Erectile dysfunction: drug treatment

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Erectile dysfunction is the recurrent and persistent inability of having and/or maintain a sufficient penile erection for satisfactory sexual intercourse. It is considered a disease that impairs psychosocial health and quality of life.

By means of the PICO methodology, each clinical question was structured, using the following descriptors: (P) Patients with erectile dysfunction, (I) Injectable treatment associated with PDE5i, penile revascularization, use of a penile implant, (O) Adverse events/ International index of erectile function. We performed a systematic review of the literature for each clinical question, with no time restriction, in the MEDLINE database, using 59 papers to answer all the questions. The details about the methodology and the results are set out in Appendix I.

INTRODUCTION

Erectile dysfunction is the recurrent and persistent inability of having and/or maintaining a sufficient penile erection for satisfactory sexual intercourse[1](D). It is a prevalent disease that compromises the psychosocial health and quality of life[2-4](B).

Its causes are disorders of vascular, neurogenic, structural, hormonal, or psychogenic nature, or induced by drugs or by trauma[5](D).

The assistant physician must identify and treat the reversible causes, such as the psychogenic, associated with hormone deficiencies and those arising from the use of drugs. In the absence of a response, the treatment should be discussed with the patient. The involvement of the partner is always interesting since it promotes dialog and improves the chances of success and satisfaction with the treatment. Often times, the treatment of the male problem may not be enough to restore a satisfying sex life for the couple. The choice of treatment or the option of non-intervention should be shared with the patient or, preferably, with the couple, taking into account individual aspects. Preference should be given, initially, to oral pharmacotherapy[5](D).

RESULTS

1. What are the oral drugs most currently used for the treatment of erectile dysfunction?

The phosphodiesterase type 5 inhibitors (PDE5i) now constitute the most widely used oral therapy and act by promoting the relaxation of the muscle cells of the cavernous tissue, a necessary condition for obtaining an erection[6](A).

The most commonly used are:

- Sildenafil
- Tadalafil
- Vardenafil
- Lodenafil

2. What is the absolute contraindication for the use of phosphodiesterase type 5 inhibitors (PDE5i)?

The absolute contraindications of PDE5i are hypersensitivity to the components of the drug and concomitant use with nitrates[7](A).

3. What is the average duration of action of the main PDE-5 inhibiting drugs?

- Onset of action[8](D):
- Sildenafil: 30-60 min
- Tadalafil: 15-45 min
- Vardenafil: 15-30 min
- Lodenafil: 40 minutes

Duration of action:

- Sildenafil: 4-6h, up to 12h
- Tadalafil: 24-36h
- Vardenafil: 4-6h
- Lodenafil: 6h

4. Can PDE-5 inhibitors be used in patients who use drugs to control blood pressure or in users of alpha-blockers?

The use of PDE5i concomitantly with alpha-blockers or anti-hypertensive drugs can accentuate the hypotensive effect, without, however, contraindication of the simultaneous use of such drug classes[9-13](A). A study[13](A) demonstrated that the pressure variation after the use of anti-hypertensive medication with sildenafil was small, -3.6 mmHg in systolic pressure, while the placebo with anti-hypertensive had a variation of -0.8 mmHg.

5. What are the precautions that should be used for the employment of PDE-5 inhibitors in patients with liver failure, kidney failure, and in users of antiretroviral drugs?

Liver failure: In patients with liver cirrhosis (class A and B of Child-Pugh), the *clearance* of PDE5i is reduced, resulting in an increase in the drug's plasma levels. The pharmacokinetics of sildenafil in patients with Child-Pugh class C liver failure was not studied[14](B).

Kidney failure: In volunteers with severe kidney failure (creatinine clearance ≤ 30 mL/min), the PDE5i clearance is reduced, leading to an increase in the serum levels of the drug[15](A).

The concomitant administration of PDE5i and ritonavir or saquinavir (antiretroviral drugs), which is also a potent inhibitor of the P450 cytochrome, results in an increase in the plasma concentration of PDE5i. Sildenafil does not have any effect on the pharmacokinetics of ritonavir[15](A).

6. What are the possible causes when there is an inadequate response to the treatment of erectile dysfunction with PDE-5 inhibitors?

Comorbidities: Some comorbidities, such as diabetes and cardiovascular diseases, can induce endothelial dysfunction, which is a risk factor for erectile dysfunction[16](B).

