoline is a semi synthetic ergot derivative which has been registered in over fifty countries and has been used for more than four decades for the treatment of cognitive, affective, and behavioural disorders of older people.¹ During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Although cholinergic deficits are the major current targets for pharmacological intervention in Alzheimer's dementia, a wide variety of other neurotransmitter changes can be identified in the disease.

Nicergoline has been demonstrated to increase the availability of acetylcholine both through an increased release from cholinergic terminals and a selective inhibition of acetyl cholinesterase.²

Nicergoline may also enhance noradrenalin and dopamine turnover in some areas of the brain.³

Nicergoline has a positive effect on the signal transduction system stimulating the phosphoinositide pathway which is specifically impaired in Alzheimer's dementia.⁴ Other useful actions of Nicergoline in dementia are an increase of phosphoinosiphosphoinositide-PKC translocation which helps in combating beta-amyloid deposition and in retarding the reduction in nerve-growth factor (NGF) which may help in preventing the loss of cholinergic neurons.⁴

The side effects of Nicergoline are usually limited to nausea, hot flushes, mild gastric upset, hypotension and dizziness. At high dosages bradycardia, increased appetite, agitation, diarrhoea and perspiration have been known to occur. Nicergoline has a better safety profile compared to ergot derivates which are associated with increased risk of fibrosis (formation of excess

connective tissue that can damage organs and body structures) and ergotism (symptoms of ergot poisoning, such as spasms and obstructed blood circulation) with these medicines.

Nicergoline is not associated with either fibrosis or ergotism however; concerns about its safety have been raised, especially after the European Medicines Agency's (EMA) restriction on nicergoline because it is an ergot derivative.⁵ Most of the available literature suggests that the adverse events with nicergoline are mild and transient. Hence, a systematic review of literature and meta-analysis was conducted to compare the safety profile of nicergoline with placebo and other active comparators.

Methods

Search strategy

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. The following databases were examined since inception up to 16th August 2013; Medline, Medline-in-process, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register. Medical subject headings (MeSH terms) and free keywords like "randomised controlled trial", "Nicergoline", "Adverse effects", "toxicity" and "side effects" were used (Appendix 1). This review was not restricted to studies conducted in English language and hence studies published in other languages were also included and translated for data extraction.

Selection criteria

To meet the study objective, we pre-decided on inclusion criteria which include RCTs reporting adverse events in patients undergoing nicergoline treatment for psychiatric disorders. To be included in the analysis, a trial had to fulfill the following criteria: 1) randomized trials which

1
2
3 could be be open-label, single-blind, or double-blind, parallel group studies; 2) use of nicergoline
4
5 for Alzheimer's disease, dementia or cognitive disorders; 3) use of nicergoline as one of the
6
7 interventions; 3) Studies comparing nicergoline with ergot derivatives, placebo, or other active
8
9 agents were included; 4) Studies should report safety and tolerability data for nicergoline.
10

11
12 Studies were excluded if: 1) presented data for children only; 2) study design was not of interest;
13
14 3) disease was other than of interest; 4) study was not presenting safety and tolerability
15
16 outcomes; 5) full-text could not be sourced.
17
18
19

20 **Data extraction**

21
22 Bibliographic details and abstracts of all citations retrieved by the literature search were
23
24 downloaded into Endnotes version X3. Cochrane methodology was used to conduct this
25
26 systematic review. All studies were screened by two independent reviewers with discrepancies
27
28 resolved by a third reviewer.
29
30
31
32

33 **Study quality and risk of bias**

34
35
36
37 Jadad score was used to assess the quality of included studies. Risk of bias in the individual
38
39 studies included for meta-analysis was assessed using Cochrane risk assessment tool.⁶
40
41

42 **Outcomes assessed**

43
44
45 In most of the included studies, safety evaluation included monitoring of adverse events, vital
46
47 signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at
48
49 baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-
50
51 emergent adverse events (elicited or observed); physical examination including ECG recording;
52
53 vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to
54
55 adverse event were reported.
56
57
58
59
60

1
2
3 The data from these studies were pooled for total withdrawals, withdrawals due to AEs,
4 incidence rates for any AEs, SAEs, and specific AEs including anxiety, constipation, diarrhoea,
5 hot flushes, itching, gastric upset, hypotension, headache, dizziness, insomnia, drowsiness and
6 fatigue. Only studies which presented data for same comparators were included in direct meta-
7 analysis for each outcome.
8
9
10
11
12

13 14 15 **Statistical analysis**

16
17
18 Comparison of safety and tolerability outcomes were made between interventions by pooling
19 data from studies using direct meta-analysis technique. Only head-to-head comparisons between
20 interventions were included for meta-analysis. Review Manager (RevMan v 5.1) software was
21 used for meta-analysis of the available data. Dichotomous outcomes were summarised as risk
22 (relative) ratios.
23
24
25
26
27
28
29

30 31 **Results**

32 33 34 **Study selection**

35
36
37 A trial flow of the review process (as per PRISMA statement) is presented along with
38 manuscript (Figure 1). The search of the literature yielded 437 separate references. Due to the
39 overlap of coverage between the databases, 96 of the references were found to be duplicates. A
40 total of 341 citations were reviewed for abstract screening (first pass). Following the first pass of
41 the citations, 56 potentially relevant references were identified. Full-text reports of these
42 citations were obtained for more detailed evaluation. Following detailed examination of the
43 reports, 26 citations were excluded. Thirty studies met inclusion criteria however one of them
44 was a secondary publication which was linked to its primary publication. Finally, a total of 29
45 references reporting trials were extracted. Table 1 presents an overview of the study methods in
46 included studies. Fifteen studies were not included in meta-analysis as data from these could not
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 be pooled. These were studies reporting standalone adverse events, or for standalone
4
5 comparators.
6
7

8 **Baseline Characteristics**

9
10
11 Most of the included studies were in cerebrovascular disease (n=15), followed by Dementia
12 (n=8). Two studies were for Alzheimer's disease and four were in other disease areas. The mean
13
14 age of included patients ranged from 48 years (Dubreuil 1986) to 81 years (Saletu 1995) across
15
16 the studies. The % of male patients ranged from 17.9% (Saletu 1995) to 76.7% (Nakashima
17
18 2011) in Nicergoline group and was comparable with control group in all studies). The number
19
20 of patients randomized in these studies ranged from 16 (Ronchi 1982) to 346 (Winblad
21
22 2001). The treatment/study duration ranged from 6 days (Ronchi 1982) to 24 months (Bes 1999)
23
24 across included studies with most studies with duration ≥ 3 months (n=17). The daily dose of
25
26 nicergoline used was ≤ 30 mg/day in 16 studies and was reported to be 60 mg/daily in 12 studies.
27
28
29
30
31

32 **Critical Appraisal**

33
34 Included studies were critically appraised using the Jadad scale which is a standard scale used for
35
36 evaluating quality of randomised trials in systematic reviews. Method used to generate random
37
38 allocation sequence was reported in only nine of the included studies and were judged as
39
40 adequate. The Jadad score was ≥ 3 in 20 studies and less than 3 in nine studies. Majority of the
41
42 studies were good quality studies as per Jadad scale. All of included studies reported comparable
43
44 baseline characteristics between treatment groups being studied.
45
46
47
48
49

50 **Risk of bias assessment**

51
52 The risk of bias was low in the individual studies that were included for meta-analysis. The
53
54 method used to generate the allocation sequence was reported in sufficient detail to allow an
55
56 assessment in most of the studies. None of the included studies reported any inadequate method.
57
58
59
60

1
2
3 Method for allocation concealment was not reported by any of the included studies. Method used
4
5 for blinding was adequate in most of the study reporting it. Study withdrawals and patients
6
7 inclusion for outcome assessment were similar within study groups.
8
9

10 **Withdrawals**

11
12
13 Total withdrawals with nicergoline ranged from 0% (Kugler 1985, Materna 1985) to 22.2% (Bes
14
15 1999) and from 0%- 27.8% with other comparator drugs/placebo. Six studies reported lower
16
17 number of patient withdrawals from nicergoline group as compared to other comparator/placebo
18
19 groups. Withdrawals due to AE were similar in nicergoline group as compared to other groups
20
21 across the studies, Figure 2.
22
23

24
25
26 The meta-analyzed risk ratios between nicergoline and the other comparators and their
27
28 corresponding 95% confidence intervals for study withdrawals are shown in Tables 2. Results of
29
30 meta-analysis showed a non-significant lower rate of withdrawals from nicergoline compared to
31
32 placebo ($p=0.57$) and other active agents ($p=0.28$). For withdrawals due to AE, the withdrawal
33
34 rate was slightly higher with nicergoline when compared to placebo but the difference was only
35
36 apparent and non-significant ($p=0.7$).
37
38

39 **Adverse Events**

40
41
42
43 There was adequate data to perform meta-analysis for safety outcomes including any AE, any
44
45 serious AE, diarrhoea, hot flushes, gastric upset, itching, hypertension, headache, dizziness,
46
47 anxiety, insomnia, drowsiness and fatigue (Supplementary Table 1). However, there was no
48
49 reference to cases with fibrosis and/or ergotism.
50
51

52
53 The meta-analyzed risk ratios between nicergoline and the other comparators and their
54
55 corresponding 95% confidence intervals for study withdrawals and safety outcomes are shown in
56
57 Tables 2, and 3, respectively. Results of meta-analysis showed a non-significant lower rate of
58
59
60

1
2
3 withdrawals from nicergoline compared to placebo ($p=0.57$) and other active agents ($p=0.28$).

4
5 For withdrawals due to AE, the withdrawal rate was slightly higher with nicergoline when
6
7 compared to placebo but again the difference was non-significant ($p=0.7$).

8
9
10 The risk of any adverse event was similar with nicergoline compared to placebo (10 studies),
11
12 ergot derivatives and other active comparators, all comparisons being non-significant. Risk of
13
14 any serious adverse event was slightly lower in the nicergoline group compared to placebo but
15
16 was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline
17
18 as compared to placebo ($p=0.01$). Nicergoline was associated with lower risk of diarrhoea as
19
20 compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence
21
22 of dizziness was similar in nicergoline group as compared to placebo or other active agents. A
23
24 comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but
25
26 the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo
27
28 group.

29
30
31
32
33 Higher risk of fatigue was associated with nicergoline compared to active comparators including
34
35 ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported
36
37 with nicergoline compared to other comparators. Risk of headache and hypotension was higher
38
39 with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with
40
41 nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any
42
43 significant difference was observed compared to the other intervention or placebo, Figure 3.

44
45
46
47
48 Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in
49
50 eight studies during the entire study duration, while remaining studies reported excellent or good
51
52 tolerability in nicergoline treated patients. None of these studies reported any incidence of
53
54 ergotism or fibrosis with nicergoline.

