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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005090
Article Type:	Research
Date Submitted by the Author:	20-Feb-2014
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice, Mental health
Keywords:	Meta-analysis, Nicergoline, ergot derivatives, fibrosis, ergotism

Title of the article:

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Keywords:

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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-

significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline treatment.

Conclusions: Nicergoline is an ergot derivatives but the safety profile is better than other ergot derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest that nicergoline has a good safety profile. None of the studies included in this systematic review reported any incidence of fibrosis or ergotism with nicergoline.

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 (EMEA) 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 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.

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

Data extraction

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnotes version X3. Cochrane methodology was used to conduct this systematic review. All studies were screened by two independent reviewers with discrepancies resolved by a third reviewer.

Outcomes assessed

The outcomes assessed included total withdrawals, withdrawals due to AEs, incidence rates for any AEs, SAEs, and specific AEs including anxiety, constipation, diarrhoea, hot flushes, itching, gastric upset, hypotension, headache, dizziness, insomnia, drowsiness and fatigue.

Statistical analysis

Comparison of safety and tolerability outcomes were made between interventions by pooling data from studies using standard meta-analytic techniques. 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) in 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 publications 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.

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

Critical Appraisal

Included studies were critically appraised using the Jadad scale which is a standard scale used for evaluating quality of randomised trials in systematic reviews. Method used to generate random allocation sequence was reported in only nine of the included studies and were judged as adequate. None of the study reported the method used for concealment of allocation sequence. The Jadad score was ≥3 in 20 studies and less than 3 in nine studies. Majority of the studies were

good quality studies as per Jadad scale. All of included studies reported comparable baseline characteristics between treatment groups being studied.

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 1.

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. 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 3, and 4, respectively. 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 again the difference was non-significant (p=0.7).

The risk of any adverse event was similar with nicergoline compared to placebo (10 studies), ergot derivatives and other active comparators, all comparisons being non-significant. Risk of any serious adverse event was slightly lower in the nicergoline group compared to placebo but was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline as compared to placebo (p=0.01). Nicergoline was associated with lower risk of diarrhoea as compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence of dizziness was similar in nicergoline group as compared to placebo or other active agents. A comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo group.

Higher risk of fatigue was associated with nicergoline compared to active comparators including ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported with nicergoline compared to other comparators. Risk of headache and hypotension was higher with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any significant difference was observed compared to the other intervention or placebo. Figure 2.

Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in eight studies during the entire study duration, while remaining studies reported excellent or good tolerability in nicergoline treated patients. None of these studies reported any incidence of ergotism or fibrosis with nicergoline.

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

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

Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-infarct dementia.[1,31] Also, nicergoline has shown efficacy in conditions like post-hemodialysis pruritus,[38] tinnitus and vertigo.[39] Nicergoline has a positive effect on cognition and behaviour in addition to an effect on clinical global impression in older patients with mild to moderate cognitive and behavioural impairment of various clinical origins including chronic cerebrovascular disorders and Alzheimer's dementia.[1]

Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and increased appetite.[7,21] Cardiovascular events like temporary rise in BP, syncope, bradycardia, and hypotension have been reported with nicergoline by few studies.[17,40]

Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure, and interstitial nephritis.[41,42]

Results of this meta-analysis showed comparable safety profile of nicergoline with other active agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to adverse events were similar with nicergoline compared to placebo & active agents. Incidence of any adverse event when compared to placebo and ergot derivatives was slightly higher in the nicergoline group but the difference was non-significant. Significantly lower rates of anxiety were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like

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

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

In its current recommendation, the EMEA has overlooked the efficacy and safety profile of nicergoline and has cautioned against its use in conditions with blood circulation problems, memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA has probably considered the safety profile of all ergot derivatives as similar. The CHMP review has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest incidence of these AEs with other ergot derivatives as well.

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

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

two reviewers of all data elements prior to entry into the database and the quality control review of every element of this report. In addition, the quality of the studies and manuscripts used to provide data were relatively high. Only RCTs were included in this systematic review/meta-analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this review could be the publication timeframe of the included studies. Most of the studies were published in 1980s and 1990s. There were hardly any trials published in recent years on safety evaluation for nicergoline.

Conclusions

This systematic review & meta-analysis has included the evidence to date with regards to tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is categorized under ergot derivatives. However, the adverse events with nicergoline are mild and transient unlike other ergot derivatives (ergotamine & ergotoxine) which have been associated with fibrosis and ergotism.

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

List of abbreviations

AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; SAEs: serious adverse event

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 explainsl the reason for inclusion and exclusion if individual studies.

