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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CAPS	Clinician Administered PTSD Scale
CI	confidence interval
CIDI	Comprehensive International Diagnostic Interview
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
IES-R	Impact of Event Scale Revised
MAGIC	Missouri Assessment of Genetics Interview for Children, PTSD Section
N	number of participants
PCL	PTSD Checklist
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS-I	Post-traumatic Symptom Scale—Interview Version
PTSD	post-traumatic stress disorder
RCT	randomized controlled trial
RR	risk ratio
SMD	standardized mean difference
WAIS-III	Wechsler Adult Intelligence Scale third edition

Context and Policy Issues

Post-traumatic stress disorder (PTSD) is a chronic mental health condition that may develop in individuals following direct or indirect exposure to a traumatic event.[1] Research indicates that the lifetime prevalence of trauma, which can be caused by numerous distressing events (e.g., exposure to actual or threatened death, serious injury, or sexual violence), is as high as 70% in the general population.[2,3] Although not every individual who experiences trauma will develop subsequent mental health issues such as PTSD, acute stress disorder, or depression, these conditions are associated with decreased quality of life and disability[4,5] and are among the leading contributors to the global burden of disease.[6] It is estimated that nearly 1 in 10 Canadians will experience PTSD at some point in their lifetime.[7]

Research dating back to the 1980s has postulated that epinephrine and norepinephrine may play a role in the formation of traumatic memories, and thus in the development of PTSD.[8] Although the mechanism is not fully understood, literature suggests that epinephrine and norepinephrine released by the beta-adrenergic system as a result of trauma may enhance the formation of memories associated with emotional experiences and strengthen fear conditioning.[9,10] These findings have prompted subsequent research investigating the use of propranolol, a beta-blocker that inhibits the effects of these catecholamines by acting as a competitive antagonist on beta-adrenergic receptors,[11] for the treatment and prevention of PTSD. Research in this field has primarily focused on two main indications: 1) propranolol given to individuals prior to trauma memory reactivation in patients diagnosed with PTSD, and 2) propranolol given following trauma as a preventative measure for subsequent PTSD or acute stress disorder.[12]

The purpose of this report is to summarize the clinical evidence regarding the effectiveness of propranolol for the treatment and prevention of PTSD.

Research Questions

1. What is the clinical effectiveness of administering propranolol before trauma memory reactivation for patients with post-traumatic stress disorder?
2. What is the clinical effectiveness of propranolol for the prevention of post-traumatic stress disorder or acute stress disorder?

Key Findings

This report included four systematic reviews (that summarized nine unique relevant primary studies), three randomized controlled trials, and one non-randomized study regarding the clinical effectiveness of propranolol for the treatment and prevention of post-traumatic stress disorder (PTSD).

Based on the findings from the included literature, propranolol administered prior to trauma memory reactivation decreased the severity of PTSD symptoms, reduced physiological responses (e.g., heart rate, skin conductance, blood pressure), and improved cognitive performance in individuals with PTSD. Although these findings were largely consistent, one included study did not show a significant difference between treatment with propranolol and placebo with respect to severity of PTSD symptoms.

When used as a preventative measure following trauma, propranolol did not significantly reduce the risk for subsequent PTSD or acute stress disorder compared to placebo or no treatment. In addition, those who received propranolol did not consistently demonstrate improvements to PTSD symptom severity scores compared to those who received placebo or no treatment.

Regardless of the indication, individuals treated with propranolol experienced similar side effects to those who received placebo (when adverse events were reported); however, the included studies were not designed to thoroughly investigate the harms associated with the use of propranolol and these findings are indeterminate.

The findings summarized in this report come with a high degree of uncertainty due to the methodological limitations of the included literature (e.g., lack of long-term follow-up data, unclear clinical significance). These limitations should be considered when interpreting the findings of this report.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were propranolol and post-traumatic stress disorder. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and Feb 13, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1: Individuals with a diagnosis of PTSD Q2: Individuals who have experienced trauma
Intervention	Q1: Propranolol administered before trauma memory reactivation Q2: Propranolol administered immediately or shortly after the traumatic event
Comparator	Q1: Trauma memory reactivation with a placebo; trauma memory reactivation alone; usual care for PTSD (e.g., exposure therapy, cognitive processing therapy) Q2: No propranolol; placebo; any active comparator (e.g., gabapentin)
Outcomes	Q1: Clinical effectiveness (e.g., PTSD symptoms, memory, cognitive effects, heart rate), and adverse events Q2: PTSD diagnosis, acute stress disorder diagnosis, PTSD symptoms, anxiety, depression, adverse events
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, and non-randomized studies

PTSD = post-traumatic stress disorder.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Systematic reviews that had relevant included studies fully captured in other, more recent or more comprehensive (e.g., outcome data from relevant primary studies was more completely summarized) systematic reviews were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) II[13] and the clinical studies were critically appraised using the Downs and Black checklist.[14] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 38 citations were identified in the literature search. Following screening of titles and abstracts, 17 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, six potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 27 potentially relevant articles, 19 publications were excluded for various reasons, while eight publications met the inclusion criteria and were included in this report. These comprised four systematic reviews with meta-analyses,[15-18] three randomized controlled trials

(RCTs),[19-21] and one non-randomized study.[22] Appendix 1 presents the PRISMA[23] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Four systematic reviews with meta-analyses,[15-18] three RCTs,[19-21] and one non-randomized study[22] were identified for inclusion in this review. No relevant health technology assessments were identified. Detailed study characteristics are available in Appendix 2, Table 2 and Table 3.

Three of the included systematic reviews[15,16,18] had objectives and inclusion criteria that were broader than the current report (i.e., wider in scope). Specifically, the Astill Wright et al. (2019)[15] and Sijbrandij et al. (2015)[18] reviews evaluated the effectiveness of any pharmacological interventions (e.g., propranolol, hydrocortisone, dexamethasone, escitalopram) delivered following exposure to a traumatic event for the prevention of PTSD or acute stress disorder. The review by Steenen and colleagues[16] was specific to propranolol; however, the review also included studies on the effectiveness of propranolol for the treatment of other anxiety disorders that are not eligible for the current report (e.g., panic disorder, specific phobia, social phobia). Only the characteristics and results of the subset of relevant studies will be described in this report.

Study Design

The Astill Wright et al. (2019)[15] systematic review and meta-analysis included RCTs (including cluster and cross-over trials) published up to May 2018. A total of 19 RCTs were included in the systematic review[15] (five RCTs[24-28] were relevant to the current report). The systematic review and meta-analysis by Steenen and colleagues,[16] published in 2016, included comparative parallel group and crossover RCTs. Systematic searches for relevant literature for this systematic review were performed in multiple databases from inception until March 2014. Of the eight RCTs included in the review,[16] one RCT[29] was relevant to the current report. The Argolo et al. (2015)[17] systematic review and meta-analysis searched for randomized and non-randomized primary studies up to November 2014. Five primary studies[24-26,30,31] were identified and included in both the qualitative and quantitative syntheses (all were relevant to the current report). The fourth systematic review and meta-analysis, authored by Sijbrandij and colleagues[18] in 2015, included RCTs, controlled clinical trials, and longitudinal cohort studies published up to May 2013. The review included 15 primary studies in total, six[24-26,30,32,33] of which were relevant for this report. In total, the systematic reviews[15-18] included nine unique clinical studies[24-33] that were relevant to the current report.

The relevant primary study overlap between these systematic reviews[15-18] is summarized in Appendix 5, Table 8. When possible, findings from primary studies included in multiple systematic reviews were only summarized once. Specifically, if the findings from a primary study were pooled in meta-analytic results extracted from a systematic review, the findings of that study were not also summarized narratively. If the findings were not pooled in an extracted meta-analysis, the results from the primary were narratively described once (i.e., they were not reported in duplicate from multiple systematic reviews). There were some instances where meta-analytic results extracted from different systematic reviews pooled data from some of the same primary studies; thus, some primary studies have contributed to more than one of the summarized meta-analytic results.

With respect to the included primary studies, all three relevant RCTs[19-21] were double-blind placebo-controlled studies. The RCTs by Brunet and colleagues[19] and Mahabir and colleagues[20] were conducted at single centres, while the Orrey et al. (2015)[21] RCT included individuals recruited from multiple hospitals.

The non-randomized study by Brunet and colleagues[22] enrolled participants into a single treatment group and compared the outcomes experienced by their study participants with those from a previously published trial.[29]

Country of Origin

The included systematic reviews and meta-analyses were by authors in Brazil,[17] the Netherlands,[16,18] and the United Kingdom.[15] Relevant primary studies included in the systematic reviews were conducted in France,[30] the United States,[24-28,32,33] or their country of origin was not reported[29,31] within the systematic reviews.

The RCTs by Brunet and colleagues[19] and Mahabir and colleagues[20] were conducted Canada, whereas the Orrey et al. (2015)[21] RCT was conducted in the Untied States. The non-randomized study by Brunet and colleagues[22] was conducted in Canada.

Patient Population

Three systematic reviews[15,18] included primary studies that recruited individuals who had experienced a traumatic event. Of these, two reviews[15,18] did not place any restrictions on participant age, while the review by Argolo and colleagues[17] was specific to adults (≥18 years of age). The fourth systematic review, conducted by Steenen and colleagues,[16] included primary studies that enrolled individuals (of all ages) with any of the anxiety disorders (e.g., PTSD, panic disorder, specific phobia, social phobia) listed in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*; both the 5th edition and previous versions).Overall, a total of 625 participants were included in the nine unique relevant clinical studies[24-33] summarized within the systematic reviews.[15-18] The complete characteristics of participants from relevant clinical studies[24-33] (e.g., age, sex, type of trauma, baseline PTSD symptom severity) was not available in the systematic reviews.[15-18]

The Brunet et al. (2018)[19] RCT enrolled 60 adults (≥18 and ≤65 years of age) who suffered from PTSD for at least six consecutive months and who had a PTSD Checklist—Specific (PCL-S) score ≥44 at time of recruitment. Individuals who were pregnant, breastfeeding, currently receiving psychotherapy, or who had current substance dependence, psychotic or bipolar disorder, traumatic brain injury, acute suicidal ideation, or medical conditions contraindicating propranolol use were ineligible for the study. Participants' mean age was 39.4 years and the proportion of female participants was 58.3%. The RCT by Mahabir and colleagues[20] recruited individuals who experienced a traumatic event, were diagnosed with chronic PTSD, and had a Clinician Administered PTSD Scale (CAPS) score of ≥50 points. Individuals who were pregnant, diagnosed with bipolar disorder, who had a history of head injury, or who had medical conditions contraindicating propranolol use were excluded from the study. A total of 41 participants were enrolled in the study (mean age = 43.4 years). The proportion of female participants was 73.2%. The third RCT, conducted by Orrey and colleagues,[21] enrolled individuals admitted to burn centres within 72 hours of a thermal burn injury that involved ≤20% of total body surface area. All participants were required to be not homozygous for the high activity catechol-*O*-methyltransferase haplotype. Individuals with an estimated hospital stay <5 days or >40 days, intentional injury, substantial concomitant non-burn injury, a history of asthma, diabetes, coronary artery disease, psychotic disorder, hepatic failure, renal failure, or congestive heart failure, and those who were already

receiving beta-blocker medication, were on opioid medications prior to their burn injury, or were clinically unstable were excluded from the study. The number of participants included in the study was 43. The mean age of participants was 31.5 years and the proportion of female participants was 20.9%.

