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Living FRIendly Summaries Of The Body Of Evidence Using Epistemonikos (FRISBEE)
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Is N-acetylcysteine effective in the treatment of pulmonary fibrosis?

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Abstract

Idiopathic pulmonary fibrosis is a progressive chronic respiratory disease that in final stages carries high mortality. Several treatment options have been proposed, including N-acetylcysteine, but its role is not clearly established. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified eight systematic reviews including 16 trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded N-acetylcysteine might increase the risk of hospitalizations and exacerbations. While it is unclear whether this leads to increased mortality because the certainty of the evidence is very low, in general there is consensus that it should not be used except in the context of a new clinical trial.

Problem

A substantial amount of evidence has appeared in the last years regarding different therapies potentially effective for idiopathic pulmonary fibrosis. This is not surprising since the only intervention that clearly increases survival is lung transplantation [1].

N-acetylcysteine, by its reducing character, exerts a cytoprotective activity in the human respiratory tract, acting against the harmful action of oxidative stress generated by free radicals of diverse etiology. Based on its structure derived from cysteine, N-acetylcysteine has a precursor role in the synthesis of the antioxidant molecule glutathione and normalizes its levels when they are reduced by a continuous oxidizing action on the respiratory system. This mechanism would explain a potential benefit in idiopathic pulmonary fibrosis[2].

In addition, N-acetylcysteine is widely available, and according to the ATS/ERS 2011 guideline, when used alone or in combination (with prednisolone and azathioprine) was a reasonable choice in a minority of patients with this disease [1]. However, an update of the same guideline in 2015 proposed banning its use due to an increased risk of hospitalization and death in a pivotal trial [3].

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- N-acetylcysteine might increase the risk of hospitalization and exacerbation in idiopathic pulmonary fibrosis.
- Even though an important study was stopped early due to an increase in deaths with N-acetylcysteine, the overall certainty of the evidence is very low, so it can only be said it is unclear whether or not it increases mortality.
- There is general consensus that N-acetylcysteine should not be used except in the context of a new clinical trial.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found eight systematic reviews published in nine references [4],[5],[6],[7],[8],[9],[10],[11],[12] including 16 randomized controlled trials published in 18 references [13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30].
What types of patients were included	All of the trials included patients over 18 years. In thirteen trials diagnosis was based on ATS/ERS/JRS/ALAT standards [13],[15],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30]. One trial also included patients with diagnosis based on imaging or biopsy [16]. Another trial also required markers of lung injury [14] and in one trial diagnosis was only based on images and biopsy [18]. Patients were included based on pulmonary function tests or arterial blood gases in three trials [14],[16],[18], and one trial specified a dyspnea score for inclusion [18].
What types of interventions were included	Two trials used oral N-acetylcysteine monotherapy [15],[17], one trial used inhaled monotherapy [14], ten trials used a combination with prednisone 0,4 to 0,5 mg/kg/day[13],[20],[21],[23],[24],[25],[26],[27],[30], one trial used it associated with interferon [22], one study refers it associated N-acetylcysteine to antiinflammatory treatment but does not specifies which one [29], one trial administered it associated to prednisolone and azathioprine [18], and another trial that used N-acetylcysteine associated to prednisolone and azathioprine was interrupted early due to an increase in mortality risk[16]. All of the studies compared against placebo or standard therapy (placebo, prednisolone and azathioprine), except for one study that compared against bromhexine [15].
What types of outcomes were measured	The systematic reviews identified pooled outcomes as follows: • Mortality: defined as 1-year mortality. • Death from respiratory cause. • Adverse events: mild to moderate, and severe (including death). • Acute exacerbations. • Hospitalizations: for any reason. • Change in forced vital capacity: defined as a change in forced vital capacity in liters or percentage of predicted value for age. • Patients with change in forced vital capacity after intervention > or = 10%. • Change in DLCO (percentage of predicted for age). • Quality of life: SF-36, E5-QD, SGRQ. • Score of dyspnea at the end of treatment. • 6 minutes walk at the end of treatment. • TLCO: change in percentage predicted for age. • PaCO2 at the end of treatment.

Summary of findings

The information on the effects of N-acetylcysteine is based on four randomized trials [14],[15],[16],[18]including 694 patients. The rest of the trials did not report the outcomes of interest, or did not present data in a format suitable for meta-analysis. Four trials [14],[15],[16],[18] measured the outcome mortality, and only one trial [16] reported hospitalizations and acute exacerbations. The summary of findings is as follows:

- It is unclear whether N-acetylcysteine increases or decreases mortality in idiopathic pulmonary fibrosis because the certainty of the evidence is very low.
- N-acetylcysteine might increase the risk of hospitalization in idiopathic pulmonary fibrosis, but the certainty of the evidence is low.
- N-acetylcysteine might increase the risk of acute exacerbations in idiopathic pulmonary fibrosis, but the certainty of the evidence is low.

N-acetylcysteine for idiopathic pulmonary fibrosis

Patients Adults with idiopathic pulmonary fibrosis
Intervention N-acetylcysteine
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT N-acetylcysteine	**WITH N-acetylcysteine**		
	Difference: patients per 1000			
Mortality	49 per 1000	55 per 1000	RR 1.11 (0.54 to 2.26)	⨁◯◯◯[1 2 3 4] Very low
	Difference: 6 patients more per 1000 (Margin of error: 22 less to 61 more)			
Hospitalizations	90 per 1000	299 per 1000	RR 3.33 (1.52 to 7.30)	⨁⨁◯◯[2 4] Low
	Difference: 209 patients more per 1000 (Margin of error: 47 to 565 more)			
Acute exacerbations	8 per 1000	23 per 1000	RR 3.00 (0.31 to 29.22)	⨁⨁◯◯[3] Low
	Difference: 15 patients more per 1000 (Margin of error: 5 less to 215 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT N-acetylcysteine** is based on the risk in the control group of the trials. The risk **WITH N-acetylcysteine** (and its margin of error) is calculated from relative effect (and its margin of error).