Discussion

Nicergoline is a potent and selective alpha-1A adrenergic receptor antagonist.³⁶ Nicergoline is reported to enhance catecholaminergic turnover,³ stimulate cholinergic neuro-transmission,⁴ stimulate phosphoinositide pathway,³ promote cerebral metabolic activity,³⁷ and has neuroprotective and antioxidant properties.³⁷ Nicergoline is used clinically to improve the apathy and affective disorders caused by cerebral infarction (such as reduced mental alertness, inattention, impairment of recent memory, hypobulia, depression, etc.). It is useful in the treatment of acute and chronic peripheral circulation disorders (such as obliterative vascular disease of the limbs, Raynaud's syndrome and other peripheral circulation dysfunction symptoms). Nicergoline has also been prescribed for the treatment of vascular dementia, especially for the improvement in cognitive dysfunction and memory, and to reduce the severity of this disease.

In addition, studies have been reported showing the usefulness of nicergoline in conditions such as post-hemodialysis pruritus, tinnitus and vertigo, ocular conditions such as arterial obstructions, venous thrombosis, diabetic retinopathies, senile macular degenerations, papilla ischaemic oedema and central serous chorioretinopathies. Dosages for known conditions are usually administered at 5–10 mg three times a day, however anti-aging preventative purposes may limit this to 5 mg once or twice a day. Higher doses of up to 60 mg/day have also been prescribed in clinical practice but have been associated with increased risk of adverse events.⁴

The EMEA's Committee for Medicinal Products for Human Use (CHMP) in its recommendations has suggested that ergot containing medicines, including nicergoline, should no longer be used to treat conditions involving blood circulation problems (such as peripheral artery disease, Raynaud's syndrome and retinopathies of vascular origin), memory and sensation problems and migraine headaches. This recommendation has been supported by the EMEA

1
2
3 citing that these ergot derivatives have a high likelihood of causing serious adverse events such
4 as fibrosis and ergotism.⁵ However, in this recommendation, the EMEA suggests that healthcare
5 professionals can continue prescribing nicergoline and other ergot derivatives in dementia
6 (including Alzheimer's disease) and acute migraine.
7
8
9
10

11
12 Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-
13 infarct dementia.^{1,32} Also, nicergoline has shown efficacy in conditions like post-hemodialysis
14 pruritus,³⁹ tinnitus and vertigo.⁴⁰ Nicergoline has a positive effect on cognition and behaviour in
15 addition to an effect on clinical global impression in older patients with mild to moderate
16 cognitive and behavioural impairment of various clinical origins including chronic
17 cerebrovascular disorders and Alzheimer's dementia.¹
18
19
20
21
22
23
24
25

26
27 Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep
28 disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and
29 increased appetite.^{8,22} Cardiovascular events like temporary rise in BP, syncope, bradycardia, and
30 hypotension have been reported with nicergoline by few studies.^{18,41}
31
32
33
34
35
36

37
38 Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and
39 abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have
40 reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure,
41 and interstitial nephritis.^{42,43}
42
43
44
45

46
47 Results of this meta-analysis showed comparable safety profile of nicergoline with other active
48 agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to
49 adverse events were similar with nicergoline compared to placebo & active agents. Incidence of
50 any adverse event when compared to placebo and ergot derivatives was slightly higher in the
51 nicergoline group but the difference was non-significant. Significantly lower rates of anxiety
52 were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like
53
54
55
56
57
58
59
60

1
2
3 diarrhoea, dizziness, drowsiness, gastric upset and fatigue were slightly lower with nicergoline as
4
5 compared to placebo but the difference was non-significant for all comparisons.
6
7

8 Nicergoline was associated with higher rates of hot flushes, headache, hypotension, insomnia
9
10 and itching. None of the comparisons showed a significant difference but some of these adverse
11
12 events are probably because of the vasodilation action of nicergoline. Higher doses of
13
14 nicergoline (60 mg/day) were associated with higher rates of adverse events compared to the 30
15
16 mg/day dosing but the difference was not significant. None of the studies included in this meta-
17
18 analysis reported any incidence of fibrosis or ergotism with nicergoline.
19
20
21

22
23 In its current recommendation, the EMEA has overlooked the efficacy and safety profile of
24
25 nicergoline and has cautioned against its use in conditions with blood circulation problems,
26
27 memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban
28
29 on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA
30
31 has probably considered the safety profile of all ergot derivatives as similar. The CHMP review
32
33 has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest
34
35 incidence of these AEs with other ergot derivatives as well.
36
37
38

39 EMEA has suggested that echocardiography should be done within 3–6 months of starting
40
41 treatment with ergot derivatives and subsequently at 6–12-month interval.⁴⁴ In the current meta-
42
43 analysis, most of the included studies were >3 months and up to 24 months in duration and none
44
45 of the included studies reported any incidence of fibrosis or ergotism with nicergoline. There is
46
47 no evidence in literature to suggest any incidence of fibrosis and ergotism with nicergoline.
48
49
50

51 The strengths of this systematic review include the clear definition of the research question,
52
53 adherence to an explicit research protocol that was developed prior to the analysis, the
54
55 comprehensive nature of the data search (employing both electronic databases and manual
56
57 bibliography searches resulting in the inclusion of all relevant publications), consensus between
58
59
60

1
2
3 two reviewers of all data elements prior to entry into the database and the quality control review
4
5 of every element of this report. In addition, the quality of the studies and manuscripts used to
6
7 provide data were relatively high. Only RCTs were included in this systematic review/meta-
8
9 analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to
10
11 compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this
12
13 review could be the publication timeframe of the included studies. Most of the studies were
14
15 published in 1980s and 1990s. There were hardly any trials published in recent years on safety
16
17 evaluation for nicergoline.
18
19

20 21 22 **Conclusions**

23
24
25 This systematic review & meta-analysis has included the evidence to date with regards to
26
27 tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is
28
29 categorized under ergot derivatives. However, the adverse events with nicergoline are mild and
30
31 transient unlike other ergot derivatives (ergotamine & ergotamine) which have been associated
32
33 with fibrosis and ergotism.
34
35

36
37 The results from this systematic review/meta-analysis suggest that nicergoline has a comparable
38
39 safety profile as placebo and other active comparators. None of the studies included in this
40
41 systematic review reported any incidence of fibrosis or ergotism with nicergoline. The evidence
42
43 generated by this review suggests that despite being an ergot derivative, nicergoline is a safe and
44
45 well-tolerated drug. This systematic review/meta-analysis concludes that nicergoline is a safe
46
47 option for therapeutic management in patients with dementia and cerebrovascular disorders.
48
49

50 51 52 **List of abbreviations**

53
54 AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA:
55
56 European Medicines Agency; SAEs: serious adverse event
57
58
59
60

Tables

Table 1: Study methods for included RCTs

| Study Name | Study duration | Country | Blinding | Intervention | Comparator | Daily Dose of Nicergoline |
|---------------------------------|----------------|-----------|--------------|--------------|--------------------|---------------------------|
| Arrigo 1982 ⁷ | 14 weeks | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1989 ⁸ | 6 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1990 ⁹ | 6 months | Italy | Double-blind | Nicergoline | Ergot mesylate | 60mg |
| Battaglia 1995 ¹⁰ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Bes 1999 ¹¹ | 24 months | France | Double-blind | Nicergoline | Placebo | 60mg |
| Boss 1985 ¹² | - | Italy | Double-blind | Nicergoline | Buflomedil | 8mg |
| Brola 1997 ¹³ | 1 month | Poland | Single-blind | Nicergoline | Pentoxifylline | 30mg |
| Cascone 1978 ¹⁴ | 1 month | Italy | Double-blind | Nicergoline | Placebo | 15mg |
| Colombeau 1987 ¹⁵ | 15 days | France | Double-blind | Nicergoline | Placebo | 40mg |
| Crook 1997 ¹⁶ | 6 months | USA | Double-blind | Nicergoline | Placebo | 60mg |
| Dubreuil 1986 ¹⁷ | 1 month | France | Double-blind | Nicergoline | GBE | NR |
| Felisati 2002 ¹⁸ | 3 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Forette 1980 ¹⁹ | 3 weeks | France | Double-blind | Nicergoline | Placebo | 30mg |
| Gessner 1985 ²⁰ | 12 weeks | Germany | Double-blind | Nicergoline | GBE | 15mg |
| Herrmann 1997 ²¹ | 6 months | Germany | Double-blind | Nicergoline | Placebo | 60mg |
| Kugler 1985 ²² | 6 months | Germany | Double-blind | Nicergoline | Dihydro-ergotamine | 30mg |
| Lu 2001 ²³ | 12 weeks | China | Double-blind | Nicergoline | Aniracetam | 60mg |
| Marolda 1978 ²⁴ | 20 days | Italy | Double-blind | Nicergoline | Eburnamonine | 15-20mg |
| Materna 1985 ²⁵ | 12 weeks | Germany | Double-blind | Nicergoline | Flunarizine | 10-30mg |
| Nakashima 2011 ²⁶ | 6 months | Japan | Double-blind | Nicergoline | Imidapril | 15mg |
| Nappi 1997 ²⁷ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Nishiyama 2010 ²⁸ | 4 weeks | Japan | Open-label | Nicergoline | Placebo | 45mg |
| Pilkowska 2002 ²⁹ | 3 months | Poland | Double-blind | Nicergoline | Placebo | 60mg |
| Pogliani 1979 ³⁰ | 3 months | Germany | Double-blind | Nicergoline | Placebo | 15mg |
| Ronchi 1982 ³¹ | 6 Days | Italy | Double-blind | Nicergoline | Placebo | |
| Saletu 1995 ³² | 8 weeks | Austria | Double-blind | Nicergoline | Placebo | 30-60mg |
| Setyopranoto 2009 ³³ | - | Indonesia | Double-blind | Nicergoline | Placebo | 60mg |
| Winblad 2001 ³⁴ | 6 months | Europe | Double-blind | Nicergoline | Placebo | 60mg |
| Zucconi 1974 ³⁵ | 1 month | Italy | Double-blind | Nicergoline | Dihydro-ergotoxine | 2mg i.m. |

Table 2: Meta analysis of withdrawal rate across included studies

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|-----------------------|--------------|---------------|---------|------|-------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Total withdrawals | Nicergoline | Placebo | 8 | 1234 | 0.92 (0.70, 1.21) | 0.57 | 0% |
| | Nicergoline | Active agents | 3 | 201 | 0.45 (0.10, 1.95) | 0.28 | 18% |
| Withdrawals due to AE | Nicergoline | Placebo | 3 | 565 | 1.13 (0.61, 2.09) | 0.7 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Table 3: Meta analysis of overall adverse events