The non-randomized study by Brunet and colleagues[22] enrolled 28 adults (≥18 and ≤65 years of age) with PTSD as assessed by a structured clinical interview. Individuals with asthma, heart failure, heart block, certain cardiac arrhythmias, insulin-requiring diabetes, previous adverse reaction to a beta blocker, or those who were pregnant, breastfeeding, had a mean score of >20 on the Dissociative Experiences Scale, or were on medications that could adversely interact with propranolol were ineligible. Participants' mean age was 37.9 years and the proportion of female participants was 58.3%.

The type of trauma experienced by participants in three RCTs[19-21] and the non-randomized study[22] was diverse. Although the Orrey et al. (2015)[21] study was specific to those with major thermal burn injury, the three remaining primary studies[19,20,22] did not restrict their population by type of trauma.

Interventions and Comparators

One systematic review[16] examined the effectiveness of propranolol for the treatment of patients with anxiety disorders (including PTSD). The review by Steenen and colleagues[16] included one relevant primary study[29] that compared propranolol (40 mg of short acting propranolol plus 60 mg of long-acting propranolol) versus placebo administered prior to script-driven imaginary exposure in patients with PTSD.

Three systematic reviews[15,17,18] included primary studies that investigated the effectiveness of propranolol for the prevention of PTSD or acute stress disorder. The Astill Wright et al. (2019)[15] review included five relevant primary studies that compared propranolol to placebo,[24-27] gabapentin,[26] or standard therapy[28] (defined as nonpropranolol controls). The review by Argolo and colleagues[17] included five primary studies that compared propranolol administered following a traumatic event to placebo[24-26] or no treatment.[30,31] Similarly, the Sijbrandij et al. (2015)[18] review included six relevant primary studies that compared propranolol to placebo[24-26,32,33] or no treatment.[30]

Two included RCTs[19,20] and one non-randomized study[22] examined the clinical effectiveness of administering propranolol before trauma memory reactivation for patients with PTSD. The RCT by Brunet et al. (2018)[19] compared propranolol (0.67 mg/kg of short acting propranolol plus 1.0 mg/kg of long-acting propranolol) versus placebo administered prior to a brief memory reactivation session. The RCT by Mahabir and colleagues[20] randomized participants to receive propranolol (short-acting; oral dose; 1 mg/kg) or placebo prior to script-driven traumatic imagery. The intervention in the non-randomized study by Brunet and colleagues[22] was six weekly sessions of propranolol (0.67 mg/kg of short acting propranolol plus 1.0 mg/kg of long-acting propranolol) administered prior to script-driven traumatic imagery (participants read an account of their traumatic event for 5 to 10 minutes). There were two comparator groups (from a previously published study[29]): one session of propranolol (40 mg short-acting plus 60 mg long-acting), or one session of placebo, prior to script-driven imaginary exposure to traumatic event.

One included RCT[21] examined the effectiveness of propranolol for the prevention of PTSD. Participants in this study[21] were randomized to receive propranolol (240 mg/day for three weeks followed by a 20 day taper) or placebo following major thermal burn injury.

Outcomes

The included systematic reviews[15-18] and additional primary studies[19-22] reported on a number of outcomes that were relevant to the current report, including: incidence of PTSD, severity of PTSD symptoms, incidence of acute stress disorder, cognitive performance, physiologic response (e.g., heart rate, blood pressure, skin conductance), and adverse events.

Incidence of PTSD was defined as the proportion of participants who met the diagnostic criteria for PTSD at follow-up. Clinical studies employed a variety of diagnostic tools or techniques in order to classify patients at follow-up, including: the CAPS; the Comprehensive International Diagnostic Interview (CIDI); the Missouri Assessment of Genetics Interview for Children, PTSD Section (MAGIC); the PTSD Checklist (PCL); the Post-traumatic Symptom Scale—Interview Version (PSS-I); or clinical interview. Severity of PTSD symptoms was measured in the included studies using the CAPS, the Impact of Event Scale Revised (IES-R), the PCL, and the Treatment Outcome PTSD scale (TOPs). A brief explanation of the scales used to assess PTSD incidence and PTSD symptom severity is provided below.

(1) CAPS: a 30-item structured interview that corresponds to the *DSM* criteria for PTSD. Frequency and intensity of symptoms are each rated on a scale of 0 to 4, with higher scores indicating more severe PTSD symptoms.[34]

(2) CIDI: a structured clinical interview designed to assess psychiatric disorders according to *DSM* criteria. The PTSD module queries the individual for potentially traumatic events, and any individuals who disclose events are further asked about their symptoms.[35]

(3) IES-R: a 22-item scale used to evaluate PTSD symptoms categorized into three symptom clusters (intrusions, avoidance, and hyperarousal). The frequency of symptoms over the prior week is scored between 0 and 4, with higher scores indicating increased symptom severity.[36]

(4) MAGIC: a structured clinical interview that may be used to diagnose PTSD. The interview includes a number of questions aimed at assessing each of the PTSD criterion outlined in the *DSM*.[37]

(5) PCL: a 17-item self-report instrument that quantifies PTSD symptoms. Each item is scored between 1 and 5, with total scores ranging between 17 and 85. Higher scores indicate increased PTSD severity.[38]

(6) PSS-I: an interview that consists of 17 items, each rated on a scale of 0 (does not interfere at all) to 3 (interferes very much). Total scores range between 0 and 51, where higher scores indicate more severe PTSD symptoms.[39]

(7) TOPs: an eight-item interview based on the *DSM* criteria for PTSD. The eight questions evaluate three symptoms clusters for PTSD (i.e., re-experiencing, avoidance and numbing, hyperarousal).[40]

Cognitive performance was measured in one study[20] using the Wechsler Adult Intelligence Scale third edition (WAIS-III), which is an intelligence quotient test designed to score verbal comprehension, working memory, perceptual organization, and processing speed.[41]

No information on the minimal clinically important difference for any of these outcome assessment scales was available within the included systematic reviews[15-18] or additional primary studies.[19-22]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 4 and Table 5.

Systematic Reviews

The four included systematic reviews[15-18] were generally well-conducted according to AMSTAR II criteria. The reviews[15-18] had clearly defined objectives and inclusion criteria, searched multiple databases, described key search terms and search strategies, and provided lists of included studies. The methods for article selection, data extraction, and quality assessment were well-documented and were conducted involving at least two reviewers (with the exception of data extraction in one review,[18] where it was unclear if it was conducted by a single author or in duplicate), decreasing the likelihood for inconsistency in these processes. The authors of two systematic reviews[15,18] provided clear justification for their choice of included study designs. All four reviews[15-18] included flow charts illustrating study selection and provided reasons for study exclusion. Additionally, the four systematic reviews[15-18] performed meta-analyses using appropriate methods for the statistical combination of results and assessed heterogeneity when suitable (using I^2 statistics). However, pooled estimates from two systematic reviews[16,18] could not be extracted for the current report as the pooled data presented in the Forest plots included primary studies that were not relevant under our inclusion criteria. Risk of bias and limitations of primary study designs were assessed using appropriate tools and were considered when discussing the results of the reviews in three of the reviews.[15,16,18] Publication bias was assessed by the authors of three included systematic reviews[16-18] using various methods (e.g., Egger's test, funnel plots, examination of trial registries). Finally, the authors of all four systematic reviews[15-18] disclosed their sources of funding (which were considered unlikely to have influenced the findings of the reviews) and stated that they had no related conflicts of interest.

Methodological limitations common to all four systematic reviews[15-18] included: no structured searches for grey literature (research produced outside of traditional publishing and distribution channels), it was unclear whether the review methods were established prior to conducting the reviews (none of reviews referenced a published protocol), review authors did not report on sources of funding for their included primary studies, and lists of excluded studies were not provided. In the systematic review by Argolo and colleagues,[17] the technique for assessing the risk of bias in primary studies and the results of this assessment were not described; therefore, the potential impact of risk of bias on the findings of the review was unclear. Finally, the countries in which primary studies included in all four reviews were conducted was either not described[16,17] or they were described but conducted outside of Canada[15,18] (therefore, the generalizability of the findings to the Canadian setting was unclear).

Randomized Controlled Trials

There were several strengths common to all three RCTs,[19-21] including: 1) clearly described objectives, interventions, controls, inclusion/exclusion criteria, and main outcomes, 2) baseline participant characteristics (e.g., age, sex, type of trauma) were reported and were tested for statistically significant difference between treatment groups (there were no

significant differences between groups for any of the tested characteristics, increasing confidence that randomization was effective), 3) study participants and outcome assessors were blinded to treatment assignment, 4) main findings were clearly presented (in tabular or graphic form) and included estimates of random variability (e.g., standard deviations, confidence intervals) and actual P values, 5) compliance with the interventions was reliable, 6) participants in different treatment groups within the same study were recruited over the same period of time and were assessed at consistent follow-up intervals, and 7) study participants, care providers, and care settings appeared to be representative of the population and care settings of interest, increasing external validity. Two studies[19,20] were conducted in Montreal, Quebec, and should therefore have relatively high generalizability to Canadian settings. Finally, the authors of all three RCTs reported on their sources of funding (which were considered unlikely to have influenced the findings of the studies), while the authors of two RCTs[19,21] declared that they had no potential conflicts of interest.

As for methodological limitations, the authors of the included RCTs[19-21] did not perform power calculations prior to recruiting participants. As a result, studies may have been underpowered to detect statistically significant differences for some outcomes of interest. A large proportion of participants (N = 30/60; 50.0%) in the study by Brunet and colleagues[19] did not complete the study per protocol; this significant participant attrition may have decreased the observed between-group differences. The authors of the Mahabir et al. (2016)[20] study did not disclose their conflicts of interest, nor did they report on the adverse events that may have been associated with the use of propranolol, therefore the safety of propranolol in their study population was unclear. Finally, the study by Orrey and colleagues[21] was designed to measure study feasibility (i.e., patient consent rates and participant completion rates) and pain severity as primary outcomes (which were considered irrelevant to the current report); the findings related to PTSD severity and incidence were denoted as secondary outcomes and were not the principal focus of the analysis.

Non-Randomized Studies

The included non-randomized study[22] had clearly described objectives, interventions, main outcomes, inclusion/exclusion criteria, and methods for patient recruitment. Participant characteristics (e.g., age, sex, type of trauma) from those enrolled in the current study[22] were clearly described; however, the characteristics of the patients in the control groups (from a previously published study[29]) were not described. Additionally, the participants in the intervention and control groups were not recruited over the same period of time. As a result, it was difficult to gauge the level of balance between the non-randomized groups, increasing the risk for confounding. This was an open-label study with no blinding of participants or outcome assessors; therefore, there was a risk for bias in either direction depending on the perceptions and expectations of those involved, although the magnitude of this risk was decreased as the reported outcomes were of an objective nature (e.g., heart rate, skin conductance, left corrugator electromyogram). Adverse events that may have been associated with the use of propranolol were not reported; the safety of propranolol was unclear from the current study. Another limitation to note was that participants in the current study underwent six weekly sessions with propranolol, while the patients in the control groups from the previous study[29] only had one treatment session. The decreased physiologic response observed in participants from the current study may have been a result of the repeated exposure to trauma cues through script-driven traumatic imagery, rather than an effect caused by propranolol. Because the intervention was administered in a supervised setting, compliance with the assigned treatment (i.e., propranolol or placebo)

was reliable. Actual probability values (P values) were reported for all monitored outcomes, increasing the strength of reporting.