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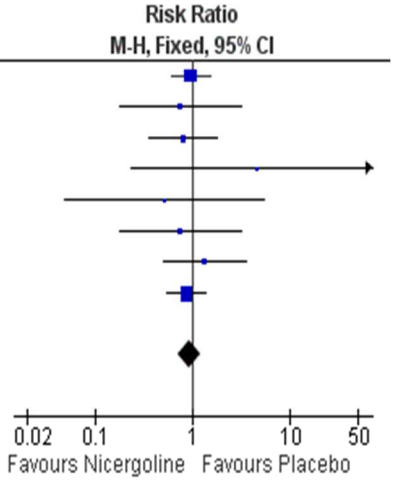
All Withdrawals: Nicergoline vs. Placebo

Study or Subgroup	Nicergoline Events	Nicergoline Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Battaglia 1989	29	159	30	157	33.8%	0.95 [0.60, 1.51]
Battaglia 1995	3	54	4	54	4.5%	0.75 [0.18, 3.19]
Bes 1999	8	36	10	36	11.2%	0.80 [0.36, 1.79]
Brola 1997	2	43	0	40	0.6%	4.66 [0.23, 94.18]
Felisati 2002	1	44	2	45	2.2%	0.51 [0.05, 5.44]
Nappi 1997	3	54	4	54	4.5%	0.75 [0.18, 3.19]
Saletu 1995	8	56	6	56	6.7%	1.33 [0.49, 3.59]
Winblad 2001	29	177	32	169	36.6%	0.87 [0.55, 1.37]
Total (95% CI)		**623**		**611**	**100.0%**	**0.92 [0.70, 1.21]**
Total events	83		88			

Heterogeneity: Chi² = 2.26, df = 7 (P = 0.94); I² = 0%

Test for overall effect: Z = 0.57 (P = 0.57)

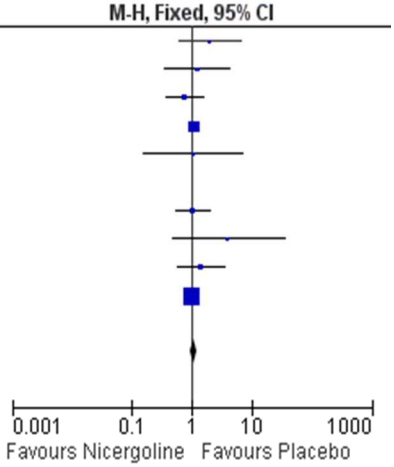


Any Adverse Event: Nicergoline vs. Placebo

Study or Subgroup	Nicergoline Events	Nicergoline Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Battaglia 1989	8	154	4	152	2.0%	1.97 [0.61, 6.42]
Battaglia 1995	5	51	4	50	2.0%	1.23 [0.35, 4.30]
Bes 1999	9	36	12	36	5.9%	0.75 [0.36, 1.56]
Crook 1997	61	75	56	75	27.3%	1.09 [0.92, 1.29]
Felisati 2002	2	44	2	45	1.0%	1.02 [0.15, 6.94]
Gessner 1985	0	16	0	16		Not estimable
Herrmann 1997	14	67	14	69	6.7%	1.03 [0.53, 1.99]
Nappi 1997	4	54	1	54	0.5%	4.00 [0.46, 34.64]
Saletu 1995	9	52	7	56	3.3%	1.38 [0.56, 3.45]
Winblad 2001	106	177	103	169	51.4%	0.98 [0.83, 1.17]
Total (95% CI)		**726**		**722**	**100.0%**	**1.05 [0.93, 1.20]**
Total events	218		203			

Heterogeneity: Chi² = 4.58, df = 8 (P = 0.80); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)



BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005090.R1
Article Type:	Research
Date Submitted by the Author:	24-May-2014
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice, Mental health
Keywords:	Meta-analysis, Nicergoline, Ergot derivatives, Fibrosis, Ergotism

Title of the article:

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

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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-

significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline treatment.

Conclusions: Nicergoline is an ergot derivatives but the safety profile is better than other ergot derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest that nicergoline has a good safety profile. None of the studies included in this systematic review reported any incidence of fibrosis or ergotism with nicergoline.

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 (EMEA) 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 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.

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

Data extraction

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnotes version X3. Cochrane methodology was used to conduct this systematic review. All studies were screened by two independent reviewers with discrepancies resolved by a third reviewer.

Outcomes assessed

In most of the included studies, safety evaluation included monitoring of adverse events, vital signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-emergent adverse events (elicited or observed); physical examination including ECG recording; vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to adverse event were reported.

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

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) in 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 publications 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

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

Critical Appraisal

Included studies were critically appraised using the Jadad scale which is a standard scale used for evaluating quality of randomised trials in systematic reviews. Method used to generate random allocation sequence was reported in only nine of the included studies and were judged as adequate. None of the study reported the method used for concealment of allocation sequence. The Jadad score was ≥3 in 20 studies and less than 3 in nine studies. Majority of the studies were good quality studies as per Jadad scale. All of included studies reported comparable baseline characteristics between treatment groups being studied.

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 1.

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 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 again the difference was non-significant (p=0.7).

The risk of any adverse event was similar with nicergoline compared to placebo (10 studies), ergot derivatives and other active comparators, all comparisons being non-significant. Risk of any serious adverse event was slightly lower in the nicergoline group compared to placebo but was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline as compared to placebo (p=0.01). Nicergoline was associated with lower risk of diarrhoea as compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence of dizziness was similar in nicergoline group as compared to placebo or other active agents. A

comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo group.