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|---------------|--------------|-------------------|---------|------|--------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Any AE | Nicergoline | Placebo | 10 | 1448 | 1.05 (0.93, 1.20) | 0.42 | 0% |
| Any AE | Nicergoline | Active agents | 4 | 292 | 1.19 (0.71, 2.01) | 0.51 | 5% |
| Any AE | Nicergoline | Ergot derivatives | 2 | 200 | 1.22 (0.63, 2.34) | 0.56 | 19% |
| Any SAE | Nicergoline | Placebo | 2 | 482 | 0.85 (0.50, 1.45) | 0.54 | 35% |
| Anxiety | Nicergoline | Placebo | 2 | 482 | 0.59 (0.39, 0.88) | 0.01 | 0% |
| Diarrhoea | Nicergoline | Placebo | 2 | 188 | 0.85 (0.24, 3.05) | 0.8 | 0% |
| Diarrhoea | Nicergoline | Ergot derivatives | 2 | 200 | 0.99 (0.14, 6.92) | 0.99 | 0% |
| Dizziness | Nicergoline | Placebo | 3 | 260 | 0.63 (0.15, 2.57) | 0.51 | 0% |
| Dizziness | Nicergoline | Active agents | 2 | 116 | 1.00 [0.18, 5.58] | 1.0 | 0% |
| Drowsiness | Nicergoline | Placebo | 2 | 442 | 0.34 (0.05, 2.12) | 0.24 | 0% |
| Fatigue | Nicergoline | Placebo | 2 | 378 | 0.71 (0.14, 3.53) | 0.68 | 18% |
| Fatigue | Nicergoline | Active agents | 3 | 260 | 1.24 (0.35, 4.47) | 0.74 | 0% |
| Fatigue | Nicergoline | Ergot derivatives | 2 | 200 | 1.79 (0.40, 7.98) | 0.45 | 0% |
| Gastric upset | Nicergoline | Placebo | 6 | 1037 | 0.94 (0.58, 1.52) | 0.8 | 0% |
| Hot Flushes | Nicergoline | All comparisons | 3 | 470 | 3.65 (0.61, 21.93) | 0.16 | 0% |
| Headache | Nicergoline | Placebo | 5 | 1004 | 1.28 (0.63, 2.60) | 0.24 | 0% |
| Hypotension | Nicergoline | Placebo | 2 | 378 | 1.49 (0.26, 8.72) | 0.66 | 0% |
| Insomnia | Nicergoline | Placebo | 3 | 498 | 1.81 (0.39, 8.29) | 0.45 | 0% |
| Itching | Nicergoline | All comparisons | 2 | 108 | 3.23 (0.35, 30.08) | 0.3 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

1
2
3 **Contributorship Statement:** AG carried out the searches in various databases. AG and JX
4 carried out the filtration of citation. AG and JX carried out the data extraction, MF and TN
5 helped to draft the manuscript and reviewed it. All authors read and approved the final
6 manuscript.
7
8

9
10 **Competing Interests:** None

11
12 **Funding:** None

13
14 **Data Sharing Statement:** In addition to the manuscript, the corresponding author
15 also has initial results of publication analysis. That explains the reason for inclusion
16 and exclusion of individual studies. If readers require additional data on the analysis
17 or the medical merits of the molecule, they can write to amitgarg.pharm@gmail.com
18
19
20
21
22
23

24 25 26 **Figure Legends**

27
28 Figure 1: PRISMA flow for included studies

29
30 Figure 2: Results of meta-analysis, all withdrawals: Nicergoline vs. Placebo

31
32 Figure 3: Results of meta-analysis, any adverse events: Nicergoline vs. Placebo
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51

52 **References**

- 53
54 1. Fioravanti M, Flicker L. Efficacy of nicergoline in dementia and other age associated forms
55 of cognitive impairment. Cochrane Database Syst Rev 2001:CD003159.
56
57
58
59
60

- 1
2
3 2. Carfagna N, Di Clemente A, Cavanus S, et al. Modulation of hippocampal ACh release by
4
5 chronic nicergoline treatment in freely moving young and aged rats. *Neurosci Lett*
6
7 1995;197:195-8.
8
- 9
10 3. Carfagna N, Rossi A. Nicergoline: biochemical studies on neuronal metabolism. *Funct*
11
12 *Neurol* 1989;4:177-85
13
- 14 4. Winblad B, Fioravanti M, Dolezal T, et al. Therapeutic use of nicergoline. *Clin Drug Investig*
15
16 2008;28:533-52.
17
- 18 5. New restrictions on use of medicines containing ergot derivatives.
19
20 [http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC50014
21
22 4861.pdf.]
23
24
- 25 6. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical
26
27 trials: Is blinding necessary? *Controlled Clinical Trials*, 17:1-12, 1996.
28
- 29 7. Arrigo A, Moglia A, Borsotti L. A double-blind, placebo-controlled, crossover trial with
30
31 nicergoline in patients with senile dementia. *International Journal of Clinical Pharmacology*
32
33 *Research* 1982;2:33-41.
34
35
- 36 8. Battaglia A, Bruni G, Ardia A, et al. Nicergoline in mild to moderate dementia. A
37
38 multicenter, double-blind, placebo-controlled study. *J Am Geriatr Soc* 1989;37:295-302.
39
- 40 9. Battaglia A, Bruni G, Sacchetti G, et al. A double-blind randomized study of two ergot
41
42 derivatives in mild to moderate dementia. *Curr Therap Res* 1990;48:597-612.
43
44
- 45 10. Battaglia A, Annoni K, Pamparana F, et al. Nicergoline in the Long Term Treatment of Mild
46
47 or Moderate Senile Dementia. A Multicenter Double-blind, Randomized, Placebo- controlled
48
49 Trial. In 8th European College of Neuropsychopharmacology Congress: 30th September -
50
51 4th October 1995; Venice.
52
53
54
55
56
57
58
59
60

- 1
2
3 11. Bes A, Orgogozo JM, Poncet M, et al. A 24-month, double-blind, placebo-controlled
4
5 multicentre pilot study of the efficacy and safety of nicergoline 60 mg per day in elderly
6
7 hypertensive patients with leukoaraiosis. *European Journal of Neurology* 1999;6:313-22.
8
- 9
10 12. Bossi L. Buflomedil and nicergolin in the treatment of acute cerebral ischaemia. A double-
11
12 blind, randomized comparative study. *Minerva Medica* 1985;76:1005-18.
13
- 14 13. Broła W. Evaluation of treatment outcome after nicergoline and pentoxifylline in patients
15
16 with ischemic stroke. *Przegląd lekarski* 1997;54:79-82.
17
- 18 14. Cascone A, Liverta C, Pollini C. A double-blind trial of nicergolin and placebo in cerebral
19
20 and peripheral cerebrovascular disturbance in the aged. *Minerva Cardioangiologica* 1978;
21
22 26:95-100.
23
- 24 15. Colombeau P, Ballanger P. Results of the double-blind use of an alpha blockader,
25
26 nicergoline, in cervico-prostatic dysfunctions. *Journal d'urologie* 1987;93:533-5.
27
- 28 16. Crook TH. Nicergoline in the treatment of probable Alzheimer's disease Preliminary results
29
30 of a double-blind, randomized, placebo-controlled study. *J Neurol Sci* 1997:S18.
31
32
- 33 17. Dubreuil C. Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo
34
35 biloba extract and nicergoline. *Presse médicale (Paris, France : 1983)* 1986;15:1559-61.
36
37
- 38 18. Felisati G, Battaglia A, Papini MG, et al. Nicergoline in balance alterations in adult and
39
40 elderly patients: A double-blind, placebo-controlled study. *Clinical Drug Investigation*
41
42 2002;22:731-40.
43
44
- 45 19. Forette F, Varin D, Henry JF, et al. Treatment of arterial hypertension in the elderly with an
46
47 alpha-blocker: nicergoline (author's transl). *La Nouvelle presse médicale* 1980, 9:3685-8.
48
- 49 20. Gessner B, Voelp A, Klasser M. Study of the long-term action of a Ginkgo biloba extract on
50
51 vigilance and mental performance as determined by means of quantitative pharmaco-EEG
52
53 and psychometric measurements. *Arzneimittel-Forschung/Drug Research* 1985;35:1459-65.
54
55
56
57
58
59
60

- 1
2
3 21. Herrmann WM. A multicenter randomized double-blind study on the efficacy and safety of
4
5 nicergoline in patients with multi-infarct dementia. *Dementia and Geriatric Cognitive*
6
7 *Disorders* 1997;8:9-17.
8
- 9
10 22. Kugler JE, Meurer-Krull BC. Electroencephalography and psychometric measurements
11
12 during the treatment of cerebral insufficiency with nicergoline and dihydroergotamine
13
14 mesylate. *Arzneimittelforschung* 1985;35:1865-70.
15
- 16 23. Lu JH. Nicergoline in treatment of vascular dementia: a consecutive, multicenter, double-
17
18 blind clinical trial. *Chinese J Neurol* 2001:88-91.
19
- 20 24. Marolda M, Fragassi N, Buscaino GA. Clinical evaluation of (-)eburnamnone in comparison
21
22 with nicergoline in patients suffering from chronic brain ischemia. *European Neurology*
23
24 1978, 17:159-66.
25
26
- 27 25. Materna F. Leading symptom vertigo: Comparative study with flunarizine and nicergoline.
28
29 *Medizinische Klinik* 1985, 80:292-5.
30
31
- 32 26. Nakashima T, Hattori N, Okimoto M, et al. Nicergoline improves dysphagia by upregulating
33
34 substance p in the elderly. *Medicine* 2011;90:279-83.
35
- 36 27. Nappi G, Bono G, Merlo P, et al. Long-term nicergoline treatment of mild to moderate
37
38 senile dementia. Results of a multicentre, double-blind, placebo-controlled study. *Clinical*
39
40 *Drug Investigation* 1997;13:308-16.
41
42
- 43 28. Nishiyama Y, Abe A, Ueda M, et al. Nicergoline increases serum substance P levels in
44
45 patients with an ischaemic stroke. *Cerebrovascular Diseases* 2010;29:194-8.
46
- 47 29. Pilkowska E, Jakubowska T, Witkowska K, et al. Nicergoline in the treatment of patients
48
49 after a mild ischemic stroke. *Neurologia i neurochirurgia polska* 2002;36:1075-85.
50
51
- 52 30. Pogliani E, Della Volpe A, Ferrari R. Inhibition of human platelet aggregation by oral
53
54 administration of nicergoline. A double blind study. *Farmaco, Edizione Pratica* 1975;30:630-
55
56 40.
57
58
59
60