Inappropriate use: Use of suboptimal doses, use with a full stomach and sexual intercourse outside the time of action of the drug may contribute to the ineffectiveness of the medication[17-19](B). A study[17](B) demonstrated that of 100 consecutive patients nonresponders to PDE5i, 56 used the drug in a suboptimal way, of which 45 used a dose below the recommended.

Incorrect diagnosis: Hypogonadism, hyperprolactinemia, and disorders of sensitivity may be causes of erectile dysfunction[20-22](B). Of the patients with hypogonadism and associated erectile dysfunction without an initial response to PDE5i, 72% will respond to treatment with testosterone replacement[22](B).

Lack of sexual stimulation: Without sexual stimulation, PDE5i is ineffective since this drug only acts upon stimulus[23](A).

Psychological disorders: Anxiety disorders or other psychological issues may interfere in sexual function[24](A).

7. Can the use of long-acting PDE-5 inhibitors be associated with short-acting PDE-5 inhibitors for the treatment of severe erectile dysfunction?

In patients with failed PDE5i monotherapy and severe erectile dysfunction, it is possible to try the joint use of short and long-acting PDE5i. There is no increase in the incidence of side effects with this combination[25](A).

8. Is there clinical evidence for the use of phytotherapics or vitamin supplements in the treatment of erectile dysfunction?

Some elements of traditional medicine can be employed in the treatment of erectile dysfunction but without scientific proof.

Yohimbine: a meta-analysis with clinical trials showed an improvement of erectile dysfunction, compared with placebo (odds ratio: 3.85; IC 95%: 6.67-2.22). Adverse reactions were infrequent and transient[26](A).

Red ginseng: a meta-analysis with randomized clinical trials showed an improvement of erectile dysfunction, compared with placebo (odds ratio of 2.40; IC 95%: 1.65-3.51). However, the assessment of the quality of the studies was low on average[27](A).

Tribulus Terrestris: a randomized, double-blind, clinical trial showed no effects on the international index of erectile function (IIEF-5)[28](A).

Ginkgo Biloba: shows improvement of erectile dysfunction, mainly for erectile dysfunction induced by antidepressants[29.21](A).

ERECTILE DYSFUNCTION: INJECTABLE TREATMENT

9. In which clinical situations are penile injections (intracavernous pharmacotherapy) indicated for the treatment of erectile dysfunction?

The use of intracavernous injections can be indicated in patients with failure or contraindications to PDE5i therapy or even if there is personal preference[8](D). The success rate of intracavernous therapy is high. It is effective in getting an erection suitable for penetration in 60-90% of men with erectile dysfunction, depending on the agent used[30](D). It requires no nerve integrity and, therefore, may be an alternative for men with spinal cord injury or post-radical prostatectomy. Despite its invasive nature, previous studies showed that the level of satisfaction could be greater with intracavernous therapy when compared with the PDE5i in men who used both methods. Even though it is considered a second-line therapy, intracavernous pharmacotherapy remains essential as part of the diagnostic arsenal of the vascular causes of erectile dysfunction and can play an important role in rehabilitation after radical prostatectomy[31](B).

10. What are the main local and/or systemic complications associated with penile injections?

The most frequent complications are local, while systemic complications are infrequent and generally mild[32-35](C):

Local complications:
- bleeding/bruising at the injection site;
- penile pain;
- fibrosis of the corpus cavernosum;
- penile tortuosity;
- priapism.

Systemic complications:
- arterial hypotension.

11. Should the risks and benefits of the injectable treatment be discussed with the patient?

Yes. If the patient does not understand the procedure and its implications, there is a risk of treatment interruption [36](B).

12. Should an initial test of the injectable treatment be conducted at the clinic?

The test has little diagnostic value regarding the vascular status of the penis. If indicated, a Doppler study can offer further information[37](C). However, the practical instruction on the use of this therapeutic alternative in a clinic setting enables titration of dosage and may reduce the occurrence of complications related to the therapy.

13. That drugs, drugs, or doses should be indicated to the injectable treatment?

Alprostadil (prostaglandin E1) can be used as monotherapy or in combination with other medications (phentolamine and papaverine)[38](B).