Study participants, care providers, and setting appeared to be representative of the "real-world", increasing the external validity of the study. Additionally, the study was conducted in Montreal, Quebec, and it should therefore have relatively high generalizability to Canadian settings. Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study. A final limitation to consider was that the authors did not disclose any potential conflicts of interest.

Summary of Findings

The overall findings of the included studies are highlighted below. Detailed summaries of the main findings are available in Appendix 4, Table 6 and Table 7.

Clinical Effectiveness of Propranolol Before Trauma Memory Reactivation for Patients with PTSD

Severity of PTSD symptoms

Two included RCTs[19,20] examined the effect of propranolol prior to trauma memory reactivation on the severity of PTSD symptoms in patients with chronic PTSD. Brunet and colleagues[19] concluded that participants treated with trauma reactivation and propranolol reported statistically significant improvements in severity of PTSD symptoms (measured using the CAPS and the PCL-S) post-treatment compared to those who received trauma reactivation and placebo. This finding was consistent in both intention-to-treat and per protocol analyses. The authors of the second RCT[20] did not detect statistically significant differences in PTSD symptom severity (measured with the IES-R) between participants who received propranolol or placebo prior to script-driven traumatic imagery.

Physiologic response

Evidence regarding the effect of propranolol before trauma memory reactivation on physiologic response was available from two primary studies[24,29] within two systematic reviews[16,17] and two additional primary studies (one RCT[20] and one non-randomized study[22]).

The findings of one RCT[29] suggested that participants who received propranolol one week prior to mental imagery of trauma had smaller overall physiological response during mental imagery than those who were given placebo (P = 0.007). Specifically, participants in the propranolol group had significantly lower heart rate and skin conductance, but there were no significant between-group differences with respect to left corrugator electromyogram. Similarly, the authors of the Mahabir et al. (2016)[20] RCT concluded that participants given propranolol had significantly reduced heart rate (P = 0.0001), diastolic blood pressure (P = 0.017), and systolic blood pressure (P = 0.014) two hours post-treatment (immediately prior to script-driven traumatic imagery) compared to those who received placebo. In the non-randomized study by Brunet and colleagues[22] the physiologic response of adults with PTSD during script-driven traumatic imagery following administration of propranolol was compared to that of those who received placebo from a previously published trial.[29]Participants in the placebo group had significantly increased skin conductance (P < 0.001) and heart rate (P < 0.05) compared to those who received propranolol. There were no significant between-group differences with respect to electromyogram (P = 0.48) post-treatment. Conversely, Hoge and colleagues[24] concluded that there were no significant differences between

participants treated with propranolol or placebo with respect to physiological reactivity during script-driven traumatic imagery within their study population.

Overall, evidence from two primary studies[29] within two systematic reviews[16,17] and two additional primary studies[20,22] suggested that propranolol administered prior to trauma memory reactivation decreased physiological responses in patients with PTSD compared to placebo.

Cognitive performance

One included RCT[20] investigated the acute effect of propranolol on cognitive performance in individuals with chronic PTSD. The authors of the Mahabir et al. (2016)[20] study noted that compared to those who received placebo, participants given propranolol prior to script-driven traumatic imagery had significantly better scores for two subtest components of the WAIS-III (i.e., the Symbol search subtest and the Processing speed total scaled score). There were no statistically significant differences between the placebo and propranolol groups for the remaining seven WAIS-III subtests.

Adverse events

Information relating to adverse events associated with propranolol administered prior to trauma memory reactivation in individuals diagnosed with PTSD was available from one RCT.[19] Side effects of treatment were reported in 10% of participants in the Brunet et al. (2018)[19] study (N = 6/60; three participants who received propranolol and three who received placebo). The reported adverse events included headache, tiredness, dizziness, nausea, suicidal thoughts, mild asthma, and decreased pulse accompanied by cold extremities. The statistical significance of these findings was not reported.

Clinical Effectiveness of Propranolol for the Prevention of PTSD or Acute Stress Disorder

Incidence of PTSD

Evidence regarding the clinical effectiveness of propranolol for the prevention of PTSD was available from eight primary studies[24-28,30-32] within three systematic reviews[15,17,18] and one additional RCT.[21]

The systematic review by Astill Wright and colleagues[15] included two meta-analyses that pooled data from five relevant RCTs[24-28] comparing propranolol to placebo or standard therapy with respect to incidence of PTSD in adult or child and adolescent populations, separately. The meta-analytic results (reported as risk ratios [RRs] with 95% confidence intervals [CIs]) suggested that there were no statistically significant differences in PTSD incidence between adults treated with propranolol or placebo at three to six month follow-up (RR [95% CI] = 0.75 [0.31 to 1.83]; participants = 96; three RCTs[24-26]. Similarly, there were no statistically significant differences in PTSD incidence between children treated with propranolol and those treated with either placebo or standard therapy (combined) at follow-up between one month and seven years (RR [95% CI] = 0.48 [0.13 to 1.77]; participants = 217; two RCTs[27,28]). The Argolo et al. (2015)[17] systematic review included a meta-analysis that pooled data from five relevant primary studies[24-28] comparing the incidence of PTSD in adults who had experienced a traumatic event and received treatment with propranolol and those who received placebo or no treatment. The findings indicated that treatment with propranolol did not result in statistically significant differences in the risk for PTSD diagnosis (RR [95% CI] = 0.92 [0.55 to 1.55]; participants = 202; five primary studies[24-26,30,31]) compared to control conditions (i.e., placebo, no treatment). There was some primary study

overlap in the meta-analytic results from the Astill Wright et al. (2019)[15] and Argolo et al. (2015)[17] systematic reviews (i.e., three RCTs[24-26] were included in both). The systematic review by Sijbrandij and colleagues[18] included one additional RCT[32] that did not report statistically significant differences in the incidence of PTSD in participants treated with propranolol or placebo following trauma (RR [95% CI] = 3.46 [0.15 to 77.86]; participants = 26). In addition to the results from the included systematic reviews,[15,17,18] the authors of the Orrey et al. (2015)[21] RCT concluded that there were no statistically significant differences in the proportion of participants who met the diagnostic criteria for PTSD post-treatment between those who received propranolol and those who received placebo within their study population.

Overall, evidence from eight primary studies[24-28,30-32] within three systematic reviews[15,17,18] and one additional RCT[21] suggested that propranolol administered immediately or shortly after trauma did not reduce the risk for subsequent PTSD compared to placebo or no treatment.

Severity of PTSD symptoms

Information relating to the effectiveness of propranolol administered following trauma with respect to the severity of PTSD symptoms was available from five primary studies[24-27,30] within two systematic reviews[15,17] and one additional RCT.[21]

The Astill Wright et al. (2019)[15] systematic review included two meta-analyses (one for adult populations and one for child and adolescent populations) that pooled data from three relevant RCTs[24,25,27] comparing propranolol versus placebo with respect to severity of PTSD symptoms. The meta-analytic results (reported as standardized mean differences [SMDs] with 95% CIs) suggested that were no statistically significant differences in severity of PTSD symptoms between adults treated with propranolol or placebo at three to six month follow-up (SMD [95% CI] = 0.06 [–0.49 to 0.61]; participants = 52; two RCTs[24,25]). Similarly, there were no statistically significant differences in severity of PTSD symptoms between children treated with propranolol and children treated with placebo at one to three month follow-up (SMD [95% CI] = 0.01 [–0.87 to 0.89]; participants = 20; one RCT[27]). The findings of two additional primary studies were narratively summarized in the systematic review by Argolo and colleagues.[17] One of these primary studies[26] reported no significant differences between treatment with propranolol, gabapentin, or placebo with respect to severity of PTSD symptoms at any time during the eight-month follow-up period. Conversely, the findings of the second primary study[30] noted that participants who received propranolol reported significantly decreased severity of PTSD symptoms at two-month follow-up (P = 0.037) compared to those who received no treatment. In addition to these findings from the included systematic reviews,[15,17] the authors of the Orrey et al. (2015)[21] RCT assessed the effect of propranolol on severity of PTSD symptoms in patients hospitalized with major thermal burn. Compared to placebo, patients treated with propranolol had no statistically significant differences in their severity of PTSD symptoms (measured with the PSS-I).

With the exception of an open-label non-randomized study,[30] the identified literature[15,17,21,24-27] suggested that propranolol administered immediately or shortly after trauma did not improve the severity of PTSD symptoms compared to placebo, gabapentin, or no treatment.

Incidence of acute stress disorder

One primary study[33] from one included systematic review[18] investigated the effectiveness of propranolol for the prevention of acute stress disorder following trauma. Sharp and colleagues[33] did not detect statistically significant differences in the proportion of participants with acute stress disorder at follow-up (as measured with acute stress disorder clinical interview) between individuals who received propranolol or no treatment.

Adverse events

Information relating to adverse events associated with propranolol administered following trauma was available from one RCT.[21] Participants in the Orrey et al. (2015)[21] study reported a number of adverse events throughout the course of the trial, including gastrointestinal, dermatologic, and metabolic/laboratory side effects; however, there were no statistically significant differences in the number of patients reporting adverse events between the propranolol and placebo groups.

Limitations

No included studies[15-22] discussed minimal clinically important difference values for any of the outcomes measured using continuous scales (e.g., severity of PTSD symptoms measured with the CAPS, cognitive performance measured with the WAIS-III). A statistically significant difference in scores does not necessarily indicate a clinically meaningful difference, and it is unclear if any of the statistically significant findings in the included studies translate into clinically meaningful differences.

While several studies had relatively long follow-up durations (six months,[19] eight months,[26] and seven years[28]), most of the included literature did not observe patients beyond three months post-treatment.[20-22,24,25,27,29-33] The long-term effectiveness of propranolol for the treatment and prevention of PTSD is uncertain.

The included studies examining the use of propranolol prior to trauma memory reactivation were specific to adult populations; thus, the effectiveness of propranolol administered in this manner in pediatric populations is unclear.

With the exception of the RCT by Orrey and colleagues,[21] included studies that reported on the sex of participants recruited a disproportionately high number of females, although this may have been a result of the higher prevalence of PTSD in women.[42]

Conclusions and Implications for Decision or Policy Making

This review was comprised of four systematic reviews with meta-analyses,[15-18] three RCTs,[19-21] and one non-randomized study.[22] Of these studies, two systematic reviews[16,17] and three additional primary studies (two RCTs[19,20] and one non-randomized study[22]) included evidence to address the effectiveness of propranolol administered prior to trauma memory reactivation for patients with PTSD, while three systematic reviews[15,17,18] and one additional RCT[21] assessed the effectiveness of propranolol administered following trauma for the prevention of PTSD or acute stress disorder.

