The use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy to decrease the severity of delirium in alcohol withdrawal in adult intensive care unit patients: a systematic review protocol

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Review question/objective
In adult intensive care unit patients experiencing alcohol withdrawal, does the use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy decrease delirium severity more effectively than benzodiazepine-based therapy alone?

The objective of the systematic review is to examine the best available evidence of the clinical effectiveness of dexmedetomidine as an adjuvant to benzodiazepine-based therapy versus benzodiazepine-based therapy alone, in decreasing delirium severity associated with alcohol withdrawal in adult intensive care unit patients over the age of 18 years.

Background
Chronic alcohol consumption is a prevalent issue throughout the world. According to the latest estimates in the Behavioral Risk Factor Surveillance System (BRFSS) from the Centers of Disease Control, 15% of surveyed adults reported binge drinking.1 For men, binge drinking is defined as five or more drinks during a single occasion and for women as four or more drinks during a single occasion.1 In addition, 5% of those surveyed reported heavy drinking: more than two drinks per day on average for men and more than one drink per day on average for women.1 Alcohol dependence is often unrecognized by the healthcare provider until the patient is admitted to an acute care setting for treatment of another underlying condition or problem. Up to 20% of hospitalized patients are dependent on alcohol.2 During the hospitalization, the patient begins to exhibit signs of alcohol withdrawal, alerting
the healthcare provider the patient has a problem with alcohol consumption. Alcohol withdrawal syndrome (AWS) left unrecognized and untreated can result in severe clinical consequences and death. While there is an abundant amount of research published on alcohol withdrawal in the outpatient and inpatient settings, there is a lack of evidence on the use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy in treating alcohol withdrawal delirium in the critical care setting with intensive care unit (ICU) patients.

Benzodiazepines are used by healthcare providers as the first choice in pharmacologic therapy for patients with AWS. Benzodiazepine therapy alone may not control the symptoms of autonomic hypersensitivity or delirium adequately in the adult ICU population. Therefore, critical care healthcare providers are turning to dexmedetomidine, an alpha-2 agonist used for sedation in critical care units, as an adjuvant to benzodiazepine-based therapy to treat AWS symptoms of autonomic hyperactivity and delirium in adult patients over 18 years of age. The reviewers ask the question: in adult ICU patients experiencing alcohol withdrawal, does the use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy, decrease delirium severity more effectively than benzodiazepine-based therapy alone?

Alcohol withdrawal syndrome (AWS) occurs when the patient no longer ingests alcohol and the neurochemical balance of inhibitory neurotransmitters and excitatory neurotransmitters is affected. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, which stimulates GABA receptors in the brain. Glutamate is an excitatory neurotransmitter that stimulates the N-methyl-D-aspartate (NMDA) receptors in the brain. When a person ingests alcohol, there is a direct effect on the GABA receptors and the neurotransmitter glutamate in the brain; the GABA action is enhanced and the glutamate action is inhibited. If a person ingests alcohol on a daily basis, the alcohol creates a compensatory decrease in the GABA receptor response to GABA and the NMDA receptors up-regulate to counterbalance the effect. If alcohol is abruptly withdrawn, NMDA excitatory receptors have no inhibition and therefore the patient exhibits signs and symptoms of alcohol withdrawal.

Alcohol withdrawal symptoms usually start within six to 12 hours after alcohol cessation. Minor withdrawal symptoms include insomnia, tremors, mild anxiety, nausea or diarrhea, headache, diaphoresis, palpitations and anorexia. Patients may experience more severe symptoms such as alcoholic hallucinosis, which may be visual, auditory, or tactile hallucinations and these symptoms usually occur within 12 to 24 hours after the last drink. If a patient is going to experience withdrawal seizures, they usually occur within 24 to 48 hours of the last drink. Some patients experience the most severe form of withdrawal called delirium tremens. Delirium tremens (DTs), which normally occur within 48 to 72 hours of the last drink, are characterized by hallucinations, disorientation, tachycardia, hypertension, low-grade fever, agitation and diaphoresis. Alcohol withdrawal symptoms can be short-lived, from 48 to 72 hours, or they can last for a week.