Higher risk of fatigue was associated with nicergoline compared to active comparators including ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported with nicergoline compared to other comparators. Risk of headache and hypotension was higher with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any significant difference was observed compared to the other intervention or placebo, Figure 2.

Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in eight studies during the entire study duration, while remaining studies reported excellent or good tolerability in nicergoline treated patients. None of these studies reported any incidence of ergotism or fibrosis with nicergoline.

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

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

Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-infarct dementia.[1,31] Also, nicergoline has shown efficacy in conditions like post-hemodialysis pruritus,[38] tinnitus and vertigo.[39] Nicergoline has a positive effect on cognition and behaviour in addition to an effect on clinical global impression in older patients with mild to moderate cognitive and behavioural impairment of various clinical origins including chronic cerebrovascular disorders and Alzheimer's dementia.[1]

Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and increased appetite.[7,21] Cardiovascular events like temporary rise in BP, syncope, bradycardia, and hypotension have been reported with nicergoline by few studies.[17,40]

Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure, and interstitial nephritis.[41,42]

Results of this meta-analysis showed comparable safety profile of nicergoline with other active agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to adverse events were similar with nicergoline compared to placebo & active agents. Incidence of any adverse event when compared to placebo and ergot derivatives was slightly higher in the nicergoline group but the difference was non-significant. Significantly lower rates of anxiety were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like

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

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

In its current recommendation, the EMEA has overlooked the efficacy and safety profile of nicergoline and has cautioned against its use in conditions with blood circulation problems, memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA has probably considered the safety profile of all ergot derivatives as similar. The CHMP review has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest incidence of these AEs with other ergot derivatives as well.

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

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

two reviewers of all data elements prior to entry into the database and the quality control review of every element of this report. In addition, the quality of the studies and manuscripts used to provide data were relatively high. Only RCTs were included in this systematic review/meta-analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this review could be the publication timeframe of the included studies. Most of the studies were published in 1980s and 1990s. There were hardly any trials published in recent years on safety evaluation for nicergoline.

Conclusions

This systematic review & meta-analysis has included the evidence to date with regards to tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is categorized under ergot derivatives. However, the adverse events with nicergoline are mild and transient unlike other ergot derivatives (ergotamine & ergotoxine) which have been associated with fibrosis and ergotism.

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

List of abbreviations

AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; SAEs: serious adverse event

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 mesylates	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.**

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.

Figure Legends

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

Figure 2: Results of meta-analysis, any adverse events: Nicergoline vs. Placebo

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Title of the article:

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

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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-

significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline treatment.

Conclusions: Nicergoline is an ergot derivatives but the safety profile is better than other ergot derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest that nicergoline has a good safety profile. None of the studies included in this systematic review reported any incidence of fibrosis or ergotism with nicergoline.

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 (EMEA) 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 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.

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

Data extraction

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnotes version X3. Cochrane methodology was used to conduct this systematic review. All studies were screened by two independent reviewers with discrepancies resolved by a third reviewer.

Outcomes assessed

In most of the included studies, safety evaluation included monitoring of adverse events, vital signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-emergent adverse events (elicited or observed); physical examination including ECG recording; vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to adverse event were reported.

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

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) in 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 publications 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

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

Critical Appraisal

Included studies were critically appraised using the Jadad scale which is a standard scale used for evaluating quality of randomised trials in systematic reviews. Method used to generate random allocation sequence was reported in only nine of the included studies and were judged as adequate. None of the study reported the method used for concealment of allocation sequence. The Jadad score was ≥3 in 20 studies and less than 3 in nine studies. Majority of the studies were good quality studies as per Jadad scale. All of included studies reported comparable baseline characteristics between treatment groups being studied.

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 1.

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 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 again the difference was non-significant (p=0.7).

The risk of any adverse event was similar with nicergoline compared to placebo (10 studies), ergot derivatives and other active comparators, all comparisons being non-significant. Risk of any serious adverse event was slightly lower in the nicergoline group compared to placebo but was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline as compared to placebo (p=0.01). Nicergoline was associated with lower risk of diarrhoea as compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence of dizziness was similar in nicergoline group as compared to placebo or other active agents. A

comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo group.

Higher risk of fatigue was associated with nicergoline compared to active comparators including ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported with nicergoline compared to other comparators. Risk of headache and hypotension was higher with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any significant difference was observed compared to the other intervention or placebo, Figure 2.

Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in eight studies during the entire study duration, while remaining studies reported excellent or good tolerability in nicergoline treated patients. None of these studies reported any incidence of ergotism or fibrosis with nicergoline.