- 1
2
3 31. Ronchi F, Margonato A, Ceccardi R. Symptomatic treatment of benign prostatic obstruction
4 with nicergoline: A placebo controlled clinical study and urodynamic evaluation. *Urological*
5 *Research* 1982;10:131-34.
6
7
8
9
10 32. Saletu B, Paulus E, Linzmayer L, et al. Nicergoline in senile dementia of Alzheimer type
11 and multi-infarct dementia: A double blind, placebo controlled, clinical and EEG/ERP
12 mapping study. *Psychopharmacology* 1995;117:385-95.
13
14
15
16 33. Setyopranoto ISP. Role of nicergoline 60 miligram per oral for improvement of the patients
17 with acute ischemic stroke. *Journal of the Neurological Sciences* 2009;285:S221-S222.
18
19
20
21 34. Winblad B, Bonura ML, Rossini BM, et al. Nicergoline in the treatment of mild-to-moderate
22 Alzheimer's disease: A European multicentre trial. *Clinical Drug Investigation* 2001;21:621-
23 32.
24
25
26
27 35. Zucconi V, Terzi Bolaffio M. Results with nicergolin and dihydroergotoxine in 30
28 hemiplegics in the postacute phase. *Minerva Medica* 1974;65:936-45.
29
30
31 36. Alvarez-Guerra M, Bertholom N, Garay RP. Selective blockade by nicergoline of vascular
32 responses elicited by stimulation of alpha 1A-adrenoceptor subtype in the rat. *conam Clin*
33 *Pharmacol* 1999;13:50-8.
34
35
36
37 37. Shintomi K, Yoshimoto K, Ogawa Y, et al. Effects of nicergoline on cerebral energy
38 metabolism in normal mice. *Yakugaku Zasshi* 1986;106:90-4.
39
40
41
42 38. Sortino MA, Battaglia A, Pamparana F, et al. Neuroprotective effects of nicergoline in
43 immortalized neurons. *Eur J Pharmacol* 1999;368:285-90.
44
45
46
47 39. Bousquet J, Rivory JP, Maheut M, et al. Double-blind, placebo-controlled study of
48 nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J*
49 *Allergy Clin Immunol* 1989;83:825-28.
50
51
52
53 40. Akisada T, Orita Y, Sato Y, et al. Effect of nicergoline on vertigo and tinnitus. *Practica*
54 *Otologica* 1994;87:845-55.
55
56
57
58
59
60

- 1
2
3 41. Boismare F, Lefrancois J. Haemodynamic effects of nicergoline in man at rest and during
4 exercise. Clin Exp Pharmacol Physiol 1980;7:105-12.
5
6
7 42. Gallego J, Forner V, Jimenez F, et al. Nicergoline in the treatment of neuropathic bladder
8 dysfunction: a preliminary report. Paraplegia 1984;22:216-24.
9
10
11 43. Kim MJ, Chang JH, Lee SK, et al. Acute interstitial nephritis due to nicergoline (Sermion).
12 Nephron 2002;92:676-79.
13
14
15 44. Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses.
16
17 <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087807>
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 Title of the article:
5
6

7 **A systematic review and meta-analysis assessing adverse event profile and tolerability of**
8
9 **nicergoline**
10

11
12 Corresponding author:
13

14 Dr. Amit Garg, M.D.

15 Physician

16 A Wing- 304, Aparna Towers

17 Kondapur, Kothaguda,

18 Hyderabad-500084

19 Email: amitgarg.pharm@gmail.com

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Tele: +918790902800

Authors:

Mario Fioravanti¹, Taku Nakashima², Jun Xu³, Amit Garg⁴

Affiliations:

1. Prof. Mario Fioravanti, M.D.

Director of the Clinical Psychology Service

University Hospital, Umberto I

Professor of Clinical Psychology

Department of Neurology and Psychiatry

University of Rome, Sapienza, Italy

E-mail: mario.fioravanti@uniroma1.it

2. Taku Nakashima, MD, PhD.

1
2
3 Dept. of Molecular & Internal Medicine,
4
5 Hiroshima University Hospital
6
7 1-2-3 Kasumi, Minami-ku Hiroshima, 734-8551 Japan
8
9
10 E-mail: tnaka@hiroshima-u.ac.jp/tnaka@eos.ocn.ne.jp

11
12 3. Prof. Jun Xu

13
14 Hospital: Jiangsu Province Geriatric Hospital, China
15
16 Email: 13611572068@126.com ; neurojun@126.com

17
18
19 4. Dr. Amit Garg, M.D.

20
21 Physician, A-Wing- 304, Aparna Towers
22
23 Kondapur, Kothaguda, Hyderabad-500084. India
24
25 Email: amitgarg.pharm@gmail.com
26
27
28
29
30

31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords:

Meta-analysis, nicergoline, ergot derivatives, fibrosis, ergotism

Word Count:

2649 words

Abstract

Objective: To evaluate the safety profile of nicergoline compared to placebo and other active agents from published randomised controlled trials.

Design: Systematic review and meta-analysis of nicergoline compared to placebo and other active agents across various indications.

Data sources: Medline, Medline-in-process, Cochrane, Embase, Embase alerts, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register (CMR) for all the randomized controlled trials, open-label or blinded, in adults treated with nicergoline. Studies published till August 2013 were included.

Review method: Twenty nine studies were included for data extraction. The studies included in this review were majorly from European countries and mostly in cerebrovascular disease (n=15) and dementia (n=8).

Results: The treatment withdrawals were comparatively lower in nicergoline group as compared to placebo group (RR: 0.92; 95%CI: 0.7, 1.21) and other active comparators (RR: 0.45; 95%CI: 0.10, 1.95) but the difference was non-significant. Incidence of any adverse events was slightly higher (RR: 1.05; 95%CI: 0.93, 1.2) while incidence of serious adverse events was lower (RR: 0.85; 95%CI: 0.50, 1.45) in nicergoline compared to placebo group. Frequency of anxiety was significantly lower in Nicergoline as compared to placebo (p=0.01). Other AEs including diarrhoea, gastric upset, dizziness and drowsiness were less frequent in Nicergoline group compared to placebo/active drugs but the difference was non-significant. Frequency of hypotension and hot flushes was slightly higher in nicergoline group but the difference was non-

1
2
3 significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline
4
5 treatment.
6

7 **Conclusions:** Nicergoline is an ergot derivatives but the safety profile is better than other ergot
8 derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest
9 that nicergoline has a good safety profile. None of the studies included in this systematic review
10 reported any incidence of fibrosis or ergotism with nicergoline.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 Article Summary:
5
6

7 **Article focus:**

- 8
9 - Currently not many options are available for management of cognitive
10 impairment including pre-dementia and dementia.
11
12 - Despite no known association of nicergoline with ergotism, regulators have
13 limited the use of same
14
15 - This meta-analysis is in effort to find the exact side effect profile and benefit
16 to risk evaluation
17
18
19
20
21

22 **Key messages:**

- 23
24 - No evidence was found to suggest any incidence of fibrosis and ergotism with
25 nicergoline
26
27 - Nicergoline is found to be a very safe alternative in a disease (cognitive
28 impairment) with lean pipeline
29
30
31
32

33 **Strengths and limitations of this study:**

- 34
35 - First meta-analysis on nicergoline to understand the adverse clinical profile
36
37 - Critical in wake of recent EMEA view of blanket limitation on use of all ergot
38 derivatives
39
40 - Limited by the availability of long term (more than 2 years) and high dose
41 studies for cognitive impairment
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Title:**A systematic review and meta-analysis assessing safety and tolerability of nicergoline****Background**

Nicergoline is a semi synthetic ergot derivative which has been registered in over fifty countries and has been used for more than four decades for the treatment of cognitive, affective, and behavioural disorders of older people.¹ During the time it has been in use, the rationale for its clinical use has evolved. Initially regarded as a vasoactive drug, it was mainly prescribed for cerebrovascular disorders. Although cholinergic deficits are the major current targets for pharmacological intervention in Alzheimer's dementia, a wide variety of other neurotransmitter changes can be identified in the disease.

Nicergoline has been demonstrated to increase the availability of acetylcholine both through an increased release from cholinergic terminals and a selective inhibition of acetyl cholinesterase.² Nicergoline may also enhance noradrenalin and dopamine turnover in some areas of the brain.³ Nicergoline has a positive effect on the signal transduction system stimulating the phosphoinositide pathway which is specifically impaired in Alzheimer's dementia.⁴ Other useful actions of Nicergoline in dementia are an increase of phosphoinosiphosphoinositide-PKC translocation which helps in combating beta-amyloid deposition and in retarding the reduction in nerve-growth factor (NGF) which may help in preventing the loss of cholinergic neurons.⁴

The side effects of Nicergoline are usually limited to nausea, hot flushes, mild gastric upset, hypotension and dizziness. At high dosages bradycardia, increased appetite, agitation, diarrhoea and perspiration have been known to occur. Nicergoline has a better safety profile compared to ergot derivates which are associated with increased risk of fibrosis (formation of excess

1
2
3 connective tissue that can damage organs and body structures) and ergotism (symptoms of ergot
4 poisoning, such as spasms and obstructed blood circulation) with these medicines.
5
6

7
8 Nicergoline is not associated with either fibrosis or ergotism however; concerns about its safety
9 have been raised, especially after the European Medicines Agency's (EMA) restriction on
10 nicergoline because it is an ergot derivative.⁵ Most of the available literature suggests that the
11 adverse events with nicergoline are mild and transient. Hence, a systematic review of literature
12 and meta-analysis was conducted to compare the safety profile of nicergoline with placebo and
13 other active comparators.
14
15
16
17
18
19
20
21

22 **Methods**

23 **Search strategy**

24
25
26
27
28
29 A comprehensive search strategy was designed to retrieve relevant clinical data from published
30 literature. The following databases were examined since inception up to 16th August 2013;
31
32 Medline, Medline-in-process, Embase, Embase alerts, Cochrane Central Register of Controlled
33
34 Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane
35
36 Methodology Register. Medical subject headings (MeSH terms) and free keywords like
37
38 “randomised controlled trial”, “Nicergoline”, “Adverse effects”, “toxicity” and “side effects”
39
40 were used (Appendix 1). This review was not restricted to studies conducted in English language
41
42 and hence studies published in other languages were also included and translated for data
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
extraction.