The goal of pharmacologic treatment of AWS is based on restoring neurotransmitter balance to treat symptoms, prevent initial and recurrent seizures and prevent and treat alcohol withdrawal delirium and DTs. The importance of identifying and treating the patient with AWS is paramount when one realizes the mortality rate of non-recognized or non-treated AWS is 5%. Treating AWS in the acute care hospital setting presents its own set of challenges due to the patient's primary diagnosis and other comorbidities which may contraindicate certain pharmacologic agents.
The standard for treating AWS is benzodiazepine-based therapy. Benzodiazepines stimulate and bind to the GABA receptors restoring neurotransmitter balance. However, in patients with severe alcohol withdrawal, such as a patient with a Clinical Institute Withdrawal Assessment Score (CIWA) greater than eight, the use of benzodiazepines alone is often inadequate to control delirium and the autonomic hyperactivity resulting in tachycardia and hypertension. Dexmedetomidine is an alpha-2 receptor agonist that is used in critical care and anesthesia for sedation. In addition to its sedative properties, dexmedetomidine reduces blood pressure and tachycardia.

A review of the literature on AWS treatment in the outpatient and acute care settings was completed. The evidence was classified based on the Rating System for the Hierarchy of Evidence by Melnyk and Fineout-Overholt. There were no systematic reviews found on the topic of benzodiazepine-based therapy and the adjuvant use of dexmedetomidine to decrease the severity of alcohol withdrawal delirium in ICU patients.

The reviewers found three clinical practice guidelines, seven systematic reviews, three meta-analyses and five randomized-controlled trials on the management of alcohol withdrawal excluding the use of dexmedetomidine. The literature discusses several drug categories to treat AWS: benzodiazepines, barbiturates, anticonvulsants and adjuvant therapies. Adjuvant therapies include beta-adrenergic blockers, alpha-2 agonists and antipsychotics. Many of these drug categories are approved for use in either the outpatient or acute care setting; however, dexmedetomidine is only indicated for use in the critical care area.

There were two systematic reviews in the Cochrane Database of Systematic Reviews that evaluated the effectiveness and safety of benzodiazepines in the treatment of AWS. In the systematic review, published in 2005 by Amato, Minozzi, Vecchi, and Davoli; the researchers reviewed 64 studies of which 4,309 participants met the inclusion criteria. In another systematic review, published in 2010 by Ntais, Pakos, Kyzas and Ioannidis, the researchers reviewed 57 studies of which 4,051 participants met the inclusion criteria. Both systematic reviews found that all benzodiazepines effectively managed symptoms of AWS including agitation, tremors, diaphoresis, insomnia, hallucinations and seizures. Not one benzodiazepine performed statistically better than the others.

Holbrook, Crowther, Lotter, Cheng and King conducted a meta-analysis in 1999 of 23 trials; 11 of which met inclusion criteria, with 1,385 participants. The meta-analysis evaluated whether benzodiazepines were superior to beta-blockers, carbamazepine and clonidine as single therapy. The research found that benzodiazepines were able to control AWS symptoms better than the other drugs. The meta-analyses and systematic reviews published to date on the subject of managing the symptoms of alcohol withdrawal support the use of benzodiazepine-based therapy as first-line management to control withdrawal symptoms including delirium.

There are two methods to deliver benzodiazepine-based therapy in the outpatient and inpatient settings; symptom-triggered therapy and fixed-scheduled treatment therapy. The research demonstrates that symptom-triggered therapy, based on the CIWA-Revised Scale, is safe and effective for patients experiencing AWS and the overall quantity of benzodiazepines was smaller and the duration of therapy was shorter with symptom-triggered therapy versus fixed-scheduled therapy.

Seizures are a very serious risk in patients going through AWS. Patients who have had alcohol withdrawal seizures in the past are at high risk for having them again during withdrawal and they tend to
be more severe. The phenomenon of having worsening withdrawal symptoms with each withdrawal episode is known as the kindling phenomenon. Research has shown that anticonvulsants, such as phenobarbital, carbamazepine and phenytoin inhibit seizure activity in patients with seizure disorders. Since seizures experienced during alcohol withdrawal are due to an imbalance of GABA and glutamate, the question remains whether or not anticonvulsants inhibit seizures during alcohol withdrawal.