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

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

Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-infarct dementia.[1,31] Also, nicergoline has shown efficacy in conditions like post-hemodialysis pruritus,[38] tinnitus and vertigo.[39] Nicergoline has a positive effect on cognition and behaviour in addition to an effect on clinical global impression in older patients with mild to moderate cognitive and behavioural impairment of various clinical origins including chronic cerebrovascular disorders and Alzheimer's dementia.[1]

Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and increased appetite.[7,21] Cardiovascular events like temporary rise in BP, syncope, bradycardia, and hypotension have been reported with nicergoline by few studies.[17,40]

Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure, and interstitial nephritis.[41,42]

Results of this meta-analysis showed comparable safety profile of nicergoline with other active agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to adverse events were similar with nicergoline compared to placebo & active agents. Incidence of any adverse event when compared to placebo and ergot derivatives was slightly higher in the nicergoline group but the difference was non-significant. Significantly lower rates of anxiety were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like

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

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

In its current recommendation, the EMEA has overlooked the efficacy and safety profile of nicergoline and has cautioned against its use in conditions with blood circulation problems, memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA has probably considered the safety profile of all ergot derivatives as similar. The CHMP review has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest incidence of these AEs with other ergot derivatives as well.

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

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

two reviewers of all data elements prior to entry into the database and the quality control review of every element of this report. In addition, the quality of the studies and manuscripts used to provide data were relatively high. Only RCTs were included in this systematic review/meta-analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this review could be the publication timeframe of the included studies. Most of the studies were published in 1980s and 1990s. There were hardly any trials published in recent years on safety evaluation for nicergoline.

Conclusions

This systematic review & meta-analysis has included the evidence to date with regards to tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is categorized under ergot derivatives. However, the adverse events with nicergoline are mild and transient unlike other ergot derivatives (ergotamine & ergotoxine) which have been associated with fibrosis and ergotism.

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

List of abbreviations

AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; SAEs: serious adverse event

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 mesylates	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.**

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.

Figure Legends

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

Figure 2: Results of meta-analysis, any adverse events: Nicergoline vs. Placebo

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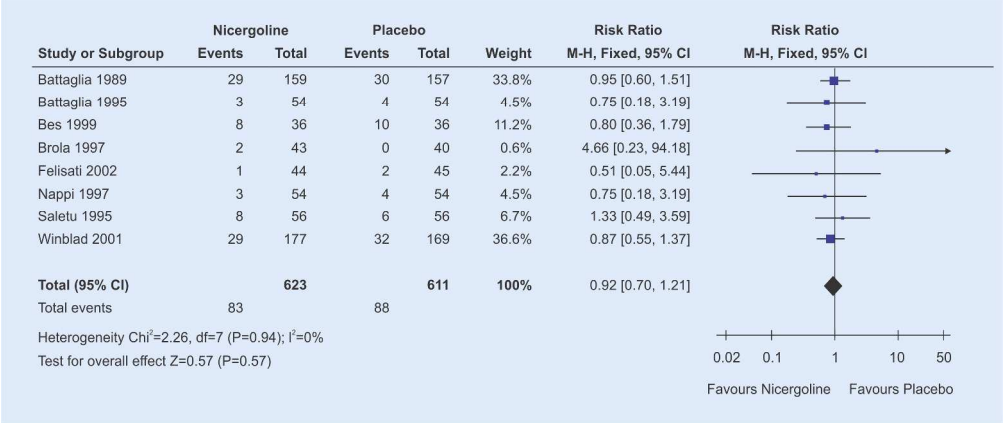

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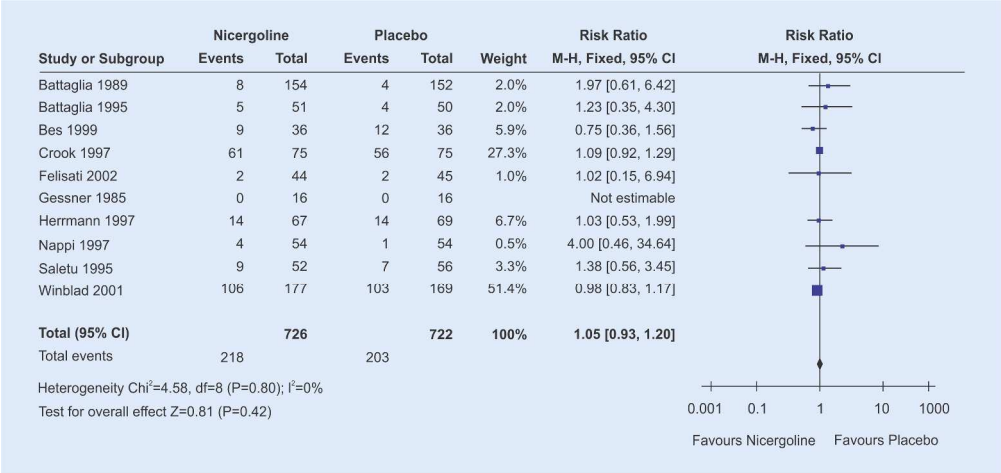