1 We downgraded the certainty of the evidence because of risk of bias.
2 We downgraded the certainty of the evidence because the trial providing information about this outcome was stopped early.
3 We downgraded the certainty of the evidence in two levels for imprecision since the confidence interval includes both an important clinical benefit and harm.
4 We downgraded the certainty of the evidence for indirectness, because heterogeneity on interventions, cointerventions and comparators.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to patients over 18 years old with a diagnosis of idiopathic pulmonary fibrosis. This evidence cannot be extrapolated to other types of interstitial lung disease.

About the outcomes included in this summary

- The outcomes that were included are those considered critical for decision making by the authors of this summary, and coincide with the most frequently reported by the reviews and guidelines analyzed.
- Functional outcomes, such as deterioration of vital capacity and functional improvement in walk test in six minutes showed positive results, with moderate certainty of evidence. However, given the existing information on critical outcomes for decision making, these were not included in the summary of findings table.

Balance between benefits and risks, and certainty of the evidence

- N-acetylcysteine has an unclear effect on mortality and may increase hospitalizations and exacerbations, which determine prognosis in this condition. On the other hand, the improvement in functional outcomes (not reported in this summary) should not be a relevant factor in making clinical decisions.
- While the certainty of the evidence is very limited, it is highly likely the benefit/risk balance is not favorable to this intervention.

What would patients and their doctors think about this intervention

- Considering it is an intervention that can cause harm, most patients and providers will be inclined against the intervention.
- The fact that one of the main guidelines recommends against the use of N-acetylcysteine will probably reinforce the decision on not using this intervention.

Resource considerations

- N-acetylcysteine has a relatively low cost and its adverse effects are rare, so the direct cost of intervention should not be relevant for decision-making.

Differences between this summary and other sources

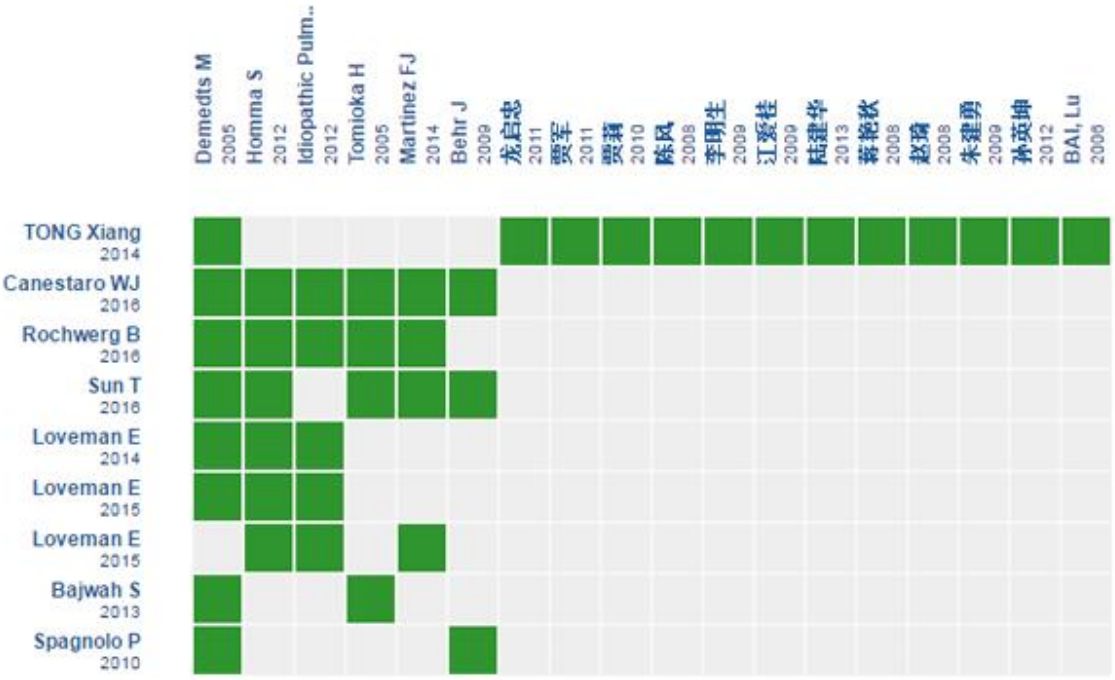
- Our summary agrees with most reviews identified, who found no benefit or conclude there is insufficient data regarding the role of N-acetylcysteine on pulmonary fibrosis.
- Our summary also agrees with the main guideline, which in its 2015 update [3]on the ATS standards for the treatment of pulmonary fibrosis in 2011, recommends against the use of N-acetylcysteine associated with prednisone and azathioprine. The recommendation of this guideline is based on data provided by the early-stopped branch of the IPF Network trial [16]. It is questionable whether this trial should have been discontinued so early (155 patients, 8 vs 1 deaths), since the evidence that provides (combined with other studies) is of very low certainty.
- Our summary coincides with the guideline and with other experts that this intervention should not be used unless it is in the context of a new trial [31].
- The NICE guideline [32] mentions the lack of certainty on the benefits of treatment with N-acetylcysteine but does not reject it as a possible treatment.

Could this evidence change in the future?

- The probability that future evidence change the conclusions of this summary is high due to the poor certainty of the evidence
- However, there are no new or ongoing studies regarding this matter.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database. The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to
display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.

Follow the link to access the **interactive version:** N-acetylcysteine for idiopathic pulmonary fibrosis

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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