There were two systematic reviews in the Cochrane Database of Systematic Reviews on this topic. In 2005, the systematic review by Polycarpou, Papanikolau, Ioannidis and Contopoulos-Ioannidis evaluated 48 studies with 3610 participants who met the criteria for inclusion. The study determined that the anticonvulsant phenytoin did not inhibit seizure activity in AWS; however, phenobarbital did exhibit a benefit for those patients experiencing alcohol related status epilepticus. Carbamazepine provided a small but insignificant benefit for some participants over a benzodiazepine. Amato, Minozzi, Vecchi and Davoli in 2005 also conducted a systematic review and included 56 studies with 4,076 participants. They found phenobarbital exhibited a benefit for those patients experiencing alcohol-related seizures.

Phenobarbital is a barbiturate that binds directly to the GABA receptor, which decreases AWS symptoms and seizures. Current research supports the use of phenobarbital in the treatment of AWS symptoms, status epilepticus, or recurrent seizures in AWS in conjunction with a benzodiazepine. Phenobarbital may be used in patients with AWS seizures who have a history of a seizure disorder not associated with AWS. Seizures associated with alcohol withdrawal are often self-limiting; therefore, there is no significant evidence or reason to recommend the use of continuous anticonvulsant therapy for the treatment of isolated alcohol withdrawal seizures.

There are several adjuvant therapies to benzodiazepines that are used in the management of AWS. Antipsychotics have been used in AWS treatment for years to control the symptoms of anxiety, delusions and auditory, visual and tactile hallucinations; however, research on the efficacy of these drug classes has been inconclusive. The use of antipsychotics is not without risks to patients. Antipsychotics lower the seizure threshold, so they should not be used in patients who are at risk for alcohol-related seizures or have a previously diagnosed seizure disorder. In addition, antipsychotics prolong the QT interval of the cardiac cycle, which increases the risk of ventricular arrhythmias. Patients who require antipsychotics as a chemical restraint need to have a pretreatment electrocardiogram prior to the initiation of therapy. The current recommendations on the use of antipsychotics in the treatment of AWS are to use them only in patients, whose symptoms are not controlled with benzodiazepines, do not have a seizure history and do not have a prolonged QT interval on their electrocardiogram.

Autonomic hypersensitivity symptoms such as tachycardia, palpitations, hypertension and diaphoresis affect many patients experiencing alcohol withdrawal. For years, beta-blockers and alpha-2 agonists have been used to control these symptoms since they work well in non-alcohol related situations. However, the research on their use to control autonomic hypersensitivity in alcohol withdrawal has been inconclusive. In a systematic review by Williams and McBride in 1998, the researchers reviewed several studies using beta-blockers and the alpha-2 agonist clonidine. The systematic review found beta-blockers and the alpha-2 agonist clonidine were ineffective in preventing major withdrawal symptoms such as delirium or seizures. Other studies have agreed with the evidence found by Williams and McBride. The recommendation for the use of beta-blockers and the alpha-2 agonist
clonidine to control withdrawal symptoms should only be considered as adjuvant therapies to treat sympathetic hypersensitivity, not to control delirium or seizures.\textsuperscript{4,17,27}

Patients who are alcohol dependent have nutritional deficits as well as folate and thiamine deficits. There is some debate in the literature regarding whether the dosing of folate, thiamine and multivitamins is sufficient for the patient experiencing alcohol withdrawal.\textsuperscript{6,26-28} Thiamine is especially important because of carbohydrate metabolism. If thiamine levels are low, Wernicke's encephalopathy can occur. Therefore, the recommendation for patients experiencing alcohol withdrawal is to supplement with folate, thiamine and multivitamins if levels are low.\textsuperscript{6,26-28}

There have been several studies done on the use of baclofen and nitrous oxide to manage alcohol withdrawal delirium and withdrawal symptoms.\textsuperscript{12,13} However, the studies lacked sufficient power due to an inadequate sample size to recommend the use of baclofen and nitrous oxide as treatment options for alcohol withdrawal delirium and autonomic hypersensitivity at this time. Further research is needed on these two drugs and their use in AWS.