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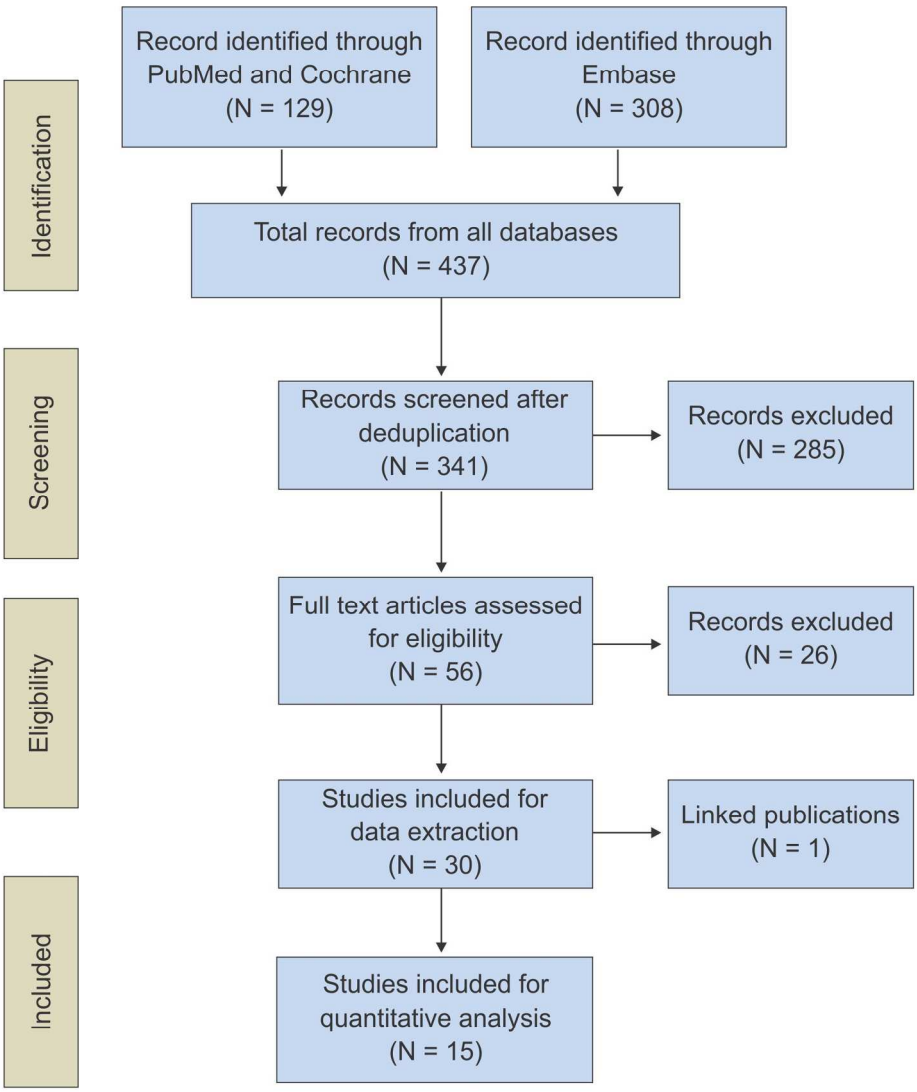

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Supplementary Table 1: Incidence of adverse events with nicergoline and comparators

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:	*BMJ Open*
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

Title of the article:

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

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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-

significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline treatment.

Conclusions: Nicergoline is an ergot derivatives but the safety profile is better than other ergot derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest that nicergoline has a good safety profile. None of the studies included in this systematic review reported any incidence of fibrosis or ergotism with nicergoline.

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 (EMEA) 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

could be 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.

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

Data extraction

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnotes version X3. Cochrane methodology was used to conduct this systematic review. All studies were screened by two independent reviewers with discrepancies resolved by a third reviewer.

Study quality and risk of bias

Jadad score was used to assess the quality of included studies. Risk of bias in the individual studies included for meta-analysis was assessed using Cochrane risk assessment tool. [6]

Outcomes assessed

In most of the included studies, safety evaluation included monitoring of adverse events, vital signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-emergent adverse events (elicited or observed); physical examination including ECG recording; vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to adverse event were reported.

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

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

Critical Appraisal

Included studies were critically appraised using the Jadad scale which is a standard scale used for evaluating quality of randomised trials in systematic reviews. Method used to generate random allocation sequence was reported in only nine of the included studies and were judged as adequate. The Jadad score was ≥3 in 20 studies and less than 3 in nine studies. Majority of the studies were good quality studies as per Jadad scale. All of included studies reported comparable baseline characteristics between treatment groups being studied.

Risk of bias assessment

The risk of bias was low in the individual studies that were included for meta-analysis. The method used to generate the allocation sequence was reported in sufficient detail to allow an assessment in most of the studies. None of the included studies reported any inadequate method.

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

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 again the difference was non-significant (p=0.7).

The risk of any adverse event was similar with nicergoline compared to placebo (10 studies), ergot derivatives and other active comparators, all comparisons being non-significant. Risk of any serious adverse event was slightly lower in the nicergoline group compared to placebo but was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline as compared to placebo (p=0.01). Nicergoline was associated with lower risk of diarrhoea as compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence of dizziness was similar in nicergoline group as compared to placebo or other active agents. A comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo group.