Overall, the identified literature suggested that propranolol administered prior to trauma memory reactivation decreased the severity of PTSD symptoms, reduced physiological response (e.g., heart rate, skin conductance, blood pressure) during trauma memory

reactivation, and improved cognitive performance compared to placebo in individuals diagnosed with PTSD.

As for the effectiveness of propranolol as a preventative measure following exposure to trauma, the included studies suggested that there was no benefit with respect to incidence of PTSD, severity of PTSD symptoms, and incidence of acute stress disorder compared to no treatment or placebo.

The safety of propranolol was investigated in two included primary studies.[19,21] Within these studies, participants treated with propranolol and participants treated with placebo both experienced adverse events; there were no statistically significant differences in the risk for side effects in individuals treated with propranolol compared to those who received placebo. The use of propranolol was associated with mild to moderate adverse events, such as headache, tiredness, dizziness, nausea, suicidal thoughts, mild asthma, decreased pulse and gastrointestinal, dermatologic, and metabolic side effects.

The limitations of the included literature[15-21] (e.g., lack of long-term follow-up data, unclear clinical significance) should be considered when interpreting the findings of this report. Future research conducted using robust methodology and that addresses current sources of uncertainty is warranted.

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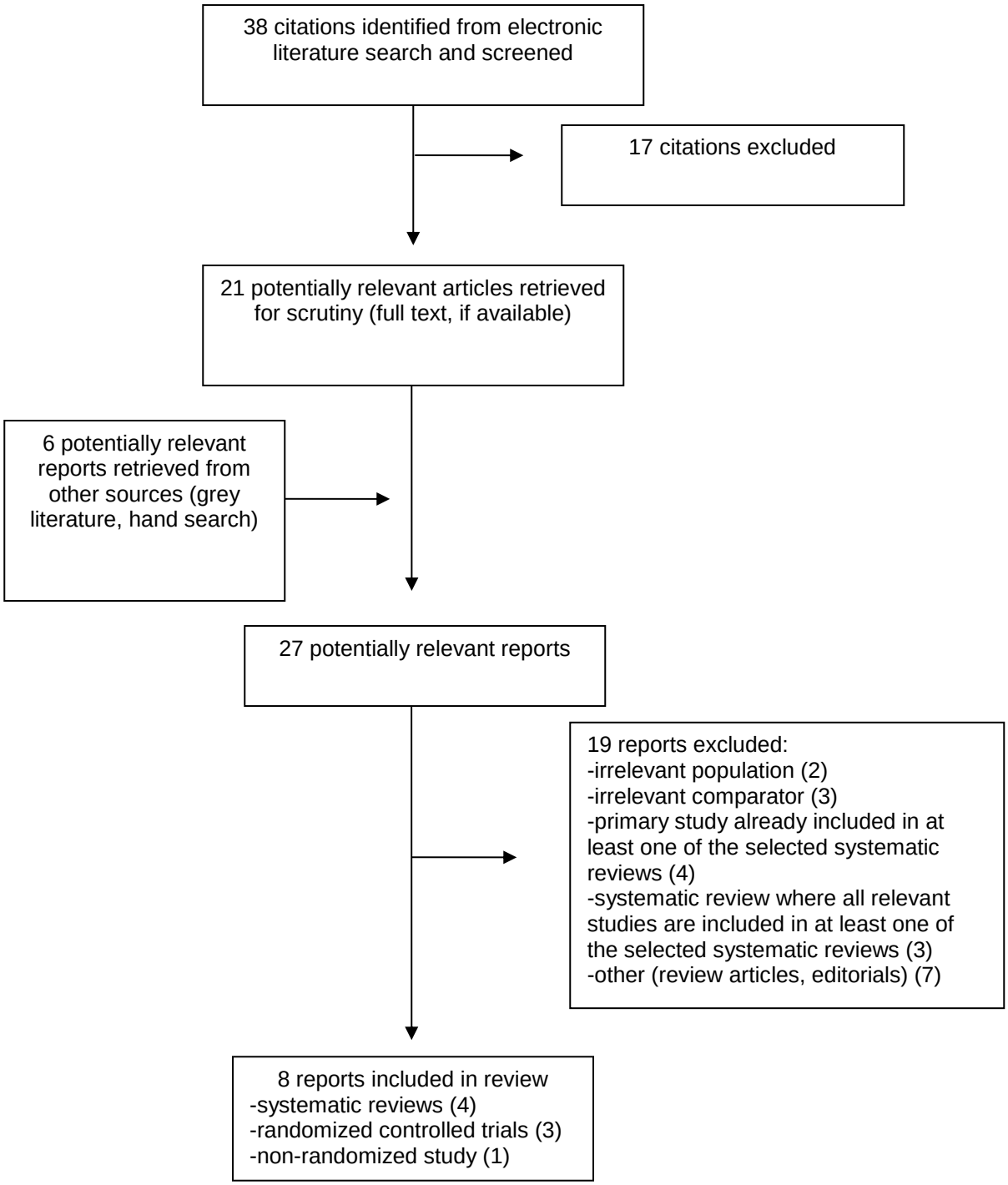
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Astill Wright et al. (2019)[15] United Kingdom **Funding source**: The review was unfunded.	**Objective**: To assess whether pharmacological interventions prevent PTSD or improve clinical outcomes compared to placebo or other active interventions. **Study design**: Systematic review and meta-analysis of RCTs (including cluster and cross-over trials). **Literature search strategy**: Electronic searches were conducted in PubMed, PsycINFO, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for articles published up to May 31, 2018. The electronic searches were supplemented by hand searching of reference lists of four narrative reviews of pharmacological prevention of PTSD. This review combined an updated search combined with the search strategy from the Sijbrandij et al. (2015)[18] review. **Number of studies included**: A total of 19 RCTs were included in the quantitative analysis (five[24-28] of which were relevant to the current report). Only information from the relevant primary studies were extracted. **Quality assessment tool:** Risk of bias in primary studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.	Individuals (of all ages) who experienced a traumatic event likely to meet the A criterion for *DSM*-5 PTSD.	**Intervention**: Pharmacological interventions delivered within three months of the traumatic event. **Comparators**: Placebo, pharmacological interventions, and psychosocial interventions. Relevant primary studies compared propranolol to placebo (four studies[24-27]), gabapentin (one study[26]), or standard therapy (i.e., defined as nonpropranolol controls; one study[28])	**Outcomes assessed in relevant studies**: - PTSD incidence (measured with the CAPS, CAPS-CA, PCL-C, or MAGIC) - PTSD severity (measured with the CAPS) - ASD severity (measured with the ASDS) **Follow-up**: Varied by individual study. Relevant studies ranged from six weeks[27] to seven years post-treatment.[28]
Steenen et al. (2016)[16] Netherlands	**Objective**: To determine the clinical effectiveness of oral propranolol for the treatment of patients with anxiety disorders compared to placebo or other medications.	Individuals (of all ages) with any of the anxiety disorders (e.g., PTSD, panic	**Intervention**: Propranolol.	**Outcomes assessed in relevant studies**: - Skin conductance - Heart rate

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Funding source: No financial support was received for the research, authorship, or publication of the review.	**Study design**: Systematic review and meta-analysis of comparative parallel group and crossover RCTs. **Literature search strategy**: Study authors searched for published and unpublished literature up to March 2014 using PubMED, Ovid Embase, PsycINFO, Web of Science SCI-EXPANDED, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). **Number of studies included**: A total of 8 RCTs were included in the review (one[29] of which was relevant to the current report). Only information from the relevant primary study was extracted. **Quality assessment tool:** Risk of bias in primary studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias.	disorder, specific phobia, social phobia) listed in the *DSM* (both the 5th edition and previous versions).	**Comparators**: Placebo or other medication. The relevant primary study[29] compared propranolol (40 mg of short acting propranolol plus 60 mg of long-acting propranolol) versus placebo administered prior to script-driven imaginary exposure.	- Left corrugator electromyogram **Follow-up**: Varied by individual study. The relevant primary study[29] had a follow-up of one week post-treatment.
Argolo et al. (2015)[17] Brazil **Funding source**: Support was received from the Brazilian National Council for Scientific and Technological Development (within the Brazilian federal government).	**Objective**: To examine the effectiveness of propranolol for the prevention of PTSD following exposure to a traumatic event. **Study design**: Systematic review and meta-analysis of clinical trials (randomized and non-randomized) and observational studies. **Literature search strategy**: Study authors searched for literature published up to November 2014 using PubMED tool (which searches MEDLINE database and additional references from the National Library of Medicine). Ongoing or cancelled clinical trials were searched using the ClinicalTrials.gov website. Additionally, reference lists of articles identified through database searches and bibliographies of systematic or	Adults (≥18 years of age) who had experienced a traumatic event.	**Intervention**: Propranolol administered following a traumatic event. **Comparators**: Placebo or no treatment.	**Outcomes assessed in relevant studies**: - PTSD incidence (according to *DSM* criteria or widely accepted and validated diagnostic tools [e.g., the CAPS, CIDI, PCL-C, PCL-M) **Follow-up**: Varied by individual study. Relevant studies ranged from two months[30] to eight months[26] post-treatment. The follow-up duration for one study[31] was unclear.

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	non-systematic review articles were examined for further relevant studies. **Number of studies included**: Five primary studies[24-26,30,31] were identified and included in both the qualitative and quantitative syntheses. These included three RCTs,[24-26] one non-randomized trial,[30] and one retrospective chart review.[31] All five were relevant to the current report. **Quality assessment tool**: The publication mentioned that primary study methods and biases were evaluated by the reviewers; however, there is no description of the tool or methods used for assessment.			
Sijbrandij et al. (2015)[18] Netherlands **Funding source**: No funding was received for the review.	**Objective**: To investigate the effectiveness of pharmacotherapies given within the first week following trauma to prevent PTSD or acute stress disorder. **Study design**: Systematic review and meta-analysis of RCTs, controlled clinical trials (i.e., non-randomized), and longitudinal cohort studies. **Literature search strategy**: Study authors searched for literature published up to May 6, 2013 using PubMed, PsycINFO, Embase, and the Cochrane database of randomized trials. The electronic searches were supplemented by hand searching of reference lists of four narrative reviews of pharmacological prevention of PTSD. **Number of studies included**: A total of 15 primary studies were included in the quantitative analysis (six[24-26,30,32,33] of which were relevant to the current report, including four RCTs[24-26,32] and two controlled clinical trials[30,33]). Only information from the relevant primary studies were extracted.	Individuals (of all ages) who experienced a traumatic event.	**Intervention**: Pharmacological interventions delivered within one week of a traumatic event. **Comparators**: Placebo or no pharmacologic treatment. Relevant primary studies compared propranolol to placebo (five studies[24-26,32,33]), or no treatment (one study[30])	**Outcomes assessed in relevant studies**: - PTSD incidence (measured with the CAPS, CAPS-CA, CIDI, PCL-C, clinical interview) - PTSD severity (measured with the CAPS or TOPs) - ASD incidence (measured with ASD clinical interview) **Follow-up**: Varied by individual study. Relevant studies ranged from less than one month[33] to eight months[26] post-treatment.