Patients experiencing severe withdrawal symptoms that are refractory to benzodiazepine-based therapy are often transferred to the ICU for more intensive management. Patients critically ill in the ICU are especially vulnerable to the symptoms of alcohol withdrawal specifically autonomic hypersensitivity and delirium. The tachycardia, hypertension and delirium associated with alcohol withdrawal can be extremely detrimental to patients who are already hemodynamically compromised.

In ICU, the drug propofol is used to provide sedation for critically ill patients who are intubated and on a ventilator for airway control. Propofol is an anesthetic agent which causes apnea and loss of consciousness.\textsuperscript{9} Propofol opens the chloride channels of the GABA receptors and therefore controls AWS symptoms.\textsuperscript{9} Patients requiring propofol are intubated and placed on mechanical ventilation and as a result require care in a critical care unit for airway protection and closer monitoring. The research has found propofol to be very effective in managing symptoms of autonomic hypersensitivity and controlling alcohol withdrawal seizures.\textsuperscript{6,9}

Delirium management and the need for sedation is common in critically ill patients. Dexmedetomidine is a selective, alpha-2 agonist used in anesthesia and critical care units for the management of analgesia and sedation.\textsuperscript{29} Dexmedetomidine's mechanism of action is different from other alpha-2 agonists such as clonidine. Dexmedetomidine is eight times more specific to the alpha-2A subtype receptor in the locus coeruleus in the brain and the alpha-2A subtype receptors in the spinal cord.\textsuperscript{29} This action results in a decrease in heart rate and blood pressure as well as sedation and analgesia. This differentiation from clonidine makes dexmedetomidine an attractive option for ICU patients experiencing alcohol withdrawal to manage delirium as well as other symptoms due to autonomic hypersensitivity.

In a search of the literature including Ovid/Medline, CINAHL, Cochrane Systematic Reviews, Scopus, and Ovid/Embase; several studies were found that evaluated the use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy in adult ICU patients experiencing alcohol withdrawal delirium.\textsuperscript{7,30-37} In a prospective study by Tolonen, Rossinen, Alho and Harjola in Finland, dexmedetomidine decreased the Richmond Agitation Sedation Score (RASS) and the Confusion Assessment Method for the ICU (CAM-ICU) scores in 16 of 18 patients who were included in the study.\textsuperscript{31}
Three retrospective studies were done to determine if dexmedetomidine in addition to benzodiazepine-based therapy decreased alcohol withdrawal delirium. These studies used the Ramsey Scale, CIWA scale, or the alcohol withdrawal scale to assess delirium. In all three of these studies, there was a decrease in delirium severity after dexmedetomidine was added to benzodiazepine-based therapy as evidenced by a decrease in each of the scores.\(^7,30,33\)

Several case-series have also been published regarding the use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy in alcohol withdrawal. Two of the three case studies showed a decline in severity of alcohol withdrawal delirium as evidenced by physical assessment evaluation or a decrease in RASS score.\(^36-38\)

While these results look promising, there has been no meta-analysis done on the topic of dexmedetomidine as an adjuvant to benzodiazepine-based therapy to decrease alcohol withdrawal delirium severity. Without a rigorous meta-analysis to determine if the evidence supports the use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy to manage alcohol withdrawal delirium in adult ICU patients, the recommendation for its use cannot be made.

This systematic review will synthesize all available evidence to determine if using dexmedetomidine as an adjuvant to benzodiazepine-based therapy in adult patients older than 18 years of age decreases the severity of delirium in alcohol withdrawal more effectively than standard benzodiazepine-based therapy. These results will assist healthcare providers in the ICU with determining if there is sufficient evidence to recommend the use of dexmedetomidine as an adjuvant therapy to benzodiazepine-based therapy in adult ICU patients experiencing alcohol withdrawal delirium.

**Keywords**

alcohol withdrawal syndrome; benzodiazepine-based therapy; delirium; dexmedetomidine; intensive care unit

**Inclusion criteria**

**Types of participants**

This review will consider studies that include adult intensive care unit patients over the age of 18 years who are experiencing delirium associated with acute alcohol withdrawal. Patients admitted to the intensive care unit with the primary diagnosis of alcohol withdrawal, as well as patients admitted with other diagnoses who experience alcohol withdrawal as a secondary diagnosis, will be considered for inclusion in the review.