50 **Selection criteria**

51
52
53
54 To meet the study objective, we pre-decided on inclusion criteria which include RCTs reporting
55
56 adverse events in patients undergoing nicergoline treatment for psychiatric disorders. To be
57
58 included in the analysis, a trial had to fulfill the following criteria: 1) randomized trials which
59
60

1
2
3 could be be open-label, single-blind, or double-blind, parallel group studies; 2) use of nicergoline
4
5 for Alzheimer's disease, dementia or cognitive disorders; 3) use of nicergoline as one of the
6
7 interventions; 3) Studies comparing nicergoline with ergot derivatives, placebo, or other active
8
9 agents were included; 4) Studies should report safety and tolerability data for nicergoline.
10

11
12 Studies were excluded if: 1) presented data for children only; 2) study design was not of interest;
13
14 3) disease was other than of interest; 4) study was not presenting safety and tolerability
15
16 outcomes; 5) full-text could not be sourced.
17
18
19

20 **Data extraction**

21
22 Bibliographic details and abstracts of all citations retrieved by the literature search were
23
24 downloaded into Endnotes version X3. Cochrane methodology was used to conduct this
25
26 systematic review. All studies were screened by two independent reviewers with discrepancies
27
28 resolved by a third reviewer.
29
30
31
32

33 **Study quality and risk of bias**

34
35
36
37 Jadad score was used to assess the quality of included studies. Risk of bias in the individual
38
39 studies included for meta-analysis was assessed using Cochrane risk assessment tool.⁶
40
41

42 **Outcomes assessed**

43
44
45 In most of the included studies, safety evaluation included monitoring of adverse events, vital
46
47 signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at
48
49 baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-
50
51 emergent adverse events (elicited or observed); physical examination including ECG recording;
52
53 vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to
54
55 adverse event were reported.
56
57
58
59
60

1
2
3 The data from these studies were pooled for total withdrawals, withdrawals due to AEs,
4
5 incidence rates for any AEs, SAEs, and specific AEs including anxiety, constipation, diarrhoea,
6
7 hot flushes, itching, gastric upset, hypotension, headache, dizziness, insomnia, drowsiness and
8
9 fatigue. Only studies which presented data for same comparators were included in direct meta-
10
11 analysis for each outcome.
12

13 14 15 **Statistical analysis**

16
17
18 Comparison of safety and tolerability outcomes were made between interventions by pooling
19
20 data from studies using direct meta-analysis technique. Only head-to-head comparisons between
21
22 interventions were included for meta-analysis. Review Manager (RevMan v 5.1) software was
23
24 used for meta-analysis of the available data. Dichotomous outcomes were summarised as risk
25
26 (relative) ratios.
27
28

29 30 31 **Results**

32 33 34 **Study selection**

35
36
37 A trial flow of the review process (as per PRISMA statement) is presented along with
38
39 manuscript (Figure 1). The search of the literature yielded 437 separate references. Due to the
40
41 overlap of coverage between the databases, 96 of the references were found to be duplicates. A
42
43 total of 341 citations were reviewed for abstract screening (first pass). Following the first pass of
44
45 the citations, 56 potentially relevant references were identified. Full-text reports of these
46
47 citations were obtained for more detailed evaluation. Following detailed examination of the
48
49 reports, 26 citations were excluded. Thirty studies met inclusion criteria however one of them
50
51 was a secondary publication which was linked to its primary publication. Finally, a total of 29
52
53 references reporting trials were extracted. Table 1 presents an overview of the study methods in
54
55 included studies. Fifteen studies were not included in meta-analysis as data from these could not
56
57
58
59
60

1
2
3 be pooled. These were studies reporting standalone adverse events, or for standalone
4
5 comparators.
6
7

8 **Baseline Characteristics**

9
10
11 Most of the included studies were in cerebrovascular disease (n=15), followed by Dementia
12 (n=8). Two studies were for Alzheimer's disease and four were in other disease areas. The mean
13
14 age of included patients ranged from 48 years (Dubreuil 1986) to 81 years (Saletu 1995) across
15
16 the studies. The % of male patients ranged from 17.9% (Saletu 1995) to 76.7% (Nakashima
17
18 2011) in Nicergoline group and was comparable with control group in all studies). The number
19
20 of patients randomized in these studies ranged from 16 (Ronchi 1982) to 346 (Winblad
21
22 2001). The treatment/study duration ranged from 6 days (Ronchi 1982) to 24 months (Bes 1999)
23
24 across included studies with most studies with duration ≥ 3 months (n=17). The daily dose of
25
26 nicergoline used was ≤ 30 mg/day in 16 studies and was reported to be 60 mg/daily in 12 studies.
27
28
29
30
31

32 **Critical Appraisal**

33
34
35 Included studies were critically appraised using the Jadad scale which is a standard scale used for
36
37 evaluating quality of randomised trials in systematic reviews. Method used to generate random
38
39 allocation sequence was reported in only nine of the included studies and were judged as
40
41 adequate. The Jadad score was ≥ 3 in 20 studies and less than 3 in nine studies. Majority of the
42
43 studies were good quality studies as per Jadad scale. All of included studies reported comparable
44
45 baseline characteristics between treatment groups being studied.
46
47
48
49

50 **Risk of bias assessment**

51
52 **The risk of bias was low in the individual studies that were included for meta-analysis. The**
53
54 **method used to generate the allocation sequence was reported in sufficient detail to allow an**
55
56 **assessment in most of the studies. None of the included studies reported any inadequate method.**
57
58
59
60

Method for allocation concealment was not reported by any of the included studies. Method used for blinding was adequate in most of the study reporting it. Study withdrawals and patients inclusion for outcome assessment were similar within study groups.

Withdrawals

Total withdrawals with nicergoline ranged from 0% (Kugler 1985, Materna 1985) to 22.2% (Bes 1999) and from 0%- 27.8% with other comparator drugs/placebo. Six studies reported lower number of patient withdrawals from nicergoline group as compared to other comparator/placebo groups. Withdrawals due to AE were similar in nicergoline group as compared to other groups across the studies, Figure 2.

The meta-analyzed risk ratios between nicergoline and the other comparators and their corresponding 95% confidence intervals for study withdrawals are shown in Tables 2. Results of meta-analysis showed a non-significant lower rate of withdrawals from nicergoline compared to placebo ($p=0.57$) and other active agents ($p=0.28$). For withdrawals due to AE, the withdrawal rate was slightly higher with nicergoline when compared to placebo but the difference was only apparent and non-significant ($p=0.7$).

Adverse Events

There was adequate data to perform meta-analysis for safety outcomes including any AE, any serious AE, diarrhoea, hot flushes, gastric upset, itching, hypertension, headache, dizziness, anxiety, insomnia, drowsiness and fatigue (Supplementary Table 1). However, there was no reference to cases with fibrosis and/or ergotism.

The meta-analyzed risk ratios between nicergoline and the other comparators and their corresponding 95% confidence intervals for study withdrawals and safety outcomes are shown in Tables 2, and 3, respectively. Results of meta-analysis showed a non-significant lower rate of

1
2
3 withdrawals from nicergoline compared to placebo ($p=0.57$) and other active agents ($p=0.28$).

4
5 For withdrawals due to AE, the withdrawal rate was slightly higher with nicergoline when
6
7 compared to placebo but again the difference was non-significant ($p=0.7$).

8
9
10 The risk of any adverse event was similar with nicergoline compared to placebo (10 studies),
11
12 ergot derivatives and other active comparators, all comparisons being non-significant. Risk of
13
14 any serious adverse event was slightly lower in the nicergoline group compared to placebo but
15
16 was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline
17
18 as compared to placebo ($p=0.01$). Nicergoline was associated with lower risk of diarrhoea as
19
20 compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence
21
22 of dizziness was similar in nicergoline group as compared to placebo or other active agents. A
23
24 comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but
25
26 the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo
27
28
29
30
31 group.

32
33
34 Higher risk of fatigue was associated with nicergoline compared to active comparators including
35
36 ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported
37
38 with nicergoline compared to other comparators. Risk of headache and hypotension was higher
39
40 with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with
41
42 nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any
43
44 significant difference was observed compared to the other intervention or placebo, **Figure 3**.

45
46
47
48 Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in
49
50 eight studies during the entire study duration, while remaining studies reported excellent or good
51
52 tolerability in nicergoline treated patients. None of these studies reported any incidence of
53
54 ergotism or fibrosis with nicergoline.
55

Discussion

Nicergoline is a potent and selective alpha-1A adrenergic receptor antagonist.³⁶ Nicergoline is reported to enhance catecholaminergic turnover,³ stimulate cholinergic neuro-transmission,⁴ stimulate phosphoinositide pathway,³ promote cerebral metabolic activity,³⁷ and has neuroprotective and antioxidant properties.³⁷ Nicergoline is used clinically to improve the apathy and affective disorders caused by cerebral infarction (such as reduced mental alertness, inattention, impairment of recent memory, hypobulia, depression, etc.). It is useful in the treatment of acute and chronic peripheral circulation disorders (such as obliterative vascular disease of the limbs, Raynaud's syndrome and other peripheral circulation dysfunction symptoms). Nicergoline has also been prescribed for the treatment of vascular dementia, especially for the improvement in cognitive dysfunction and memory, and to reduce the severity of this disease.

In addition, studies have been reported showing the usefulness of nicergoline in conditions such as post-hemodialysis pruritus, tinnitus and vertigo, ocular conditions such as arterial obstructions, venous thrombosis, diabetic retinopathies, senile macular degenerations, papilla ischaemic oedema and central serous chorioretinopathies. Dosages for known conditions are usually administered at 5–10 mg three times a day, however anti-aging preventative purposes may limit this to 5 mg once or twice a day. Higher doses of up to 60 mg/day have also been prescribed in clinical practice but have been associated with increased risk of adverse events.⁴

The EMEA's Committee for Medicinal Products for Human Use (CHMP) in its recommendations has suggested that ergot containing medicines, including nicergoline, should no longer be used to treat conditions involving blood circulation problems (such as peripheral artery disease, Raynaud's syndrome and retinopathies of vascular origin), memory and sensation problems and migraine headaches. This recommendation has been supported by the EMEA

1
2
3 citing that these ergot derivatives have a high likelihood of causing serious adverse events such
4 as fibrosis and ergotism.⁵ However, in this recommendation, the EMEA suggests that healthcare
5 professionals can continue prescribing nicergoline and other ergot derivatives in dementia
6 (including Alzheimer's disease) and acute migraine.
7
8
9

10
11
12 Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-
13 infarct dementia.^{1,32} Also, nicergoline has shown efficacy in conditions like post-hemodialysis
14 pruritus,³⁹ tinnitus and vertigo.⁴⁰ Nicergoline has a positive effect on cognition and behaviour in
15 addition to an effect on clinical global impression in older patients with mild to moderate
16 cognitive and behavioural impairment of various clinical origins including chronic
17 cerebrovascular disorders and Alzheimer's dementia.¹
18
19
20
21
22
23
24

25
26
27 Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep
28 disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and
29 increased appetite.^{8,22} Cardiovascular events like temporary rise in BP, syncope, bradycardia, and
30 hypotension have been reported with nicergoline by few studies.^{18,41}
31
32
33
34
35
36

37
38 Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and
39 abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have
40 reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure,
41 and interstitial nephritis.^{42,43}
42
43
44
45

46
47 Results of this meta-analysis showed comparable safety profile of nicergoline with other active
48 agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to
49 adverse events were similar with nicergoline compared to placebo & active agents. Incidence of
50 any adverse event when compared to placebo and ergot derivatives was slightly higher in the
51 nicergoline group but the difference was non-significant. Significantly lower rates of anxiety
52 were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like
53
54
55
56
57
58
59
60

1
2
3 diarrhoea, dizziness, drowsiness, gastric upset and fatigue were slightly lower with nicergoline as
4
5 compared to placebo but the difference was non-significant for all comparisons.
6
7