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Quality assessment tool: The validity of included RCTs was assessed using four criteria of the risk of bias assessment method developed by the Cochrane Collaboration. These included risks of bias due to sequence generation, allocation concealment, outcome assessor blinding, and the use of an intention to treat analysis. Controlled clinical trials were evaluated using the outcome assessor blinding and intention to treat criteria. In the case of cohort studies, only masked outcome assessment was rated.			

ASD = acute stress disorder; ASDS = Acute Stress Disorder Scale; CAPS = Clinician Administered PTSD Scale; CAPS-CA = Clinician Administered PTSD Scale for Children and Adolescents; CIDI = Comprehensive International Diagnostic Interview; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; MAGIC = Missouri Assessment of Genetics Interview for Children, PTSD Section; PCL-C = PTSD Checklist—civilian version; PCL-M = PTSD Checklist—military version; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; TOPs = Treatment Outcome PTSD scale.

Table 3: Characteristics of Included Primary Clinical Studies

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
Brunet et al. (2018)[19] Canada **Funding source**: Support was received from a US Army Congressionally Directed Medical Research	**Objective**: To assess the efficacy of trauma memory reactivation performed under the influence of propranolol versus placebo in reducing symptoms of PTSD. **Study design**: Single-centre, double-blinded RCT.	**Inclusion criteria**: Adults (≥18 and ≤65 years of age) who suffered from PTSD for at least six consecutive months and who had a PCL-S score ≥44 at time of recruitment. **Excluded**: Individuals with a basal systolic blood pressure <100 mm Hg, a basal heart rate <55 beats per minute, lifetime psychotic or bipolar disorder or traumatic brain injury, strong dissociative tendencies, current substance dependence, acute suicidal ideation, or who had medical conditions contraindicating propranolol use. Additionally,	**Intervention**: Propranolol (0.67 mg/kg of short acting propranolol plus 1.0 mg/kg of long-acting propranolol) administered prior to a brief memory reactivation session. **Comparator**: Placebo administered prior to a	**Clinical outcomes**: - PTSD severity (measured with the CAPS and PCL-S) **Follow-up**: Six months post-treatment.

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Program grant.	**Setting**: Participants were recruited via referrals and local advertisement to the McGill University's Douglas Institute in Montreal, Quebec. Assessment and testing were conducted at the Douglas Institute.	individuals who were pregnant, breastfeeding, or who were receiving evidence-based psychotherapy for PTSD during the treatment phase were excluded. **Number of participants**: 60 (30 in the propranolol group; 30 in the placebo group). **Mean age, years (SD)**: 37.0 (11.28) in the propranolol group; 41.8 (11.14) in the placebo group. **Sex**: 58.3% female. **Type of trauma**: Traumatic experiences included motor vehicle accidents (N = 7), physical assault (N = 16), sexual trauma (N = 19), combat, war zone, captivity (N = 6), life threatening illness or injury (N = 1), sudden unexpected death (N = 4), and other (N = 7). **Baseline PTSD severity**: Mean CAPS score of 76.07 (SD = 16.98) and PCL-S score of 61.18 (SD = 9.31) in the propranolol group; mean CAPS score of 71.04 (SD = 14.68) and PCL-S score of 56.96 (SD = 11.83) in the placebo group.	brief memory reactivation session.	
Mahabir et al. (2016)[20] Canada **Funding source**: Financial support was received from the Canadian Institutes of Health Research and from Fonds de recherché en santé Quebec.	**Objective**: To examine the acute effect of propranolol on cognitive performance in individuals with chronic PTSD. **Study design**: Single-centre, double-blinded RCT. **Setting**: Participants were recruited through advertisements to the	**Inclusion criteria**: Individuals who experienced traumatic events and were diagnosed with chronic PTSD. Those with a CAPS score of ≥ 50 points were eligible for the trial. **Excluded**: Individuals who were pregnant, diagnosed with bipolar disorder, who had a history of head injury, or who had medical conditions contraindicating propranolol use. **Number of participants**: 41 (20 in the propranolol group; 21 in the placebo group).	**Intervention**: Propranolol (short-acting; oral dose; 1 mg/kg) administered prior to script-driven traumatic imagery. **Comparator**: Placebo administered prior to script-driven traumatic imagery.	**Clinical outcomes**: - Heart rate - Blood pressure - PTSD severity (measured with IES-R) - Cognitive performance (measured with the WAIS-III) **Follow-up**: Seven days post-treatment.

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	PTSD Clinic at the Douglas Hospital in Montreal, Quebec. Assessment and testing were conducted in the clinic.	**Mean age, years (SD)**: 45.2 (10.7) in the propranolol group; 41.7 (12.5) in the placebo group. **Sex**: 73.2% female. **Type of trauma**: Traumatic experiences included accidents (N = 8), physical and sexual assaults (N = 27), combat exposure (N = 1), violent or unexpected deaths of close ones (N = 4), and other stressors (N = 1). **Baseline PTSD severity**: Mean CAPS score of 80.4 (SD = 23.3) and IES-R score of 87.8 (SD = 16.6) in the propranolol group; mean CAPS score of 78.3 (SD = 17.1) and IES-R score of 83.7 (SD = 11.4) in the placebo group.		
Orrey et al. (2015)[21] United States **Funding source**: The National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, the NC Jaycee Burn Center Fund, the Firefighters Research Fund, the DC Firefighters Burn Foundation, and UNC	**Objective**: To assess whether propranolol administration reduced pain severity (with PTSD incidence and severity as secondary outcomes) in patients hospitalized with major thermal burn who were not homozygous for the high activity COMT haplotype. **Study design**: Multi-centre, double-blinded RCT. **Setting**: All admitted burn patients at participating sites were screened using hospital electronic records. Potentially eligible patients	**Inclusion criteria**: Individuals admitted to participating burn centres within 72 hours of a thermal burn injury that involved ≤20% of total body surface area. All participants were required to be not homozygous for the high activity COMT haplotype (as measured with genotyping at rs4818). **Excluded**: Those with an estimated hospital stay <5 days or >40 days, intentional injury, substantial concomitant non-burn injury, and greater than first degree cardiac conduction blockage. Additionally, individuals who were already on β-adrenergic antagonist medication, were on opioid medications for chronic pain prior to their burn injury, were clinically unstable, were prisoners, whose highest pain score between admission and recruitment was <4 on the Numeric Rating Scale, or who had a history of asthma, diabetes, coronary artery disease, psychotic disorder, or hepatic, renal, or congestive heart failure were excluded.	**Intervention**: Propranolol (240 mg/day for three weeks followed by a 20 day taper). **Comparator**: Placebo.	**Clinical outcomes**: - Study feasibility (consent rate, protocol completion rate) - Acute pain scores (measured with the Numerical Rating Scale) - Opioid use during hospitalization - PTSD symptom severity (measured with the PSS-I) - PTSD incidence (based on PSS-I criteria) - Adverse events Note: Only information relating the PTSD

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Institutional Resources.	were approached and screened for enrollment within 48 hours of hospital admission. Participants were recruited between June 2009 and January 2011.	**Number of participants**: 43 (20 in the propranolol group; 23 in the placebo group). **Mean age, years (SD)**: 31 (9) in the propranolol group; 32 (10) in the placebo group. **Sex**: 20.9% female. **Type of trauma**: Major thermal burn injury. **Baseline PTSD severity**: Not reported (participants were not diagnosed with PTSD at baseline).		symptom severity, PTSD incidence, and adverse events were considered relevant to the current report. The findings from the remaining outcomes were not extracted. **Follow-up**: Six weeks post-injury.
Non-Randomized Studies				
Brunet et al. (2014)[22] Canada **Funding source**: Financial support was received from the Fonds de recherche du Quebec and the United States Army.	**Objective**: To assess physiological response of participants with PTSD during script-driven traumatic imagery following administration of propranolol. **Study design**: Single-centre non-randomized study. Results from a cohort of patients within the current study were compared to results from a previously published single-centre, placebo-controlled RCT.[29] **Setting**: Participants were recruited using newspaper advertisements to the Douglas Mental Health University Institute in	**Inclusion criteria**: Adults (≥18 and ≤65 years of age) with PTSD as assessed by a structured clinical interview. The inclusion criteria from the previous study[29] was not reported **Excluded**: Those with a systolic blood pressure <100 mm Hg, asthma, heart failure, heart block, certain cardiac arrhythmias, insulin-requiring diabetes, previous adverse reaction to a beta blocker, or who were on medications that could adversely interact with propranolol. Additionally, individuals who were pregnant, breastfeeding, had recovered memory of traumatic events, or who had a mean score of >20 on the Dissociative Experiences Scale were excluded. The exclusion criteria from the previous study[29] was not reported. **Number of participants**: 47 (28 in the propranolol group from the current study; 9 in the propranolol group from the previous study;[29] 10 in the placebo group from the previous study[29]).	**Intervention**: Six weekly sessions of propranolol (0.67 mg/kg of short acting propranolol plus 1.0 mg/kg of long-acting propranolol) administered prior to script-driven traumatic imagery (participants read an account of their traumatic event for 5 to 10 minutes). **Comparator**: Comparator groups were drawn from a previously published study.[29] The groups received one session of either propranolol (40 mg short-acting plus 60 mg long-acting) or	**Clinical outcomes**: - Skin conductance - Heart rate - Left corrugator electromyogram **Follow-up**: Four months after trial enrollment initiation (treatment lasted six weeks)

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Montreal, Quebec. Patients in the control group were from a previous study.[29]	**Mean age, years (SD)**: 37.9 (9.5) in the propranolol group from the current study; the mean age of patients in the control groups from the previous study[29] was not reported. **Sex**: 67.9% female in the propranolol group from the current study. The sex of patients in the control groups from the previous study[29] was not reported. **Type of trauma**: Traumatic experiences of those recruited for the current study included incest (N = 5), physical assault (N = 5), sexual abuse (N = 3), motor vehicle accidents (N = 3), participation in peacekeeping missions (N = 3), physical abuse in childhood (N = 3), assault with a weapon (N = 2), or other events (N = 4). **Baseline PTSD severity**: Not reported (all participants from the current study were diagnosed with PTSD at baseline).	placebo prior to script-driven imaginary exposure to traumatic event.	