14. What is the rate of treatment abandonment for penile injections and its reasons?

The discontinuity occurs in approximately half of patients and, in more than 50% of these, it occurs in the first two months. The main causes of treatment abandonment are the desire for definitive treatment, low response (due to the progression of vascular disease), fear of needles, or complications[36,39-41](B).

15. What is the contraindication to the use of intracavernous pharmacotherapy?

The contraindications to intracavernous pharmacotherapy are predispositions to priapism, such as sickle cell anemia, hypersensitivity to agents, coagulopathies, and penile fibrosis[8](D).

16. How often can/should the injectable treatment be carried out?

The injections may be repeated up to three times a week, with an interval of 24 hours between each injection[42](C).

17. Can the injectable treatment be carried out in association with the oral treatment for erectile dysfunction?

Yes. In patients who do not respond to the inject-

able treatment, a combination of injectable pharmacotherapy and PDE5i may be employed[43](A).

18. When should the injectable treatment be suspended? What is the alternative in its failure?

Penile fibrosis may suggest disease the onset of Peyronie's disease. In these cases, suspend the use of injectable therapy and consider the use of a penile implant[8](D).

SURGICAL TREATMENT OF ERECTILE DYSFUNCTION

19. Is there currently any indication for coronary venous ligation for venous-occlusive dysfunction?

The venous ligation for the treatment of erectile dysfunction due to venous insufficiency is not an alternative for the treatment of erectile dysfunction because it presents very low long-term effectiveness (31% in 45 months) with a risk of complications such as hematoma, local pain, and temporary penile paresthesia [44](C).

20. What is the ideal candidate for the penile revascularization surgery?

Young patients without risk factors for erectile dysfunction, which have arterial deficit due to trauma[45](D).

21. What are the results obtained from penile revascularization surgery in the literature over the past 20 years?

Young men (under 30 years) have a higher success rate in the long term (*odds ratio*, 3.7; 95% *confidence interval*, 2.2 to 6.4; P = .001). The overall success rate in five years is around 64-67%[46-48](A)[49](C).

22. What is the main complication of penile revascularization surgery?

Penile hypervascularization[49](C).

23. What are currently the main indications for penile implants?

Patients with failure to oral or injectable pharmacological therapy who opt for a definitive solution[8](D).

24. What are the preoperative cares that must be adopted to prevent infection?

All care measures regarding the procedure aseptic technique must be adopted. Antibiotic prophylaxis against Gram-positive and Gram-negative bacteria should be used. The use of antibiotic-impregnated implants can also assist in the reduction of infectious complications[50-53](A). A pre-operative routine with mandatory requirements for the penile implant can significantly reduce the rate of infection. Among important measures, are the requirement of negative preoperative urine culture; washing and genital brushing with chlorhexidine 2% two days before surgery; prophylaxis started one hour before the incision; attention to the levels of glycated hemoglobin in diabetic patients (see item 25); brushing of the hands of the surgical team for 5 minutes; genital sanitation for 10 minutes, preferably with chlorhexidine; use of topical antibiotics to irrigate the corpus cavernosum; surgical synthesis in multiple layers, giving preference to absorbable and monofilament threads; minimize the flow of people in the surgical room after incision until the bandaging[54](B).

25. Is there any glycated Hb threshold that constitutes a contraindication to penile implant in the diabetic population?

In a prospective study with multivariate analysis, the glycated hemoglobin value of 8.5% suggests a high risk of infectious complications in penile implants[55](A).

26. What are the pros and cons of a malleable implant (semi-rigid)?

Advantages: low risk of chronic pain, easy to use, surgical implantation technically easier than for inflatable implants[56-59](C).

Disadvantages: the penis remains upright at all times. Its orientation can be modified depending on the need (to urinate, adjust clothes, sexual intercourse)[60](C).

27. What are the pros and cons of a inflatable implant (2 and 3 pieces)?

Advantages: they are softer than the semi-rigid ones, better cosmetic appearance (more "natural" look)[61](B).

Disadvantages: possibility of malfunction, requiring surgical reintervention in some situations[61](B).

28. What are currently the main complications of penile implants and their treatments?

Infection and mechanical failure. The treatment

generally demands the removal of the implant and, in the case of infectious complications, systemic antibiotic therapy[51](B).