Higher risk of fatigue was associated with nicergoline compared to active comparators including ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported with nicergoline compared to other comparators. Risk of headache and hypotension was higher with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any significant difference was observed compared to the other intervention or placebo, Figure 3.

Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in eight studies during the entire study duration, while remaining studies reported excellent or good tolerability in nicergoline treated patients. None of these studies reported any incidence of 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

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

Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-infarct dementia.[1,32] Also, nicergoline has shown efficacy in conditions like post-hemodialysis pruritus,[39] tinnitus and vertigo.[40] Nicergoline has a positive effect on cognition and behaviour in addition to an effect on clinical global impression in older patients with mild to moderate cognitive and behavioural impairment of various clinical origins including chronic cerebrovascular disorders and Alzheimer's dementia.[1]

Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and increased appetite.[8,22] Cardiovascular events like temporary rise in BP, syncope, bradycardia, and hypotension have been reported with nicergoline by few studies.[18,41]

Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure, and interstitial nephritis.[42,43]

Results of this meta-analysis showed comparable safety profile of nicergoline with other active agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to adverse events were similar with nicergoline compared to placebo & active agents. Incidence of any adverse event when compared to placebo and ergot derivatives was slightly higher in the nicergoline group but the difference was non-significant. Significantly lower rates of anxiety were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like

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

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

In its current recommendation, the EMEA has overlooked the efficacy and safety profile of nicergoline and has cautioned against its use in conditions with blood circulation problems, memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA has probably considered the safety profile of all ergot derivatives as similar. The CHMP review has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest incidence of these AEs with other ergot derivatives as well.

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

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

two reviewers of all data elements prior to entry into the database and the quality control review of every element of this report. In addition, the quality of the studies and manuscripts used to provide data were relatively high. Only RCTs were included in this systematic review/meta-analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this review could be the publication timeframe of the included studies. Most of the studies were published in 1980s and 1990s. There were hardly any trials published in recent years on safety evaluation for nicergoline.

Conclusions

This systematic review & meta-analysis has included the evidence to date with regards to tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is categorized under ergot derivatives. However, the adverse events with nicergoline are mild and transient unlike other ergot derivatives (ergotamine & ergotoxine) which have been associated with fibrosis and ergotism.

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

List of abbreviations

AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; SAEs: serious adverse event

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 mesylates	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

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Title of the article:

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

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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-

significant. None of the studies reported any incidence of fibrosis or ergotism with Nicergoline treatment.

Conclusions: Nicergoline is an ergot derivatives but the safety profile is better than other ergot derivatives like ergotamine and ergotoxine. This systematic review and meta-analysis suggest that nicergoline has a good safety profile. None of the studies included in this systematic review reported any incidence of fibrosis or ergotism with nicergoline.

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 (EMEA) 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

could be 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.

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

Data extraction

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnotes version X3. Cochrane methodology was used to conduct this systematic review. All studies were screened by two independent reviewers with discrepancies resolved by a third reviewer.

Study quality and risk of bias

Jadad score was used to assess the quality of included studies. Risk of bias in the individual studies included for meta-analysis was assessed using Cochrane risk assessment tool. [6]

Outcomes assessed

In most of the included studies, safety evaluation included monitoring of adverse events, vital signs, haematology and blood chemistry. Haematology and blood chemistry were assessed at baseline and at the last assessment. Tolerability evaluation included monitoring of treatment-emergent adverse events (elicited or observed); physical examination including ECG recording; vital signs, haematology and blood chemistry testing. Withdrawals, due to any reasons or due to adverse event were reported.

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

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

Critical Appraisal

Included studies were critically appraised using the Jadad scale which is a standard scale used for evaluating quality of randomised trials in systematic reviews. Method used to generate random allocation sequence was reported in only nine of the included studies and were judged as adequate. The Jadad score was ≥3 in 20 studies and less than 3 in nine studies. Majority of the studies were good quality studies as per Jadad scale. All of included studies reported comparable baseline characteristics between treatment groups being studied.

Risk of bias assessment

The risk of bias was low in the individual studies that were included for meta-analysis. The method used to generate the allocation sequence was reported in sufficient detail to allow an assessment in most of the studies. None of the included studies reported any inadequate method.

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

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 again the difference was non-significant (p=0.7).

The risk of any adverse event was similar with nicergoline compared to placebo (10 studies), ergot derivatives and other active comparators, all comparisons being non-significant. Risk of any serious adverse event was slightly lower in the nicergoline group compared to placebo but was non-significant. A significantly lower risk of agitation/anxiety was reported with nicergoline as compared to placebo (p=0.01). Nicergoline was associated with lower risk of diarrhoea as compared to placebo or ergot derivatives, both comparisons being non-significant. The incidence of dizziness was similar in nicergoline group as compared to placebo or other active agents. A comparatively lower risk of drowsiness was reported with nicergoline compares to placebo but the difference was non-significant. Risk of gastric upset was similar in nicergoline and placebo group.

