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Protocol for a Systematic Review and Meta-analysis on The Use of Antihistamine and Antihistamine-Like Drugs for Cancer Pain

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 August 2024 and was last updated on 15 August 2024.

INTRODUCTION

Review question / Objective Antihistamines, commonly used for their anti-inflammatory properties, also possess analgesic effects, although their use in pain management, particularly cancer pain, is not widely recognized. This systematic review aimed to evaluate the efficacy of antihistamines and antihistamine-like drugs in reducing cancer-related pain intensity. Secondary objectives included assessing the impact on analgesic consumption, quality of life, and adverse event profiles among cancer patients.

Rationale The rationale behind the use of antihistamines and antihistamine-like drugs in cancer pain management is grounded in their diverse pharmacological mechanisms beyond histamine receptor antagonism. Recent studies suggest their involvement in modulating nociceptive pathways, including interactions with opioid, serotonin, and glutamatergic systems, thus offering a multi-faceted approach to pain relief. The emergence of novel antihistamine compounds with improved selectivity and reduced adverse effects warrants a systematic review of their therapeutic potential in cancer pain.

Condition being studied Antihistamines and antihistamine-like drugs, which have been traditionally utilized for allergic conditions, have garnered attention for their potential analgesic properties in the context of cancer pain management. This systematic review and meta-analysis aims to explore the efficacy of antihistamines and antihistamine-like drugs as adjuncts or alternatives to conventional analgesics in alleviating cancer-related pain.

METHODS

Search strategy PubMed and Embase databases were searched independently by two investigators for relevant RCTs until February 2024.
The search strategy was based on a combination of the following medical subject headings (MeSH) and keywords: “antihistamine + cancer pain”,

"histamine antagonist + cancer pain", "h1 antagonist + cancer pain", "h1 blocker + cancer pain" , "antihistamine + cancer + pain" , "histamine antagonist + cancer + pain", "h1 antagonist + cancer + pain", "h1 blocker + cancer + pain".

Participant or population We included human patients that were evaluated for the use of antihistamine drugs or antihistamine-like drugs in the treatment of cancer related pain.

Intervention The use of antihistamines or antihistamine like drugs for the treatment of cancer pain symptoms.

Comparator The control groups of the RCTs were not treated with antihistamines or antihistamine like drugs for cancer pain.

Study designs to be included Randomized controlled trials were included in this review.

Eligibility criteria The inclusion criteria for the systematic review were: (1) RCTs in patients with cancer related pain receiving antihistamine or antihistamine-like drug treatments; (2) clearly defined dosage and route of treatment; (3) measurements and outcome of pain control. The exclusion criteria for the study included: (1) studies written in non-English languages or (2) poorly defined or reported outcome measures.

Information sources PubMed and Embase databases were searched independently by two investigators for relevant RCTs until February 2024.

Main outcome(s) The most commonly studied conditions were oral mucositis and chemotherapy-related peripheral neuropathy, with doxepin, loratadine, and mirtazapine being the most frequently studied drugs. Of the 24 studies, 22 reported pain relief from antihistamines, with 13 showing clinical significance. Only 2 studies reported minimal to no pain relief compared to controls.

Additional outcome(s) Analysis of these studies demonstrated meaningful evidence that antihistamine and antihistamine-like drugs offer short-term and long-term benefits for treating cancer-related pain.

Quality assessment / Risk of bias analysis Risk of bias analysis was conducted to determine the quality assessment in the primary studies. A risk of bias summary was included to present the authors' judgments about each risk of bias item for each included study.

Strategy of data synthesis A descriptive analysis of all outcomes was reported based on inclusion criteria and included in the meta-analysis. The effect sizes reported in these studies exhibit significant variability, reflecting differences in study designs, patient populations, and intervention protocols. The effect sizes were reported with associated confidence intervals. We used I2 index was used to assess the heterogeneity of the effect sizes.

Subgroup analysis Key information systematically extracted from each selected study included (1) title, (2) antihistamine type, dosage, route, and duration of administration, (3) pathology of pain, (4) number of patients, (5) sex, (6) age, (7) methodology, (8) study outcome. The primary effect of interest was improvement of cancer pain with antihistamines. For each included study, 2 reviewers (A.N. and D.M.) extracted all relevant data independently, and any disagreement was resolved by a third reviewer (S.J.).

Sensitivity analysis We summarized the methodological quality of the studies. Each of the studies were RCTs with a significant level of methodological quality. Thus, the methodological bias of this study was low.

Country(ies) involved United States.

Keywords Cancer pain management; antihistamines; H1 blocker; H2 blocker; Meta-Analysis; Treatment outcome.

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