SYNTHESIS OF EVIDENCE

Erectile dysfunction is a prevalent condition with several etiologies. The treatment of patients with erectile dysfunction should focus initially on diagnosing reversible causes of erectile dysfunction. This includes a multidisciplinary approach. Cardiovascular risk factors should be investigated and properly treated. As a therapeutic option, the phosphodiesterase-5 inhibitors are the most commonly used drug. In the failure of oral therapy, intracavernous injection with prostaglandin and/or papaverine and/or phentolamine can be used, although with high rates of discontinuity. As a definite alternative, a penile implant can be used.

Restorative therapies have aroused increasing interest in various areas of medicine, and erectile dysfunction is one of them. Among them, the use of low-intensity extracorporeal shock wave therapy (Li-ESWT), therapy with platelet-rich plasma, and the use of stem cells.

Studies in animals have shown that Li-ESWT improves the hemodynamic profile and mitigates the pathological changes related to diabetes in the penis. A few other studies in humans show improvement in erectile function and in response to inhibitors of the phosphodiesterase type 5 enzyme (PDE5i). Thus, it might represent an attractive and innovative alternative, if it is effectively able to interfere in the symptoms or in the natural history of erectile dysfunction. The mechanism of such an action still requires further investigation, but it is probably due to the improvement of endothelial dysfunction and damage caused to peripheral nerves. This technique promotes the formation of new blood vessels, which induce intracavernous neovascularization and the improvement of endothelial function[62-64].

However, there are no results from multicenter, placebo-controlled studies with long follow-up to confirm this therapeutic alternative as truly effective and safe.

There is no scientific evidence that endorses the use of platelet-rich plasma or stem cells as an alternative therapy for men with erectile dysfunction[65.66].

APPENDIX I

The evidence used was retrieved by the following steps: elaboration ofthe clinical question, structuring of the question, search for evidence, presentation of results, and recommendations.

Clinical Questions

- What are the oral drugs most currently used for the treatment of erectile dysfunction?
- What is the absolute contraindication for the use of phosphodiesterase type 5 inhibitors (PDE5i)?
- What is the average duration of action of the main PDE-5 inhibiting drugs?
- Can PDE-5 inhibitors be used in patients who use drugs to control blood pressure or in users of alpha-blockers?
- What are the precautions that should be used for the employment of PDE-5 inhibitors in patients with liver failure, kidney failure, and in users of antiretroviral drugs?
- What are the possible causes when there is an inadequate response to the treatment of erectile dysfunction with PDE-5 inhibitors?
- Can the use of long-acting PDE-5 inhibitors be associated with short-acting PDE-5 inhibitors for the treatment of severe erectile dysfunction?
- Is there clinical evidence for the use of phytotherapics or vitamin supplements in the treatment of erectile dysfunction?
- In which clinical situations are penile injections (intracavernous pharmacotherapy) indicated for the treatment of erectile dysfunction?
- What are the main local and/or systemic complications associated with penile injections?
- Should the risks and benefits of the injectable treatment be discussed with the patient?
- Should an initial test of the injectable treatment be conducted at the clinic?
- That drugs, drug,s or doses should be indicated to the injectable treatment?
- What is the rate of treatment abandonment for penile injections and its reasons?
- What is the contraindication to the use of intracavernous pharmacotherapy?
- How often can/should the injectable treatment be carried out?
- Can the injectable treatment be carried out in association with the oral treatment for erectile dysfunction?

- When should the injectable treatment be suspended? What is the alternative in its failure?
- Is there currently any indication for coronary venous ligation for venuso-occlusive dysfunction?
- What is the ideal candidate for the penile revascularization surgery?
- What are the results obtained from penile revascularization surgery in the literature over the past 20 years?
- What is the main complication of penile revascularization surgery?
- What are currently the main indications for penile implants?
- What are the preoperative cares that must be adopted to prevent infection?
- Is there any glycated Hb threshold that constitutes a contraindication to penile implant in the diabetic population?
- What are the pros and cons of a malleable implant (semi-rigid)?
- What are the pros and cons of a inflatable implant (2 and 3 pieces)?
- What are currently the main complications of penile implants and their treatments?

Structured clinical question

The PICO approach was structured according to the clinical question.

Below, the description of the specific structures.