CAPS = Clinician Administered PTSD Scale; COMT = catechol-*O*-methyltransferase; IES-R = Impact of Event Scale Revised; N = number of participants; PCL-S = PTSD Checklist—Specific; PSS-I = Post-traumatic Symptom Scale—Interview Version; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SD = standard deviation; WAIS-III = Wechsler Adult Intelligence Scale third edition.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[13]

Strengths	Limitations
Astill Wright et al. (2019)[15]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • The choice of included study designs (i.e., RCTs, including cluster and crossover trials) was explained • Multiple databases were searched (PubMed, PsycINFO, Embase, and CENTRAL). Additionally, reference lists of four narrative reviews of pharmacological prevention of PTSD were examined • Key search terms and publication restrictions were provided • Study selection, data extraction, and quality assessment processes were described and conducted in duplicate (disagreements were resolved through discussion and consensus) • A flow chart of study selection was provided • The review authors described the included primary studies in adequate detail • The risk of bias of included primary studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Statistical heterogeneity was assessed using the I^2 statistic • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (there was no funding received for this review)	• It was unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • A grey literature search was not completed • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on sources of funding for the included primary studies • There was no discussion on the possibility of publication bias • Relevant primary studies were conducted outside of Canada; the generalizability to the Canadian setting was unclear
Steenen et al. (2016)[16]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (PubMED, Ovid Embase, PsycINFO, Web of Science SCI-EXPANDED, and WHO ICTRP) • Key search terms and publication restrictions were provided • Study selection and quality assessment processes were described and conducted in duplicate (disagreements were resolved through discussion by discussion with a third person) • The process for data extraction was described (data extraction was conducted by one reviewer and verified by a second reviewer) • A flow chart of study selection was provided	• It was unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • The authors did not explain their selection of study designs for inclusion in the review (i.e., only comparative parallel group and crossover RCTs) • A grey literature search was not completed • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors stated that the source of funding of included primary studies was extracted from each trial; however, this information was not reported in the review • The country in which the relevant primary study was conducted was not described; the generalizability to the Canadian setting was unclear

Strengths	Limitations
• The review authors described the included primary studies in adequate detail • The risk of bias of included primary studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Statistical heterogeneity was assessed using the I^2 statistic • Publication bias was assessed using an inspection of trial registries (three RCTs that were terminated due to inadequate recruitment were identified) • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (there was no funding received for this review)	
Argolo et al. (2015)[17]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched using the PubMED tool (which searches the MEDLINE database and additional references from the National Library of Medicine). Ongoing or cancelled clinical trials were searched using the ClinicalTrials.gov website. Additionally, reference lists of articles identified through database searches and bibliographies of systematic or non-systematic review articles were examined for further relevant studies • Key search terms and publication restrictions were provided • Study selection, data extraction, and quality assessment processes were described and conducted in duplicate (disagreements were resolved through discussion and consensus) • A flow chart of study selection was provided • The review authors described the included primary studies in adequate detail • Appropriate methods for the statistical combination of results were used in the meta-analyses • Statistical heterogeneity was assessed using the I^2 statistic • Publication bias was assessed using visual inspection of funnel plots and Egger's test (none was detected) • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (support was received from the Brazilian National Council for Scientific and Technological Development) and was unlikely to have had an effect on the findings of the review	• It was unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • The authors did not explain their selection of study designs for inclusion in the review (i.e., clinical trials and observational studies) • A grey literature search was not completed • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on sources of funding for the included primary studies • Although the authors noted biases were evaluated by the reviewers, the technique for assessing the risk of bias in primary studies and the results of this assessment were not described • The risk of bias and limitations of primary study methodology were not adequately considered when discussing the results • The countries in which relevant primary studies were conducted were not described; the generalizability to the Canadian setting was unclear

Strengths	Limitations
Sijbrandij et al. (2015)[18]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • The choice of included study designs (i.e., RCTs, controlled clinical trials, and cohort studies) was explained • Multiple databases were searched (PubMed, PsycINFO, Embase, and the Cochrane database of randomized trials). Additionally, reference lists of four narrative reviews of pharmacological prevention of PTSD were examined • Key search terms and publication restrictions were provided • Study selection and quality assessment processes were described and conducted in duplicate (a third reviewer was available to arbitrate disagreements) • A flow chart of study selection was provided • The review authors described the included primary studies in adequate detail • The risk of bias of included primary studies was assessed using criteria of the risk of bias assessment method developed by the Cochrane Collaboration • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Statistical heterogeneity was assessed using the I^2 statistic • Publication bias was assessed using visual inspection of funnel plots and Egger's test (none was detected) • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (there was no funding received for this review)	• It was unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • A grey literature search was not completed • It was unclear if data extraction was done in duplicate • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on sources of funding for the included primary studies • Relevant primary studies were conducted outside of Canada; the generalizability to the Canadian setting was unclear

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; RCT = randomized controlled trial; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

Table 5: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[14]

Strengths	Limitations
Randomized Controlled Trials	
Brunet et al. (2018)[19]	
• The objectives, interventions, controls, and main outcomes were clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics (e.g., age, sex, type of trauma) were clearly described and were tested for statistically significant differences at baseline (there were no significant differences between treatment groups)	• The number of participants who did not complete the study per protocol was ≥ 10% (N = 30/60; 50.0%) and the characteristics of participants who withdrew from the study were not reported • No power calculation was performed

Strengths	Limitations
• Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • Adverse events relating to the use of propranolol were documented • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Study participants and outcome assessors were blinded to treatment assignment • The length of follow-up was consistent across treatment groups • Compliance with the assigned treatment was reliable • Participants in different treatment groups were recruited over the same period of time • The study was conducted in Montreal, Quebec; there should be relatively high generalizability to Canadian settings • The authors declared that they had no potential conflicts of interest • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study	
Mahabir et al. (2016)[20]	
• The objectives, interventions, controls, and main outcomes were clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics (e.g., age, sex, type of trauma) were clearly described and were tested for statistically significant differences at baseline (there were no significant differences between treatment groups) • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • No participants were lost to follow-up • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Study participants and outcome assessors were blinded to treatment assignment • The length of follow-up was consistent across treatment groups • Compliance with the assigned treatment was reliable • Participants in different treatment groups were recruited over the same period of time • The study was conducted in Montreal, Quebec; there should be relatively high generalizability to Canadian settings • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study	• Adverse events that may have been associated with the use of propranolol were not reported • No power calculation was performed • Conflicts of interest were not disclosed by the authors

Strengths	Limitations
Orrey et al. (2015)[21]	
• The objectives, interventions, controls, and main outcomes were clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics (e.g., age, sex, type of trauma) were clearly described and were tested for statistically significant differences at baseline (there were no significant differences between treatment groups) • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in graphic form and clearly described • Adverse events relating to the use of propranolol were documented • The number of participants who withdrew from the study was less than 10% (N = 4/47; 8.5%) • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Study participants and outcome assessors were blinded to treatment assignment • The length of follow-up was consistent across treatment groups • Compliance with the assigned treatment was reliable (initial doses were administered by a nurse and adherence following discharge was monitored using a medication monitoring system) • Participants in different treatment groups were recruited over the same period of time • The authors declared that they had no potential conflicts of interest • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study	• No power calculation was performed • The study was designed to measure study feasibility and pain severity as primary outcomes, rather than PTSD severity or incidence (outcomes relevant to the current report)
Non-Randomized Studies	
Brunet et al. (2014)[22]	
• The objectives, interventions, and main outcomes were clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics (e.g., age, sex, type of trauma) from those enrolled in the current study were clearly described • Actual probability values (P values) were reported • The major findings of the study were presented in graphic form and clearly described • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Compliance with the assigned treatment was reliable	• The characteristics of the patients in the control group were not described (e.g., age, sex, time since trauma, type of trauma); it was unclear how similar or dissimilar patients in the control groups were to those in the intervention group, increasing the risk for bias due to confounding • Effect sizes (Cohen's *d* values) were reported without 95% confidence intervals • Adverse events that may have been associated with the use of propranolol were not reported • The number of participants who were excluded from the analysis was ≥ 10% (N = 6/28; 21.4%) and the characteristics of participants who withdrew from the study were not reported • This was an open-label study with no blinding of study participants or outcome assessors

Strengths	Limitations
• The study was conducted in Montreal, Quebec; there should be relatively high generalizability to Canadian settings • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study	• The length of treatment and follow-up duration were not consistent between intervention groups • Intervention assignment was not done at random (all participants in the current trial received propranolol; findings from these participants were compared to those from a previous study[29]); therefore, a number of uncontrolled factors may have contributed to the findings of the study • Participants in different intervention groups were not recruited over the same period of time • No power calculation was performed • Conflicts of interest were not disclosed by the authors

N = number of participants.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Astill Wright et al. (2019)[15]</td></tr>
<tr><td>Systematic review and meta-analysis that investigated whether pharmacological interventions prevent PTSD or improve clinical outcomes in individuals (of all ages) who experienced a traumatic event compared to placebo or other active interventions. Outcomes of interest were severity of PTSD symptoms and incidence of PTSD.

Relevant primary studies: The systematic review included five relevant RCTs[24-28] that compared propranolol to placebo or standard therapy. The authors conducted several meta-analyses that pooled data from the five RCTs[24-28] relevant to the current report that could be extracted entirely.

Summary of relevant findings:
- <u>Adult populations</u>
• Low-quality evidence (as assessed by the authors of the systematic review using GRADE) indicated that there were no statistically significant differences in PTSD incidence between adults treated with propranolol or placebo at three to six month follow-up (RR [95% CI] = 0.75 [0.31 to 1.83]; participants = 96; 3 RCTs[24-26]; I^2 = 0%)
• Low-quality evidence (as assessed by the authors of the systematic review using GRADE) indicated that there were no statistically significant differences in severity of PTSD symptoms between adults treated with propranolol or placebo at three to six month follow-up (SMD [95% CI] = 0.06 [–0.49 to 0.61]; participants = 52; 2 RCTs[24,25]; I^2 = 0%)
- <u>Child and adolescent populations</u>
• Very low-quality evidence (as assessed by the authors of the systematic review using GRADE) indicated that there were no statistically significant differences in PTSD incidence between children treated with propranolol or placebo at follow-up between one month and seven years (RR [95% CI] = 0.48 [0.13 to 1.77]; participants = 217; 2 RCTs[27,28]; I^2 = not applicable)
• Very low-quality evidence (as assessed by the authors of the systematic review using GRADE) indicated that there were no statistically significant differences in severity of PTSD symptoms between children treated with propranolol and children treated with placebo at one to three month follow-up (SMD [95% CI] = 0.01 [–0.87 to 0.89]; participants = 20; 1 RCT[27]; I^2 = not applicable)</td><td>"This systematic review identified 19 RCTs with 16 included in the meta-analysis and found some evidence for the potential efficacy of hydrocortisone in the prevention of PTSD in adults. There was no evidence to support the efficacy of propranolol in terms of prevention of PTSD or ASD. Considering the paucity of evidence available, it remains difficult to draw firm conclusions on other agents, although no RCT was able to demonstrate an overall beneficial effect without sub-group analysis."[15] (p. 4)</td></tr>
<tr><td colspan="2">Steenen et al. (2016)[16]</td></tr>
<tr><td>Systematic review and meta-analysis regarding the clinical effectiveness of oral propranolol for the treatment of individuals with anxiety disorders (including PTSD) compared to placebo or other medications.