Higher risk of fatigue was associated with nicergoline compared to active comparators including ergot derivatives but the difference was non-significant. Higher risk of hot flushes was reported with nicergoline compared to other comparators. Risk of headache and hypotension was higher with nicergoline compared to placebo. Higher risk of insomnia and itching was reported with nicergoline. For none of the adverse events, where risk was higher for nicergoline group, any significant difference was observed compared to the other intervention or placebo, Figure 3.

Of the 14 studies included in qualitative analysis, no incidence of adverse events was reported in eight studies during the entire study duration, while remaining studies reported excellent or good tolerability in nicergoline treated patients. None of these studies reported any incidence of 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

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

Nicergoline has proven efficacy in the treatment of senile dementia of Alzheimer type and multi-infarct dementia.[1,32] Also, nicergoline has shown efficacy in conditions like post-hemodialysis pruritus,[39] tinnitus and vertigo.[40] Nicergoline has a positive effect on cognition and behaviour in addition to an effect on clinical global impression in older patients with mild to moderate cognitive and behavioural impairment of various clinical origins including chronic cerebrovascular disorders and Alzheimer's dementia.[1]

Nicergoline has been reported to cause CNS disturbances including diaphoresis, sleep disturbances, fainting, agitation, drowsiness, dizziness, insomnia, restlessness, flushing, and increased appetite.[8,22] Cardiovascular events like temporary rise in BP, syncope, bradycardia, and hypotension have been reported with nicergoline by few studies.[18,41]

Nicergoline has been known to cause minor gastrointestinal side effects such as heartburn and abdominal pain, gastric pain, pyrosis, vomiting, diarrhoea, abdominal pain. Various studies have reported other minor effects with nicergoline including hot flushes, dizziness, ejaculation failure, and interstitial nephritis.[42,43]

Results of this meta-analysis showed comparable safety profile of nicergoline with other active agents (including ergot derivatives) or placebo. The withdrawal rates and withdrawal due to adverse events were similar with nicergoline compared to placebo & active agents. Incidence of any adverse event when compared to placebo and ergot derivatives was slightly higher in the nicergoline group but the difference was non-significant. Significantly lower rates of anxiety were reported with nicergoline compared to placebo (p=0.01). Incidence of adverse events like

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

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

In its current recommendation, the EMEA has overlooked the efficacy and safety profile of nicergoline and has cautioned against its use in conditions with blood circulation problems, memory and sensation problems and migraine headaches. The CHMP at EMEA suggested a ban on use of ergot derivatives as they have been associated with fibrosis and ergotism. The EMEA has probably considered the safety profile of all ergot derivatives as similar. The CHMP review has reported highest incidence of fibrosis and ergotism with dihydro-ergotamine and suggest incidence of these AEs with other ergot derivatives as well.

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

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

two reviewers of all data elements prior to entry into the database and the quality control review of every element of this report. In addition, the quality of the studies and manuscripts used to provide data were relatively high. Only RCTs were included in this systematic review/meta-analysis. The main limitation of this meta-analysis is the scarcity of head-to-head trials to compare the safety of nicergoline with other ergot derivatives. Another possible limitation of this review could be the publication timeframe of the included studies. Most of the studies were published in 1980s and 1990s. There were hardly any trials published in recent years on safety evaluation for nicergoline.

Conclusions

This systematic review & meta-analysis has included the evidence to date with regards to tolerability and safety of nicergoline as reported by randomised controlled trials. Nicergoline is categorized under ergot derivatives. However, the adverse events with nicergoline are mild and transient unlike other ergot derivatives (ergotamine & ergotoxine) which have been associated with fibrosis and ergotism.

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

List of abbreviations

AEs: adverse events; CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; SAEs: serious adverse event

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 mesylates	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