8 Nicergoline was associated with higher rates of hot flushes, headache, hypotension, insomnia
9
10 and itching. None of the comparisons showed a significant difference but some of these adverse
11
12 events are probably because of the vasodilation action of nicergoline. Higher doses of
13
14 nicergoline (60 mg/day) were associated with higher rates of adverse events compared to the 30
15
16 mg/day dosing but the difference was not significant. None of the studies included in this meta-
17
18 analysis reported any incidence of fibrosis or ergotism with nicergoline.
19
20
21

22
23 In its current recommendation, the EMEA has overlooked the efficacy and safety profile of
24
25 nicergoline and has cautioned against its use in conditions with blood circulation problems,
26
27 memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban
28
29 on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA
30
31 has probably considered the safety profile of all ergot derivatives as similar. The CHMP review
32
33 has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest
34
35 incidence of these AEs with other ergot derivatives as well.
36
37
38

39 EMEA has suggested that echocardiography should be done within 3–6 months of starting
40
41 treatment with ergot derivatives and subsequently at 6–12-month interval.⁴⁴ In the current meta-
42
43 analysis, most of the included studies were >3 months and up to 24 months in duration and none
44
45 of the included studies reported any incidence of fibrosis or ergotism with nicergoline. There is
46
47 no evidence in literature to suggest any incidence of fibrosis and ergotism with nicergoline.
48
49
50

51 The strengths of this systematic review include the clear definition of the research question,
52
53 adherence to an explicit research protocol that was developed prior to the analysis, the
54
55 comprehensive nature of the data search (employing both electronic databases and manual
56
57 bibliography searches resulting in the inclusion of all relevant publications), consensus between
58
59
60

1
2
3 two reviewers of all data elements prior to entry into the database and the quality control review
4
5 of every element of this report. In addition, the quality of the studies and manuscripts used to
6
7 provide data were relatively high. Only RCTs were included in this systematic review/meta-
8
9 analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to
10
11 compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this
12
13 review could be the publication timeframe of the included studies. Most of the studies were
14
15 published in 1980s and 1990s. There were hardly any trials published in recent years on safety
16
17 evaluation for nicergoline.
18
19

20 21 22 **Conclusions**

23
24
25 This systematic review & meta-analysis has included the evidence to date with regards to
26
27 tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is
28
29 categorized under ergot derivatives. However, the adverse events with nicergoline are mild and
30
31 transient unlike other ergot derivatives (ergotamine & ergotamine) which have been associated
32
33 with fibrosis and ergotism.
34
35

36
37 The results from this systematic review/meta-analysis suggest that nicergoline has a comparable
38
39 safety profile as placebo and other active comparators. None of the studies included in this
40
41 systematic review reported any incidence of fibrosis or ergotism with nicergoline. The evidence
42
43 generated by this review suggests that despite being an ergot derivative, nicergoline is a safe and
44
45 well-tolerated drug. This systematic review/meta-analysis concludes that nicergoline is a safe
46
47 option for therapeutic management in patients with dementia and cerebrovascular disorders.
48
49

50 51 52 **List of abbreviations**

53
54 AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA:
55
56 European Medicines Agency; SAEs: serious adverse event
57
58
59
60

Tables

Table 1: Study methods for included RCTs

| Study Name | Study duration | Country | Blinding | Intervention | Comparator | Daily Dose of Nicergoline |
|---------------------------------|----------------|-----------|--------------|--------------|--------------------|---------------------------|
| Arrigo 1982 ⁷ | 14 weeks | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1989 ⁸ | 6 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Battaglia 1990 ⁹ | 6 months | Italy | Double-blind | Nicergoline | Ergot mesylate | 60mg |
| Battaglia 1995 ¹⁰ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Bes 1999 ¹¹ | 24 months | France | Double-blind | Nicergoline | Placebo | 60mg |
| Boss 1985 ¹² | - | Italy | Double-blind | Nicergoline | Buflomedil | 8mg |
| Brola 1997 ¹³ | 1 month | Poland | Single-blind | Nicergoline | Pentoxifylline | 30mg |
| Cascone 1978 ¹⁴ | 1 month | Italy | Double-blind | Nicergoline | Placebo | 15mg |
| Colombeau 1987 ¹⁵ | 15 days | France | Double-blind | Nicergoline | Placebo | 40mg |
| Crook 1997 ¹⁶ | 6 months | USA | Double-blind | Nicergoline | Placebo | 60mg |
| Dubreuil 1986 ¹⁷ | 1 month | France | Double-blind | Nicergoline | GBE | NR |
| Felisati 2002 ¹⁸ | 3 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Forette 1980 ¹⁹ | 3 weeks | France | Double-blind | Nicergoline | Placebo | 30mg |
| Gessner 1985 ²⁰ | 12 weeks | Germany | Double-blind | Nicergoline | GBE | 15mg |
| Herrmann 1997 ²¹ | 6 months | Germany | Double-blind | Nicergoline | Placebo | 60mg |
| Kugler 1985 ²² | 6 months | Germany | Double-blind | Nicergoline | Dihydro-ergotamine | 30mg |
| Lu 2001 ²³ | 12 weeks | China | Double-blind | Nicergoline | Aniracetam | 60mg |
| Marolda 1978 ²⁴ | 20 days | Italy | Double-blind | Nicergoline | Eburnamonine | 15-20mg |
| Materna 1985 ²⁵ | 12 weeks | Germany | Double-blind | Nicergoline | Flunarizine | 10-30mg |
| Nakashima 2011 ²⁶ | 6 months | Japan | Double-blind | Nicergoline | Imidapril | 15mg |
| Nappi 1997 ²⁷ | 12 months | Italy | Double-blind | Nicergoline | Placebo | 60mg |
| Nishiyama 2010 ²⁸ | 4 weeks | Japan | Open-label | Nicergoline | Placebo | 45mg |
| Pilkowska 2002 ²⁹ | 3 months | Poland | Double-blind | Nicergoline | Placebo | 60mg |
| Pogliani 1979 ³⁰ | 3 months | Germany | Double-blind | Nicergoline | Placebo | 15mg |
| Ronchi 1982 ³¹ | 6 Days | Italy | Double-blind | Nicergoline | Placebo | |
| Saletu 1995 ³² | 8 weeks | Austria | Double-blind | Nicergoline | Placebo | 30-60mg |
| Setyopranoto 2009 ³³ | - | Indonesia | Double-blind | Nicergoline | Placebo | 60mg |
| Winblad 2001 ³⁴ | 6 months | Europe | Double-blind | Nicergoline | Placebo | 60mg |
| Zucconi 1974 ³⁵ | 1 month | Italy | Double-blind | Nicergoline | Dihydro-ergotoxine | 2mg i.m. |

Table 2: Meta analysis of withdrawal rate across included studies

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|-----------------------|--------------|---------------|---------|------|-------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Total withdrawals | Nicergoline | Placebo | 8 | 1234 | 0.92 (0.70, 1.21) | 0.57 | 0% |
| | Nicergoline | Active agents | 3 | 201 | 0.45 (0.10, 1.95) | 0.28 | 18% |
| Withdrawals due to AE | Nicergoline | Placebo | 3 | 565 | 1.13 (0.61, 2.09) | 0.7 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Table 3: Meta analysis of overall adverse events

| Outcome | Intervention | Comparator | Studies | N | Fixed effects | | |
|---------------|--------------|-------------------|---------|------|--------------------|---------|----------------|
| | | | | | RR (95% CI) | P value | I ² |
| Any AE | Nicergoline | Placebo | 10 | 1448 | 1.05 (0.93, 1.20) | 0.42 | 0% |
| Any AE | Nicergoline | Active agents | 4 | 292 | 1.19 (0.71, 2.01) | 0.51 | 5% |
| Any AE | Nicergoline | Ergot derivatives | 2 | 200 | 1.22 (0.63, 2.34) | 0.56 | 19% |
| Any SAE | Nicergoline | Placebo | 2 | 482 | 0.85 (0.50, 1.45) | 0.54 | 35% |
| Anxiety | Nicergoline | Placebo | 2 | 482 | 0.59 (0.39, 0.88) | 0.01 | 0% |
| Diarrhoea | Nicergoline | Placebo | 2 | 188 | 0.85 (0.24, 3.05) | 0.8 | 0% |
| Diarrhoea | Nicergoline | Ergot derivatives | 2 | 200 | 0.99 (0.14, 6.92) | 0.99 | 0% |
| Dizziness | Nicergoline | Placebo | 3 | 260 | 0.63 (0.15, 2.57) | 0.51 | 0% |
| Dizziness | Nicergoline | Active agents | 2 | 116 | 1.00 [0.18, 5.58] | 1.0 | 0% |
| Drowsiness | Nicergoline | Placebo | 2 | 442 | 0.34 (0.05, 2.12) | 0.24 | 0% |
| Fatigue | Nicergoline | Placebo | 2 | 378 | 0.71 (0.14, 3.53) | 0.68 | 18% |
| Fatigue | Nicergoline | Active agents | 3 | 260 | 1.24 (0.35, 4.47) | 0.74 | 0% |
| Fatigue | Nicergoline | Ergot derivatives | 2 | 200 | 1.79 (0.40, 7.98) | 0.45 | 0% |
| Gastric upset | Nicergoline | Placebo | 6 | 1037 | 0.94 (0.58, 1.52) | 0.8 | 0% |
| Hot Flushes | Nicergoline | All comparisons | 3 | 470 | 3.65 (0.61, 21.93) | 0.16 | 0% |
| Headache | Nicergoline | Placebo | 5 | 1004 | 1.28 (0.63, 2.60) | 0.24 | 0% |
| Hypotension | Nicergoline | Placebo | 2 | 378 | 1.49 (0.26, 8.72) | 0.66 | 0% |
| Insomnia | Nicergoline | Placebo | 3 | 498 | 1.81 (0.39, 8.29) | 0.45 | 0% |
| Itching | Nicergoline | All comparisons | 2 | 108 | 3.23 (0.35, 30.08) | 0.3 | 0% |

*RR value greater than 1 denotes higher rate of adverse events with Nicergoline compared to the comparator drug and a value less than 1 denotes vice versa.

Contributorship Statement: AG carried out the searches in various databases. AG and JX carried out the filtration of citation. AG and JX carried out the data extraction, MF and TN helped to draft the manuscript and reviewed it. All authors read and approved the final manuscript.