PICO for Question 4:

P - Patients with erectile dysfunction
I - Use of PDE5i associated with anti-hypertensive drug
C - Does not apply
O - Adverse events

PICO for Question 5:

P - Patients with erectile dysfunction and liver failure/liver failure/use of antiretroviral drugs
I - Use of PDE5i
C - Does not apply
O - Adverse events/plasma concentration of PDE5i

PICO for Question 8:

P - Patients with erectile dysfunction
I - Udenafil, Mirodenafil Tadalafil, Vardenafil, Lodenafil, Avanafil
C - Sildenafil
O - Effectiveness of the treatment

PICO for Question 15:

P - Patients with erectile dysfunction
I - Penile injections
C - Does not apply
O - Therapy interruption

PICO for Question 18:

P - Patients with erectile dysfunction
I - Injectable treatment associated with PDE5i
C - Sildenafil
O - Adverse events/International index of erectile function

PICO for Question 22:

P - Patients with erectile dysfunction
I - Penile revascularization
C - Does not apply
O - Adverse events/International index of erectile function

PICO for Question 29:

P - Patients with erectile dysfunction
I - Penile implant
C - Does not apply
O - Adverse events

Search strategy

The scientific database searched was Medline via PubMed. A manual search was conducted on reviews in references (narrative or systematic) and on the selected papers.

Strategy described according to the clinical question:

Question 4: Date of last search: 22/03/2019

Search: ("erectile dysfunction"[MeSH Terms] OR ("erectile"[All Fields] AND "dysfunction"[All Fields]) OR "erectile dysfunction"[All Fields]) AND ("phosphodiesterase 5 inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[MeSH Terms] OR "phosphodiesterase 5 inhibitors"[All Fields]) AND ("antihypertensive agents"[Pharmacological Action] OR "antihypertensive agents"[MeSH Terms] OR ("antihypertensive"[All Fields] AND "agents"[All Fields]) OR "antihypertensive agents"[All Fields]) AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) NOT ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "hypertension, pulmonary"[All Fields])

Question 5: Date of last search: 22/03/2019

Search: ("phosphodiesterase inhibitors"[Pharmacological Action] OR "phosphodiesterase inhibitors"[MeSH Terms] OR ("phosphodiesterase"[All Fields] AND "inhibitors"[All Fields]) OR "phosphodiesterase inhibitors"[All Fields]) AND ("kidney diseases/metabolism"[Mesh Terms] OR "liver/metabolism"[Mesh Terms] OR "liver diseases/metabolism"[Mesh Terms] OR ("thiazoles"[MeSH Terms] OR "thiazoles"[All Fields]))

Question 8: Date of last search: 22/03/2019

Search: ("phosphodiesterase inhibitors"[Pharmacological Action] OR "phosphodiesterase inhibitors"[MeSH Terms] OR ("phosphodiesterase"[All Fields] AND "inhibitors"[All Fields]) OR "phosphodiesterase inhibitors"[All Fields]) AND ("treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields]) AND ((Clinical Trial[ptyp] OR Review[ptyp]) AND "humans"[MeSH Terms])

Question 15: Date of last search: 22/03/2019

Search: "erectile dysfunction"[MeSH Terms] OR ("erectile"[All Fields] AND "dysfunction"[All Fields]) OR "erectile dysfunction"[All Fields] OR ("dysfunction"[All Fields] AND "erectile"[All Fields]) OR "dysfunction, erectile"[All Fields] AND ("alprostadil"[MeSH Terms] OR "alprostadil"[All Fields]) AND ("treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields])

Question 18: Date of last search: 22/03/2019

Search: ("erectile dysfunction"[MeSH Terms] OR ("erectile"[All Fields] AND "dysfunction"[All Fields]) OR "erectile dysfunction"[All Fields] OR ("dysfunction"[All Fields] AND "erectile"[All Fields]) OR "dysfunction, erectile"[All Fields]) AND ("alprostadil"[MeSH Terms] OR "alprostadil"[All Fields]) AND ("phosphodiesterase 5 inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[MeSH Terms] OR "phosphodiesterase 5 inhibitors"[All Fields])

Question 22: Date of last search: 22/03/2019

Search: (("treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "outcomes"[All Fields]) OR "treatment outcomes"[All Fields]) AND "Vascular Surgical Procedures"[Mesh]) AND "Erectile Dysfunction/surgery"[Mesh] AND ("1999/01/01"[PDAT] : "2019/12/31"[PDAT])