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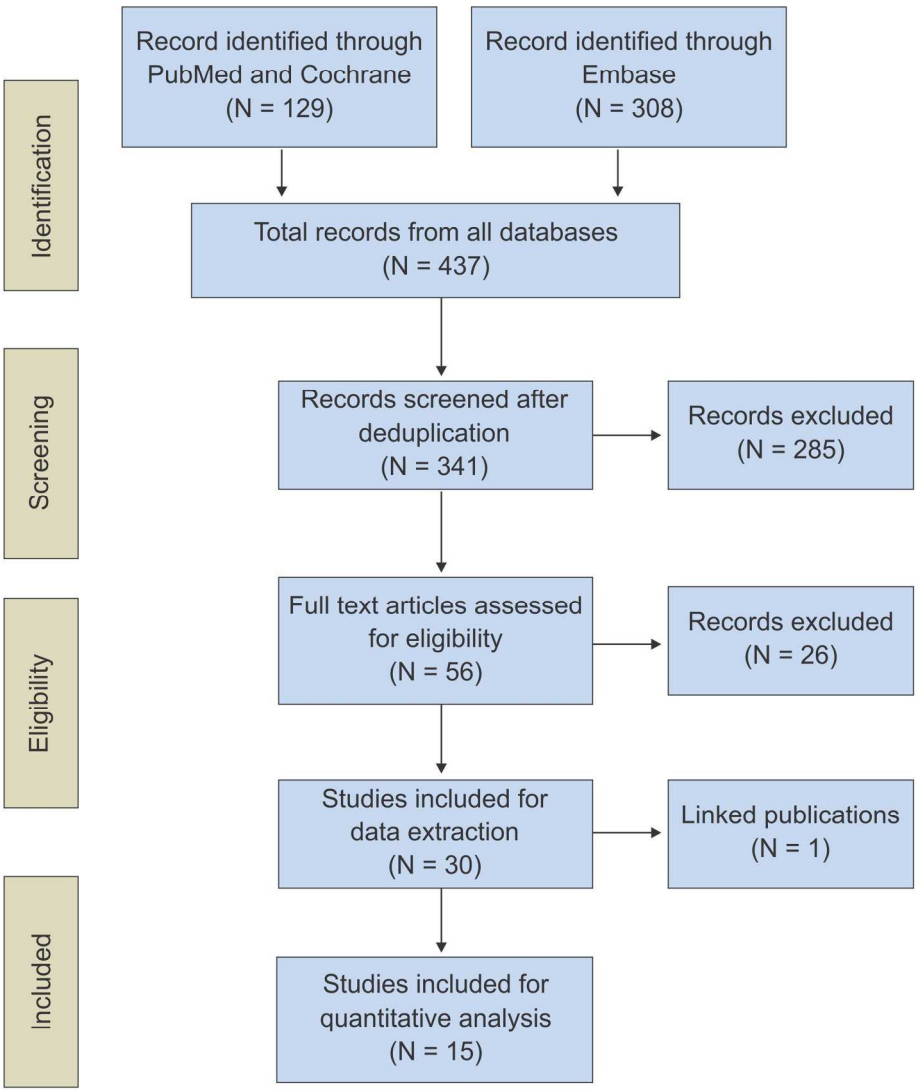

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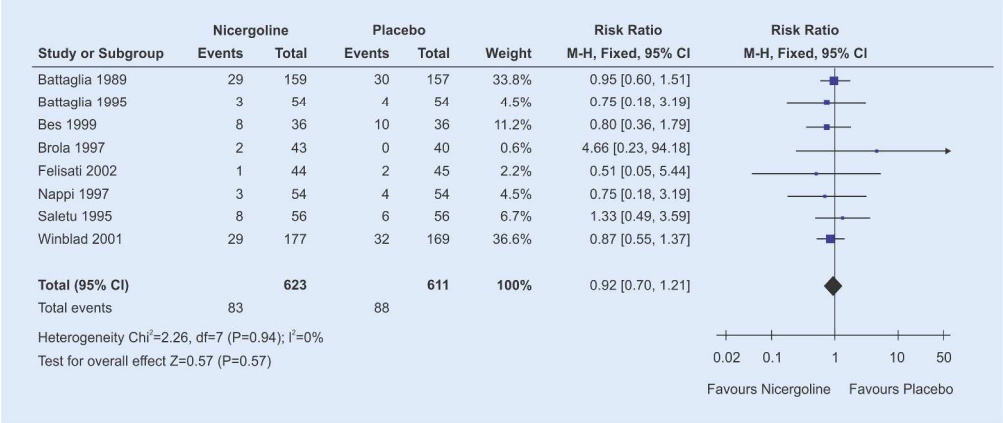

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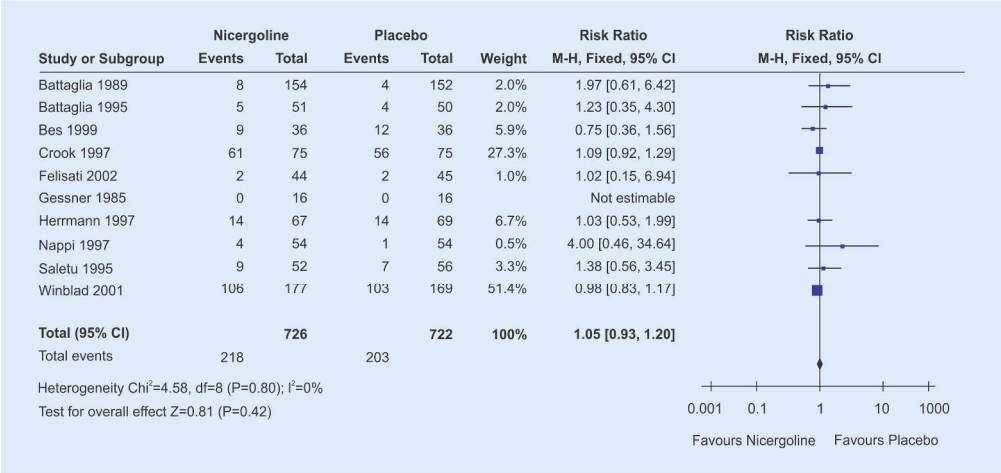

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Search strategy for EMBASE

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.	9

PRISMA 2009 Checklist

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

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