**Types of intervention(s)**

This review will consider studies that evaluate dexmedetomidine as an adjuvant therapy to benzodiazepine-based therapy, compared to the use of benzodiazepine-based therapy alone, in patients with alcohol withdrawal experiencing alcohol withdrawal delirium.

**Types of outcomes**

The systematic review will evaluate dexmedetomidine as an adjuvant to benzodiazepine-based therapy to decrease delirium severity in alcohol withdrawal.
The general outcome of delirium severity will be used as the outcome since there are a variety of tools used to measure severity of delirium in the ICU. The tool that is often used to measure alcohol withdrawal symptoms is the CIWA-Revised scale and tools to measure agitation and sedation levels in the ICU include: the Ramsey Scale, the Richmond Agitation Sedation Score and the Confusion Assessment Method for the ICU (CAM-ICU).\textsuperscript{39,40}

**Types of studies**

This review will consider both experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies for inclusion. This review will also consider descriptive epidemiological study designs including case series, individual case reports and descriptive cross sectional studies for inclusion. The researchers will search for the best available evidence on the topic.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of Ovid/ MEDLINE and CINAHL will be undertaken, followed by analysis of the text words contained in the title and abstract and of the index terms used to describe the articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles will be searched for additional studies. Studies published in the English language will be considered for inclusion in this review. Studies published after 1997 will be considered for inclusion in this review.

The databases to be searched include:

Ovid/MEDLINE, CINAHL, Ovid/EMBASE, Web of Science, PsycINFO, Cochrane Library, DARE, TRIP and GIN. The search for unpublished studies will include: NLM, New York Academy of Medicine, Geneva Foundation for Medication Education and Research, OpenGrey and BioMedical Central. The following journals will be hand searched: Critical Care Medicine, Critical Care Nurse, Heart and Lung, AACN’s Advanced Clinical Practice, Anesthesiology and Anesthesia & Analgesia.

The databases and journals will be searched from 1997 through October 2013 for relevant studies. The year 1997 was chosen as a search limit since alpha-2 agonists, specifically clonidine and dexmedetomidine, were being tested on their use in controlling alcohol withdrawal delirium from that date forward.

Initial key words to be used will be: alcohol withdrawal, alcohol withdrawal syndrome, alcohol withdrawal delirium, benzodiazepine-based therapy, delirium, DTs, delirium tremens and dexmedetomidine and its derivatives. All studies identified during the database search will be assessed for relevance to the review based on the information provided in the title, abstract and descriptor/MeSH terms. A full report will be retrieved for all studies that meet the inclusion criteria.
Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratios (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square and also explored using subgroup analyses based on the different study designs included in this review. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

There are no conflicts of interest associated with this systematic review, or the primary reviewer, the secondary reviewer and the associate reviewer.

Acknowledgements

The reviewers would like to acknowledge Texas Christian University, Penn Medicine Chester County Hospital, the Joanna Briggs Institute and Michelle Brewer, Librarian for their assistance in preparing this protocol.
References


Appendix I: Appraisal instruments

MAStARI Appraisal instrument

**JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial**

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<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>7. Were groups treated identically other than for the named interventions</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (including reason for exclusion)

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# JBI Critical Appraisal Checklist for Descriptive / Case Series

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<td>1. Was study based on a random or pseudo-random sample?</td>
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<td>4. Were outcomes assessed using objective criteria?</td>
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<td>5. If comparisons are being made, was there sufficient descriptions of the groups?</td>
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**Overall appraisal:** Include □ Exclude □ Seek further info □

**Comments (Including reason for exclusion):**

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doi:10.11124/jbisrir-2014-1285  
Page 86
## JBI Critical Appraisal Checklist for Comparable Cohort/Case Control

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Author .................................  Year  ............ Record Number .........  

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Overall appraisal: Include □ Exclude □ Seek further info. □  

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Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer   Date
Author     Year
Journal    Record Number

Study Method
RCT         Quasi-RCT  Longitudinal
Retrospective Observational Other

Participants
Setting
Population

Sample size
Group A    Group B

Interventions
Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:
### Study results

#### Dichotomous data

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