Question 29: Date of last search: 22/03/2019

Search: ("erectile dysfunction"[MeSH Terms] OR ("erectile"[All Fields] AND "dysfunction"[All Fields]) OR "erectile dysfunction"[All Fields] OR ("dysfunction"[All Fields] AND "erectile"[All Fields]) OR "dysfunction, erectile"[All Fields]) AND ("prosthesis implantation"[MeSH Terms] OR ("prosthesis"[All Fields] AND "implantation"[All Fields]) OR "prosthesis implantation"[All Fields]) AND ("postoperative complications"[MeSH Terms] OR ("postoperative"[All Fields] AND "complications"[All Fields]) OR "postoperative complications"[All Fields] OR ("complications"[All Fields] AND "postoperative"[All Fields]) OR "complications, postoperative"[All Fields])

Eligibility criteria

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the database consulted were independently and blindly conducted by two researchers with expertise in the development of systematic reviews, in total accordance with the inclusion and exclusion criteria established and described in the PICO. The studies with potential relevance were separated, accordingioh the studies design.

We included in our evaluation systematic reviews with meta-analysis of randomized clinical trials, and before and after studies, considering the best evidence available to answer the clinical questions. Narrative reviews were considered for full reading with the purpose of retrieving references which may have had been during the initial search strategy.

We included studies available without restriction to the language.

Only studies with texts available in its entirety were considered for critical evaluation.

Results

Question 4 - 48 papers
Question 5 - 2,587 papers
Question 8 - 2,581 papers
Question 15 - 162 papers
Question 18 - 184 papers
Question 22 - 24 papers
Question 29 - 264 papers

The level of scientific evidence was classified by type of study, according to Oxford[67](Table 1).

TABLE 1. GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE

A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case/study reports.
D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models.

The selected evidence was defined as a randomized controlled clinical trial (RCT) and submitted to an appropriate critical evaluation checklist (Table 2). The critical evaluation of RCTs allows to classify them according to the Jadad score[68], considering Jadad trials < three (3) as inconsistent (grade B) and those with score ≥ three (3 , consistent (grade A), and according to the Grade[70] score (strong or moderate evidence).

When the evidence selected was defined as a comparative study (observational cohorts, or non-randomized clinical trial), it was subjected to an adequate critical assessment checklist (Table 3), allowing for the classification of the study according to the Newcastle Ottawa Scale[69], which considered consistent cohort studies with scores ≥ 6, and inconsistent < 6.

TABLE 2. PROCESS FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED TRIALS

Study data Reference, study design, Jadad, level of evidence	Sample size calculation Estimated differences, power, significance level, he ttotal number of patients
Patient selection Inclusion and exclusion criteria	Patients Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	Patient follow-up Time, losses, migration
Treatment protocol Intervention, control, and blinding	Analysis Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	Results Benefits or harmful effects in absolute data, benefits or harmful effects on average

Method of extraction and result analysis

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful effects, and controversy will be specifically defined whenever possible.

The results will be presented preferably in absolute data, absolute risk,the number needed to treat (NNT) or number needed to harm (NNH) and, eventually, in mean and standard deviation values (Table 4)

TABLE 4. SPREADSHEET USED FOR DESCRIBING AND PRESENTING THE RESULTS OF EACH STUDY

Evidence included
Study design
Selected population
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ratio, mean

Application of evidence - Recommendation

The recommendations will be elaborated by the authors of the review, with the initial characteristic of synthesis of evidenc,g subject to validation by all authors who participated in creating the Guideline.

The global synthesis will be based on the evidence described. Its strength will be estimated (Oxford[67]/Grade[70]) as 1b and 1c (grade A) or strong, and as 2a, 2b and 2c (grade B) or moderate weak, or very weak.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decisio- making process. The information contained in this project must be submitted to the evaluation and criticism of the physicia , responsible for the conduct to be followed, given the reality and clinical condition of each patient.

TABLE 3. PROCESS FOR CRITICAL EVALUATION OF COHORT STUDIES

Representativeness of the exposed and selection os the non-exposed (Max. 2 points)	Exposure definition (Max. 1 point)	Demonstration that the outcome of interest was not presentatn the beginning of the study (Max. 1 point)	Comparability on the basis of the design or the analysis (Max. 2 points)	Outcome assessment (Max. 1 point)	Adequate follow-up time (Max. 2 points)	Scores and level of evidence

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