Competing Interests: None

Funding: None

Data Sharing Statement: In addition to the manuscript, the corresponding author also has initial results of publication analysis. That explains the reason for inclusion and exclusion of individual studies. If readers require additional data on the analysis or the medical merits of the molecule, they can write to amitgarg.pharm@gmail.com

Figure Legends

Figure 1: PRISMA flow for included studies

Figure 2: Results of meta-analysis, all withdrawals: Nicergoline vs. Placebo

Figure 3: Results of meta-analysis, any adverse events: Nicergoline vs. Placebo

References

1. Fioravanti M, Flicker L. Efficacy of nicergoline in dementia and other age associated forms of cognitive impairment. Cochrane Database Syst Rev 2001:CD003159.
2. Carfagna N, Di Clemente A, Cavanus S, et al. Modulation of hippocampal ACh release by chronic nicergoline treatment in freely moving young and aged rats. Neurosci Lett 1995;197:195-8.
3. Carfagna N, Rossi A. Nicergoline: biochemical studies on neuronal metabolism. Funct Neurol 1989;4:177-85

- 1
2
3 4. Winblad B, Fioravanti M, Dolezal T, et al. Therapeutic use of nicergoline. *Clin Drug Investig*
4
5 2008;28:533-52.
6
- 7
8 5. New restrictions on use of medicines containing ergot derivatives.
9
10 [http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC50014
11 4861.pdf.]
12
- 13
14 6. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical
15
16 trials: Is blinding necessary? *Controlled Clinical Trials*, 17:1-12, 1996.
17
- 18
19 7. Arrigo A, Moglia A, Borsotti L. A double-blind, placebo-controlled, crossover trial with
20
21 nicergoline in patients with senile dementia. *International Journal of Clinical Pharmacology*
22
23 *Research* 1982;2:33-41.
24
- 25
26 8. Battaglia A, Bruni G, Ardia A, et al. Nicergoline in mild to moderate dementia. A
27
28 multicenter, double-blind, placebo-controlled study. *J Am Geriatr Soc* 1989;37:295-302.
29
- 30
31 9. Battaglia A, Bruni G, Sacchetti G, et al. A double-blind randomized study of two ergot
32
33 derivatives in mild to moderate dementia. *Curr Therap Res* 1990;48:597-612.
34
- 35
36 10. Battaglia A, Annoni K, Pamparana F, et al. Nicergoline in the Long Term Treatment of Mild
37
38 or Moderate Senile Dementia. A Multicenter Double-blind, Randomized, Placebo- controlled
39
40 Trial. In 8th European College of Neuropsychopharmacology Congress: 30th September -
41
42 4th October 1995; Venice.
- 43
44 11. Bes A, Orgogozo JM, Poncet M, et al. A 24-month, double-blind, placebo-controlled
45
46 multicentre pilot study of the efficacy and safety of nicergoline 60 mg per day in elderly
47
48 hypertensive patients with leukoaraiosis. *European Journal of Neurology* 1999;6:313-22.
49
- 50
51 12. Bossi L. Buflomedil and nicergolin in the treatment of acute cerebral ischaemia. A double-
52
53 blind, randomized comparative study. *Minerva Medica* 1985;76:1005-18.
54
- 55
56 13. Broła W. Evaluation of treatment outcome after nicergoline and pentoxifylline in patients
57
58 with ischemic stroke. *Przegląd lekarski* 1997;54:79-82.
59
60

- 1
2
3 14. Cascone A, Liverta C, Pollini C. A double-blind trial of nicergolin and placebo in cerebral
4
5 and peripheral cerebrovascular disturbance in the aged. *Minerva Cardioangiologica* 1978;
6
7 26:95-100.
8
- 9
10 15. Colombeau P, Ballanger P. Results of the double-blind use of an alpha blockader,
11
12 nicergoline, in cervico-prostatic dysfunctions. *Journal d'urologie* 1987;93:533-5.
13
- 14 16. Crook TH. Nicergoline in the treatment of probable Alzheimer's disease Preliminary results
15
16 of a double-blind, randomized, placebo-controlled study. *J Neurol Sci* 1997:S18.
17
- 18 17. Dubreuil C. Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo
19
20 biloba extract and nicergoline. *Presse médicale (Paris, France : 1983)* 1986;15:1559-61.
21
- 22 18. Felisati G, Battaglia A, Papini MG, et al. Nicergoline in balance alterations in adult and
23
24 elderly patients: A double-blind, placebo-controlled study. *Clinical Drug Investigation*
25
26 2002;22:731-40.
27
- 28 19. Forette F, Varin D, Henry JF, et al. Treatment of arterial hypertension in the elderly with an
29
30 alpha-blocker: nicergoline (author's transl). *La Nouvelle presse médicale* 1980, 9:3685-8.
31
32
- 33 20. Gessner B, Voelp A, Klasser M. Study of the long-term action of a Ginkgo biloba extract on
34
35 vigilance and mental performance as determined by means of quantitative pharmaco-EEG
36
37 and psychometric measurements. *Arzneimittel-Forschung/Drug Research* 1985;35:1459-65.
38
39
- 40 21. Herrmann WM. A multicenter randomized double-blind study on the efficacy and safety of
41
42 nicergoline in patients with multi-infarct dementia. *Dementia and Geriatric Cognitive*
43
44 *Disorders* 1997;8:9-17.
45
46
- 47 22. Kugler JE, Meurer-Krull BC. Electroencephalography and psychometric measurements
48
49 during the treatment of cerebral insufficiency with nicergoline and dihydroergotamine
50
51 mesylate. *Arzneimittelforschung* 1985;35:1865-70.
52
53
- 54 23. Lu JH. Nicergoline in treatment of vascular dementia: a consecutive, multicenter, double-
55
56 blind clinical trial. *Chinese J Neurol* 2001:88-91.
57
58
59
60

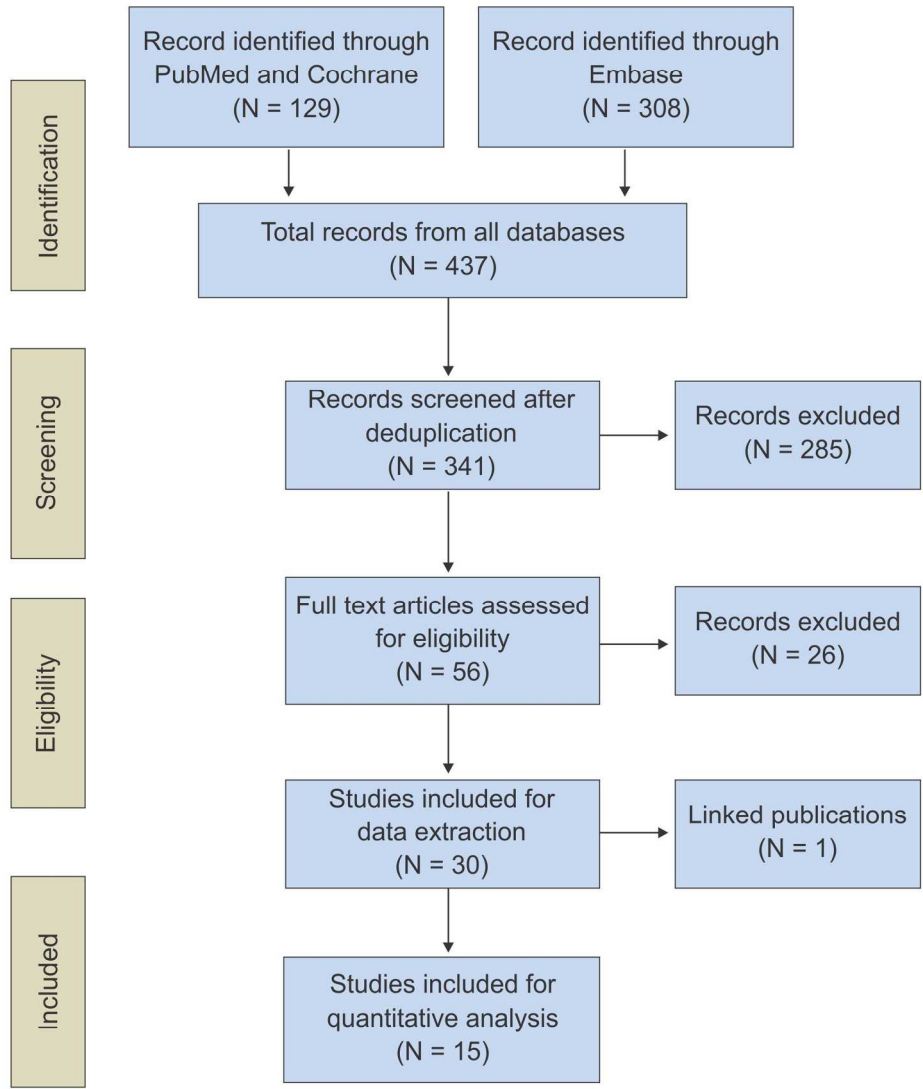
- 1
2
3 24. Marolda M, Fragassi N, Buscaino GA. Clinical evaluation of (-)eburnamonine in comparison
4 with nicergoline in patients suffering from chronic brain ischemia. *European Neurology*
5 1978, 17:159-66.
6
7
8
9
10 25. Materna F. Leading symptom vertigo: Comparative study with flunarizine and nicergoline.
11 *Medizinische Klinik* 1985, 80:292-5.
12
13
14 26. Nakashima T, Hattori N, Okimoto M, et al. Nicergoline improves dysphagia by upregulating
15 substance p in the elderly. *Medicine* 2011;90:279-83.
16
17
18
19 27. Nappi G, Bono G, Merlo P, et al. Long-term nicergoline treatment of mild to moderate
20 senile dementia. Results of a multicentre, double-blind, placebo-controlled study. *Clinical*
21 *Drug Investigation* 1997;13:308-16.
22
23
24
25 28. Nishiyama Y, Abe A, Ueda M, et al. Nicergoline increases serum substance P levels in
26 patients with an ischaemic stroke. *Cerebrovascular Diseases* 2010;29:194-8.
27
28
29
30 29. Pilkowska E, Jakubowska T, Witkowska K, et al. Nicergoline in the treatment of patients
31 after a mild ischemic stroke. *Neurologia i neurochirurgia polska* 2002;36:1075-85.
32
33
34
35 30. Pogliani E, Della Volpe A, Ferrari R. Inhibition of human platelet aggregation by oral
36 administration of nicergoline. A double blind study. *Farmaco, Edizione Pratica* 1975;30:630-
37 40.
38
39
40
41 31. Ronchi F, Margonato A, Ceccardi R. Symptomatic treatment of benign prostatic obstruction
42 with nicergoline: A placebo controlled clinical study and urodynamic evaluation. *Urological*
43 *Research* 1982;10:131-34.
44
45
46
47 32. Saletu B, Paulus E, Linzmayer L, et al. Nicergoline in senile dementia of Alzheimer type
48 and multi-infarct dementia: A double blind, placebo controlled, clinical and EEG/ERP
49 mapping study. *Psychopharmacology* 1995;117:385-95.
50
51
52
53
54 33. Setyopranoto ISP. Role of nicergoline 60 miligram per oral for improvement of the patients
55 with acute ischemic stroke. *Journal of the Neurological Sciences* 2009;285:S221-S222.
56
57
58
59
60