Relevant primary studies: The systematic review included one RCT[29] that compared propranolol versus placebo administered prior to script-driven imaginary exposure in participants with PTSD. Although the systematic review included meta-analyses, there was no meta-analysis specific to the primary study relevant to the current report. Therefore, the relevant results from this primary study are summarized narratively.
<table>
<tr><th>Primary study citation</th><th>Summary of relevant results</th><th>Statistical significance[a]</th></tr>
<tr><td colspan="3">Outcome: physiologic response</td></tr>
<tr><td>Brunet et al. (2008)[29]
(N = 19)</td><td>- Compared to placebo, participants who received propranolol one week prior to mental imagery of trauma had smaller overall physiological responses during mental imagery (P = 0.007)</td><td>S

S</td></tr>
</table>
</td><td>"The present systematic review was limited by the moderate number of small studies examining the effects of propranolol on anxiety disorders, and by the risk of bias these trials presented. Notably, the average loss to follow-up was nearly one-fifth of all participants. As withdrawal reasons were seldom reported, the possibility of selective loss to follow-up in some studies could not be</td></tr>
</table>

Main Study Findings			Authors' Conclusion
	- Heart rate and skin conductance were significantly smaller in the propranolol group during mental imagery (P = not reported) - There were no statistically significant between-group differences with respect to left corrugator electromyogram during mental imagery (P = not reported)	NS	ruled out. In conclusion, the quality of evidence for the efficacy of propranolol at present is insufficient to support the routine use of propranolol in the treatment of any of the anxiety disorders."[16] (p. 138)

[a]The threshold for statistical significance was set to P < 0.05.
N = number of participants; NS = non-significant; S = significant.

Argolo et al. (2015)[17]

Systematic review and meta-analysis that examined the effectiveness of propranolol for the prevention of PTSD in adults following exposure to a traumatic event.

Relevant primary studies: The systematic review included five relevant primary studies (three RCTs,[24-26] one non-randomized trial,[30] and one retrospective chart review[31]) that compared propranolol to placebo or no treatment. The relevant results from included primary studies were summarized narratively. Additionally, the review authors conducted a meta-analysis that pooled data from the five primary studies[24-28] relevant to the current report that could be extracted entirely.

Primary study citation	Summary of relevant results	Statistical significance[a]
Outcome: incidence of PTSD		
Hoge et al. (2012)[24] (N = 41)	- There were no significant differences between participants treated with propranolol or placebo with respect to incidence of PTSD (P = NR; as assessed with the CAPS)	NS
McGhee et al. (2009)[31] (N = 65)	- The incidence of PTSD, as measured with the PCL-M, was not significantly different between participants who received propranolol or those who did not receive propranolol (P = NR)	NS
Stein et al. (2007)[26] (N = 48)	- There were no significant differences between treatment with propranolol, gabapentin, or placebo with respect to incidence of PTSD (measured with the CIDI and PCL-C) one-, four-, or eight-months post-injury (P = NR)	NS
Vaiva et al. (2003)[30] (N = 19)	- There were no significant differences between participants treated with propranolol or no treatment with respect to incidence of PTSD at two-month follow-up (P = NR; method of measuring PTSD symptoms was NR in the systematic review)	NS
Pitman et al. (2002)[25] (N = 41)	- There were no significant differences between participants treated with propranolol or placebo with respect to incidence of PTSD (as assessed with the CAPS)	NS
Outcome: severity of PTSD symptoms		
Hoge et al. (2012)[24] (N = 41)	- There were no significant differences between participants treated with propranolol or placebo with respect to severity of PTSD symptoms (as assessed with the CAPS)	NS
Stein et al. (2007)[26] (N = 48)	- There were no significant differences between treatment with propranolol, gabapentin, or placebo with respect to severity of PTSD symptoms (measured with the CIDI and PCL-C) one-, four-, or eight-months post-injury (P = NR)	NS
Vaiva et al. (2003)[30] (N = 19)	- Compared to no treatment, participants who received propranolol reported significantly decreased severity of PTSD symptoms at two-month follow-up (P = 0.037; method of measuring PTSD symptoms was NR in the systematic review)	S

"The findings of this meta-analysis support the null hypothesis: propranolol treatment after the traumatic event probably does not reduce PTSD incidence. Results were consistent and heterogeneity is unlikely. However, studies included small sample sizes, which can preclude the detection of significant results. We believe future studies should focus on reducing the time between trauma and intervention, as well as achieving larger sample sizes and longer follow-up periods."[17] (p. 93)

Main Study Findings			Authors' Conclusion
Pitman et al. (2002)[25] (N = 41)	- There were no significant differences between participants treated with propranolol or placebo with respect to incidence of PTSD (P = NR; as assessed with the CAPS)	NS	
Outcome: physiologic response			
Hoge et al. (2012)[24] (N = 41)	- There were no significant differences between participants treated with propranolol or placebo with respect to physiological reactivity during script-driven traumatic imagery	NS	
Pitman et al. (2002)[25] (N = 41)	- During script-driven imagery performed 3 months post-treatment, 0/8 participants in the propranolol group and 8/14 participants in the placebo group showed a significantly elevated physiologic response (P = NR)	NR	

[a]The threshold for statistical significance was set to P < 0.05.
CAPS = clinician-administered PTSD scale; CIDI = Comprehensive International Diagnostic Interview; N = number of participants; NR = not reported; NS = non-significant; PCL-C = PTSD Checklist—civilian version; PCL-M = PTSD Checklist—military version PTSD = post-traumatic stress disorder; S = significant.
Note: Studies are presented in reverse chronological and alphabetical order.

Summary of relevant meta-analytic findings:
- A meta-analysis using data from the five included primary studies[24-26,30,31] suggested that treatment with propranolol did not result in statistically significant differences in the risk for PTSD diagnosis (RR [95% CI] = 0.92 [0.55 to 1.55]; participants = 202; 5 primary studies[24-26,30,31]; I^2 = 0%; P = 0.795) compared to control conditions (e.g., placebo, no treatment)

Sijbrandij et al. (2015)[18]	
Systematic review and meta-analysis that investigated the effectiveness of pharmacotherapies (including propranolol) given within the first week following trauma to prevent PTSD or acute stress disorder. **Relevant primary studies**: The systematic review included six relevant primary studies (four RCTs[24,25,26 ,32] and two non-randomized trials[30,33]) that compared propranolol to placebo or standard therapy. Although the systematic review included meta-analyses, there was no meta-analysis specific to the primary studies relevant to the current report. Therefore, the relevant results from these primary studies, as calculated by the authors of the systematic review, were summarized narratively. **Summary of relevant findings**: - Primary study citation: Hoge et al. (2012)[24] • Proportion of participants with PTSD at follow-up: ○ Propranolol group: 5/21 ○ Placebo group: 5/20 • IRR (95% CI) = 1.30 (0.34 to 4.97) • P = 0.70 - Primary study citation: Nugent et al. (2010)[32] • Proportion of participants with PTSD at follow-up: ○ Propranolol group: 1/12 ○ Placebo group: 0/14 • IRR (95% CI) = 3.46 (0.15 to 77.86) • P = 0.43 - Primary study citation: Sharp et al. (2010)[33] • Proportion of participants with ASD at follow-up: ○ Propranolol group: 10/127 ○ No treatment group: 12/237 • IRR (95% CI) = 1.56 (0.69 to 3.50) • P = 0.29 - Primary study citation: Stein et al. (2007)[26] • Proportion of participants with PTSD at follow-up:	"In summary, although no convincing evidence was found for the efficacy of all pharmacotherapies in the prevention of PTSD or ASD, hydrocortisone appeared to be beneficial in the prevention of PTSD. For future research, larger RCTs in various trauma samples, taking into account acceptability, side-effects, the timing of administration, and cost-effectiveness need to be done to determine whether hydrocortisone will have a role in the prevention of PTSD."[18] (p. 420)

Main Study Findings	Authors' Conclusion
○ Propranolol group: 3/12 ○ Placebo group: 14/16 • IRR (95% CI) = 1.00 (0.27 to 3.66) • P = 1.00 - Primary study citation: Vaiva et al. (2003)[30] • Proportion of participants with PTSD at follow-up: ○ Propranolol group: 1/11 ○ No treatment group: 3/8 • IRR (95% CI) = 0.24 (0.03 to 1.92) • P = 0.18 - Primary study citation: Pitman et al. (2002)[25] • Proportion of participants with PTSD at follow-up: ○ Propranolol group: 2/11 ○ Placebo group: 6/20 • IRR (95% CI) = 0.64 (0.10 to 4.27) • P = 0.65	

ASD = acute stress disorder; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; IRR = incidence risk ratio; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trials	
Brunet et al. (2018)[19]	
A single-centre, double-blinded RCT that compared severity of PTSD symptoms in individuals diagnosed with chronic PTSD following treatment with six weekly sessions of trauma memory reactivation performed under the influence of either propranolol (N = 30) or placebo (N = 30). **Summary of findings**: - Participants in the trauma reactivation and propranolol group reported statistically significant improvements in their severity of PTSD symptoms post-treatment compared to those who received trauma reactivation and placebo. - Intention-to-treat analysis (N = 30 for each group) • Mean CAPS score ○ Baseline ▪ Propranolol group (SD): 76.07 (16.98) ▪ Placebo group (SD): 71.04 (14.68) ○ Post-treatment ▪ Propranolol group (SD): 47.16 (25.36) ▪ Placebo group (SD): 53.69 (26.95) ▪ Adjusted (for baseline scores) between group difference (SE): 11.50 (5.24) ▪ P = 0.034 • Mean PCL-S score ○ Baseline ▪ Propranolol group (SD): 61.18 (9.31) ▪ Placebo group (SD): 56.96 (11.83) ○ Post-treatment ▪ Propranolol group (SD): 36.60 (18.46) ▪ Placebo group (SD): 51.20 (18.62) ▪ Adjusted (for baseline scores) between group difference (SE): 14.58 (3.30) ▪ P < 0.001	"Pre-reactivation propranolol, a treatment protocol suggested by reconsolidation theory, appears to be a novel and efficacious treatment for PTSD. Replication studies using a long-term follow-up in various trauma populations are required."[19] (p. 427)

Main Study Findings	Authors' Conclusion
- Per protocol analysis (N = 15 for each group) • Mean CAPS score ○ Baseline ▪ Propranolol group (SD): 74.87 (16.92) ▪ Placebo group (SD): 76.13 (12.86) ○ Post-treatment ▪ Propranolol group (SD): 48.00 (26.88) ▪ Placebo group (SD): 65.31 (19.06) ▪ Adjusted (for baseline scores) between group difference (SE): 16.30 (7.45) ▪ P = 0.037 • Mean PCL-S score ○ Baseline ▪ Propranolol group (SD): 61.73 (7.94) ▪ Placebo group (SD): 61.27 (8.79) ○ Post-treatment ▪ Propranolol group (SD): 38.07 (16.73) ▪ Placebo group (SD): 55.71 (13.79) ▪ Adjusted (for baseline scores) between group difference (SE): 16.74 (4.20) ▪ P < 0.001 - Side effects of treatment were reported in 10% (N = 6/60; 3 in each treatment arm) of study participants. Within the placebo group, the participants noted the following symptoms: 1) headache, 2) tiredness and dizziness, and 3) nausea. Within the propranolol group, the participants reported the following: 1) suicidal thoughts, 2) mild asthma, and 3) a decreased pulse (below 50 beats per minutes) and cold extremities. These six participants were excluded from further participation. The statistical significance of these findings was not reported.	
Mahabir et al. (2016)[20]	
A single-centre, double-blinded RCT that examined the acute effect of propranolol on cognitive performance in individuals with chronic PTSD. Participants were randomly assigned to receive propranolol (N = 20) or placebo (N = 21) prior to script-driven traumatic imagery. **Summary of findings**: - Outcome: vital sign changes • Compared to those who received placebo, patients given propranolol had significantly reduced heart rate, diastolic blood pressure, and systolic blood pressure • Heart rate (beats/minute) ○ Change from baseline ▪ Propranolol group (SD): –14.5 (5.8) ▪ Placebo group (SD): –5.5 (6.5) ▪ P = 0.0001 • Systolic blood pressure (mm Hg) ○ Change from baseline ▪ Propranolol group (SD): –7.5 (9.9) ▪ Placebo group (SD): 2.1 (13.0) ▪ P = 0.017 • Diastolic blood pressure (mm Hg) ○ Change from baseline ▪ Propranolol group (SD): –5.0 (8.1) ▪ Placebo group (SD): 2.2 (7.4) ▪ P = 0.014 - Outcome: severity of PTSD symptoms • There were no statistically significant differences in severity of PTSD symptoms (measured with the IES-R) post-treatment between those who received propranolol and those who received placebo	"In summary, stress-related noradrenergic system dysfunction has been associated with cognitive impairments in various psychiatric illnesses (Berridge and Waterhouse, 2003). The results of this preliminary study indicate that propranolol enhanced [processing speed] performance in chronic PTSD patients. These results underscore the importance of examining emotional and cognitive processes during PTSD treatment. Future studies should examine propranolol's potential use as an adjunct to cognitive therapeutic approaches for PTSD." [20] (p. 102)