- 1
2
3 34. Winblad B, Bonura ML, Rossini BM, et al. Nicergoline in the treatment of mild-to-moderate
4
5 Alzheimer's disease: A European multicentre trial. *Clinical Drug Investigation* 2001;21:621-
6
7 32.
8
9
10 35. Zucconi V, Terzi Bolaffio M. Results with nicergolin and dihydroergotoxine in 30
11
12 hemiplegics in the postacute phase. *Minerva Medica* 1974;65:936-45.
13
14 36. Alvarez-Guerra M, Bertholom N, Garay RP. Selective blockade by nicergoline of vascular
15
16 responses elicited by stimulation of alpha 1A-adrenoceptor subtype in the rat. *conam Clin*
17
18 *Pharmacol* 1999;13:50-8.
19
20
21 37. Shintomi K, Yoshimoto K, Ogawa Y, et al. Effects of nicergoline on cerebral energy
22
23 metabolism in normal mice. *Yakugaku Zasshi* 1986;106:90-4.
24
25 38. Sortino MA, Battaglia A, Pamparana F, et al. Neuroprotective effects of nicergoline in
26
27 immortalized neurons. *Eur J Pharmacol* 1999;368:285-90.
28
29
30 39. Bousquet J, Rivory JP, Maheut M, et al. Double-blind, placebo-controlled study of
31
32 nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J*
33
34 *Allergy Clin Immunol* 1989;83:825-28.
35
36
37 40. Akisada T, Orita Y, Sato Y, et al. Effect of nicergoline on vertigo and tinnitus. *Practica*
38
39 *Otologica* 1994;87:845-55.
40
41
42 41. Boismare F, Lefrancois J. Haemodynamic effects of nicergoline in man at rest and during
43
44 exercise. *Clin Exp Pharmacol Physiol* 1980;7:105-12.
45
46 42. Gallego J, Forner V, Jimenez F, et al. Nicergoline in the treatment of neuropathic bladder
47
48 dysfunction: a preliminary report. *Paraplegia* 1984;22:216-24.
49
50 43. Kim MJ, Chang JH, Lee SK, et al. Acute interstitial nephritis due to nicergoline (Sermion).
51
52 *Nephron* 2002;92:676-79.
53
54 44. Ergot-derived dopamine agonists: risk of fibrotic reactions in chronic endocrine uses.
55
56 <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087807>
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

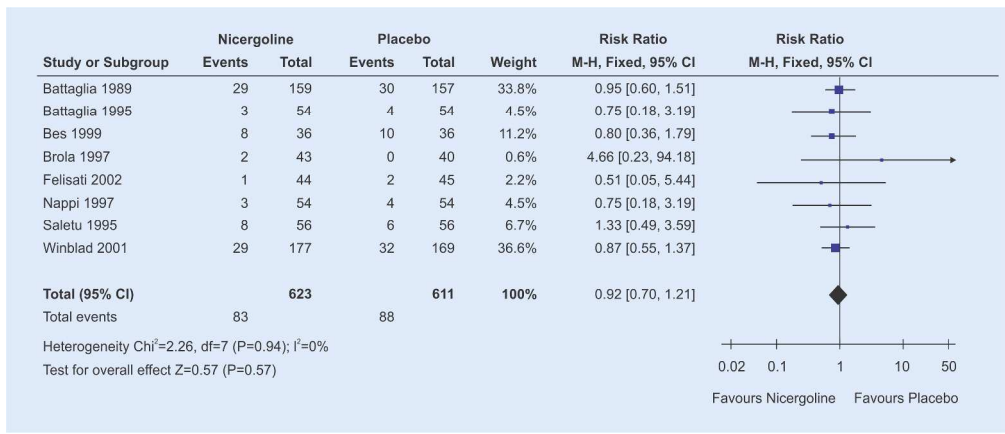
For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



168x196mm (300 x 300 DPI)

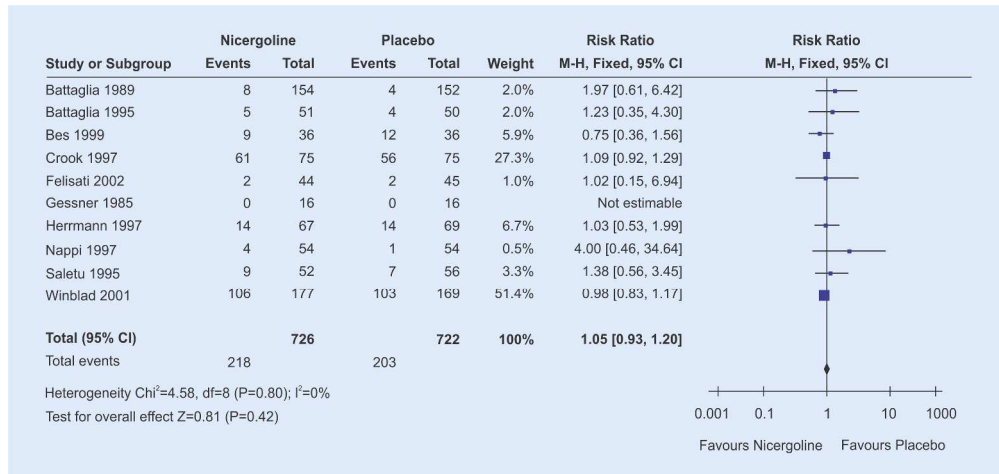
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



289x123mm (300 x 300 DPI)

Peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



294x139mm (300 x 300 DPI)

er review only

Search strategy for EMBASE

| S.No | Search string |
|------|--|
| 1 | 'clinical trial'/exp |
| 2 | 'randomization'/de |
| 3 | 'controlled study'/de |
| 4 | 'comparative study'/de |
| 5 | 'single blind procedure'/de |
| 6 | 'double blind procedure'/de |
| 7 | 'crossover procedure'/de |
| 8 | 'placebo'/de |
| 9 | 'clinical trial' OR 'clinical trials' |
| 10 | 'controlled clinical trial' OR 'controlled clinical trials' |
| 11 | 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' |
| 12 | 'randomisation' OR 'randomization' |
| 13 | rct |
| 14 | 'random allocation' |
| 15 | 'randomly allocated' |
| 16 | 'allocated randomly' |
| 17 | 'allocated NEAR/2 random' |
| 18 | (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) |
| 19 | placebo* |
| 20 | 'prospective study'/de |
| 21 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 |
| 22 | 'case study'/de |
| 23 | 'case report' |
| 24 | 'abstract report'/de |
| 25 | 'letter'/de |
| 26 | #22 OR #23 OR #24 OR #25 |
| 27 | #21 NOT #26 |
| 28 | Nicergoline/exp |
| 29 | Nicergolin* |
| 30 | Sermion/exp OR Sermion |
| 31 | #28 OR #29 OR #30 |
| 32 | Adverse event OR adverse drug reaction or side effect OR Harm |
| 33 | Safety OR tolerability OR complication OR toxicity |
| 34 | #32 OR #33 |
| 35 | #27 AND #31 AND #34 |

Supplementary Table 1: Incidence of adverse events with nicergoline and comparators

| Study Name | Intervention | Total Included | Any AEs | Any SAEs | Agitation/anxiety | Diarrhoea | Dizziness | Drowsiness | Fatigue | Gastric upset | Hot Flushes | Headache | Hypotension | Insomnia | Itching |
|-------------------|--------------------|----------------|---------|----------|-------------------|-----------|-----------|------------|---------|---------------|-------------|----------|-------------|----------|---------|
| Batalgia 1989 | Nicergoline | 154 | 8 | - | - | - | - | 1 | 1 | 4 | 2 | 1 | 1 | 1 | - |
| | Placebo | 152 | 4 | - | - | - | - | 2 | 0 | 3 | 0 | 0 | 1 | 1 | - |
| Battalgia 1990 | Nicergoline | 73 | 8 | - | - | 1 | - | - | 1 | 1 | - | 2 | - | - | - |
| | Ergoloid Mesylates | 71 | 4 | - | - | 0 | - | - | 0 | 0 | - | 1 | - | - | - |
| Battalgia 1995 | Nicergoline | 51 | 5 | - | - | - | - | - | - | - | - | - | - | - | - |
| | Placebo | 50 | 4 | - | - | - | - | - | - | - | - | - | - | - | - |
| Bes 1999 | Nicergoline | 36 | 9 | - | - | - | 2 | - | 1 | - | - | - | 2 | - | - |
| | Placebo | 36 | 12 | - | - | - | 2 | - | 3 | - | - | - | 1 | - | - |
| Crook 1997 | Nicergoline | 75 | 61 | - | - | - | - | - | - | - | - | - | - | - | - |
| | Placebo | 75 | 56 | - | - | - | - | - | - | - | - | - | - | - | - |
| Felisati 2002 | Nicergoline | 44 | 2 | - | - | - | - | - | - | 0 | - | - | - | - | - |
| | Placebo | 45 | 2 | - | - | - | - | - | - | 2 | - | - | - | - | - |
| Herrmann 1997 | Nicergoline | 67 | 14 | 0 | 0 | 3 | 0 | 0 | - | 0 | - | 2 | - | 1 | - |
| | Placebo | 69 | 14 | 3 | 1 | 4 | 1 | 2 | - | 1 | - | 2 | - | 0 | - |
| Kugler 1985 | Nicergoline | 28 | 8 | - | - | 0 | 1 | 1 | 3 | - | 1 | - | - | 1 | 1 |
| | Dihydroergotamine | 28 | 9 | - | - | 1 | 2 | 2 | 2 | - | 0 | - | - | 0 | 0 |
| Materna 1985 | Nicergoline | 30 | 8 | - | - | - | 1 | - | 0 | 3 | - | - | - | - | - |
| | Flunarizine | 30 | 8 | - | - | - | 0 | - | 1 | 1 | - | - | - | - | - |
| Nappi 1997 | Nicergoline | 54 | 4 | - | - | - | - | - | - | 1 | 1 | 2 | - | - | - |
| | Placebo | 54 | 1 | - | - | - | - | - | - | 1 | 0 | 0 | - | - | - |
| Saletu 1995 | Nicergoline (SDAT) | 24 | 7 | - | - | 1 | 0 | - | - | 1 | - | 2 | - | - | 1 |
| | Placebo (SDAT) | 28 | 4 | - | - | 1 | 1 | - | - | - | - | - | - | - | 0 |
| | Nicergoline (MID) | 28 | 2 | - | - | - | - | - | - | - | - | - | - | 2 | - |
| | Placebo (MID) | 28 | 3 | - | - | - | - | - | - | - | - | 1 | - | - | - |
| Winblad 2001 | Nicergoline | 177 | 106 | 22 | 30 | - | - | - | - | 22 | - | 9 | - | - | - |
| | Placebo | 169 | 103 | 22 | 48 | - | - | - | - | 22 | - | 9 | - | 14 | - |



PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|------------------------------------|----|---|--------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 7 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Yes, data on file |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7,8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Appendix 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7,8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis). http://bmjopen.bmj.com/site/about/guidelines.xhtml | 9 |



PRISMA 2009 Checklist

Page 1 of 2

| Section/topic | # | Checklist item | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | NA |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10,17 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 10 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 18,19 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 18,19 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 10 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 14,15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 20 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>