Main Study Findings	Authors' Conclusion

• IES-R score
  ○ Change from baseline
  ▪ Propranolol group (SD): –11.9 (16.9)
  ▪ Placebo group (SD): –10.4 (13.4)
  ▪ P = 0.75
- <u>Outcome: cognitive performance</u>
• Compared to those who received placebo, patients given propranolol had significantly better scores for some (but not all) subtest components of the WAIS-III (i.e., the Symbol search subtest and the Processing speed total scaled score)
• Mean WAIS-III subtest scores
  ○ Verbal comprehension, vocabulary
  ▪ Propranolol group (SD): 9.46 (2.44)
  ▪ Placebo group (SD): 9.52 (2.67)
  ▪ P = non-significant
  ○ Verbal comprehension, information
  ▪ Propranolol group (SD): 9.61 (3.57)
  ▪ Placebo group (SD): 10.46 (1.81)
  ▪ P = non-significant
  ○ Verbal comprehension, total scaled score
  ▪ Propranolol group (SD): 31.08 (5.90)
  ▪ Placebo group (SD): 29.58 (5.62)
  ▪ P = 0.47
  ○ Perceptual organization, block design
  ▪ Propranolol group (SD): 9.50 (3.05)
  ▪ Placebo group (SD): 9.81 (3.42)
  ▪ P = non-significant
  ○ Perceptual organization, matrix reasoning
  ▪ Propranolol group (SD): 11.37 (3.63)
  ▪ Placebo group (SD): 10.17 (3.62)
  ▪ P = non-significant
  ○ Perceptual organization, total scaled score
  ▪ Propranolol group (SD): 20.88 (5.78)
  ▪ Placebo group (SD): 20.13 (6.58)
  ▪ P = 0.73
  ○ Working memory, digit span
  ▪ Propranolol group (SD): 9.56 (3.24)
  ▪ Placebo group (SD): 8.38 (2.25)
  ▪ P = non-significant
  ○ Working memory, arithmetic
  ▪ Propranolol group (SD): 8.71 (3.53)
  ▪ Placebo group (SD): 8.47 (2.69)
  ▪ P = non-significant
  ○ Working memory, total scaled score
  ▪ Propranolol group (SD): 18.23 (6.15)
  ▪ Placebo group (SD): 16.00 (4.18)
  ▪ P = 0.29
  ○ Processing speed, digit symbol
  ▪ Propranolol group (SD): 10.25 (3.87)
  ▪ Placebo group (SD): 9.11 (2.86)
  ▪ P = non-significant
  ○ Processing speed, symbol search
  ▪ Propranolol group (SD): 13.00 (2.64)
  ▪ Placebo group (SD): 8.53 (3.95)
  ▪ P = 0.004
  ○ Processing speed, total scaled score	

Main Study Findings	Authors' Conclusion
▪ Propranolol group (SD): 23.40 (6.26) ▪ Placebo group (SD): 17.69 (4.76) ▪ P = 0.021	
Orrey et al. (2015)[21]	
A multi-centre, double-blinded RCT that assessed the clinical effectiveness of propranolol (N = 20) in patients hospitalized with major thermal burn compared to placebo (N = 23). The outcomes of interest were study feasibility (consent rate, protocol completion rate), acute pain, opioid use during hospitalization, PTSD symptom severity, PTSD incidence, and adverse events; however, only outcomes relating to PTSD and adverse events were considered relevant to the current report. The findings from the remaining outcomes were not extracted. **Summary of findings**: - Outcome: severity of PTSD symptoms • There were no statistically significant differences in severity of PTSD symptoms (measured with the PSS-I) post-treatment between those who received propranolol and those who received placebo • Mean PSS-I score ○ Change from baseline ▪ Propranolol group (SD): –8.1 (11.4) ▪ Placebo group (SD): –10.7 (13.1) ▪ P = 0.51 - Outcome: incidence of PTSD • There were no statistically significant differences in the proportion of participants who met the diagnostic criteria for PTSD post-treatment between those who received propranolol and those who received placebo • Number of participants who met the diagnostic criteria for PTSD (based on PSS-I criteria) ○ Propranolol group: 3/17 (19%) ○ Placebo group: 6/22 (27%) ○ P = 0.71 - Outcome: adverse events • There were no statistically significant differences in the number of patients reporting adverse events between the propranolol and placebo groups • Number of participants who reported any side effect ○ Propranolol group: 15/20 ○ Placebo group: 13/23 ○ P = non-significant • Number of participants who reported more than one side effect ○ Propranolol group: 9/20 ○ Placebo group: 9/23 ○ P = non-significant	"In conclusion, our study results indicate that genotype-based randomized controlled trials of patients with major thermal burn injury are feasible, and that propranolol is unlikely to be a useful adjunct to reducing pain during the first months after injury among the population of burn patients selected for this study. Further studies are needed to better understand mechanisms of post-burn pain and to continue to test interventions to reduce the suffering of patients with major thermal burn injury."[21] (p. 12)
Non-Randomized Studies	
Brunet et al. (2014)[22]	
Single-centre non-randomized study that investigated the physiological response of adults (≥18 and ≤65 years of age) with PTSD during script-driven traumatic imagery following administration of propranolol (N = 22). The results from the current study were compared with the results from participants who received propranolol (N = 9) or placebo (N = 10) from a previously published trial.[29] **Summary of findings**: - Outcome: physiological response • There were significant between-group differences for skin conductance (P < 0.001) and heart rate (P < 0.05) post-treatment (i.e., participants who received placebo had	"Though findings from our study suggest the promise of a new effective treatment for PTSD, it is important to interpret results in light of the limitations described above, particularly concerning the varying

Main Study Findings	Authors' Conclusion
significantly increased heart rate and skin conductance compared to the propranolol groups). There were no significant between-group differences for electromyogram (P = 0.48) post-treatment • Compared to the placebo group from the previously published trial,[29] participants in the current trial who received propranolol had significantly reduced skin conductance (Cohen's *d* = –1.56) and heart rate (Cohen's *d* = –1.07)	treatment dosage of propranolol across groups and the absence of randomization. Therefore, caution should be exercised in the interpretation of results. Nonetheless, results clearly point to the need for further exploration of the clinical utility of traumatic memory reactivation under the influence of propranolol as a treatment for PTSD."[22] (p. 231)

CAPS = Clinician Administered PTSD Scale; IES-R = Impact of Event Scale Revised; N = number of participants; PCL-S = PTSD Checklist—Specific; PSS-I = Post-traumatic Symptom Scale—Interview Version; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SD = standard deviation; WAIS-III = Wechsler Adult Intelligence Scale third edition.

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Relevant Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation			
	Astill Wright et al. (2019)[15]	Steenen et al. (2016)[16]	Argolo et al. (2015)[17]	Sijbrandij et al. (2015)[18]
Brunet et al. (2008)[29]		X		
Hoge et al. (2012)[24]	X		X	X
McGhee et al. (2009)[31]			X	
Nugent (2007)[27] and Nugent et al. (2010)[32]	X			X
Pitman et al. (2002)[25]	X		X	X
Rosenberg et al. (2018)[28]	X			
Sharp et al. (2010)[33]				X
Stein et al. (2007)[26]	X		X	X
Vaiva et al. (2003)[30]			X	X

X = the primary study was included in the systematic review and relevant data were extracted for the current review.

Notes: The study populations for the Rosenberg et al (2018)[28] and Sharp et al. (2010)[33] studies were the same; however, the two studies reported on different outcomes (PTSD incidence and acute stress disorder incidence, respectively) and at different follow-up periods. As a result, the findings from each study were discussed separately. The Nugent (2007) and Nugent et al. (2010) studies describe the findings of the same RCT. The Astill Wright et al. (2019)[15] systematic review included the Nugent (2007)[27] publication, which was a dissertation submitted to Kent State University, while the Sijbrandij,et al. (2017)[18] systematic review referenced the 2010 report[32] published in the *Journal of Traumatic Stress*.

Appendix 6: Additional References of Potential Interest

Previous CADTH Reports

Treatment for post-traumatic stress disorder, operational stress injury, or critical incident stress: a summary of clinical practice guidelines. Ottawa (ON) CADTH: 2016: https://www.cadth.ca/tools/treatment-post-traumatic-stress-disorder-operational-stress-injury-or-critical-incident-stress. Accessed 2020 Feb 18

Treatment for post-traumatic stress disorder, operational stress injury, or critical incident stress: a review of guidelines. (*CADTH Rapid response: summary with critical appraisal*). Ottawa (ON) CADTH: 2015: https://www.cadth.ca/treatment-post-traumatic-stress-disorder-operational-stress-injury-or-critical-incident-stress. Accessed 2020 Feb 18

Systematic Reviews and Meta-Analyses — Protocols

Bertolini F, Robertson L, Ostuzzi G, Meader N, Bisson JI, Churchill R, Barbui C. Early pharmacological interventions for preventing post-traumatic stress disorder (PTSD): a network meta-analysis. *Cochrane Database Syst Rev.* 2019, Issue 10. Art. No.: CD013443. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013443/full. Accessed 2020 Mar 17

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Forbes D, Pedlar D, Adler AB, et al. Treatment of military-related post-traumatic stress disorder: challenges, innovations, and the way forward. *Int Rev Psychiatry.* 2019 Feb;31(1):95-110.
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National Center for PTSD. Medication-Assisted Psychotherapy for PTSD. *PTSD Research Quarterly.* 2019. https://www.ptsd.va.gov/publications/rq_docs/V30N3.pdf. Accessed 2020 Mar 17

Giustino TF, Fitzgerald PJ, Maren S. Revisiting propranolol and PTSD: Memory erasure or extinction enhancement? *Neurobiol Learn Mem*. 2016 Apr;130:26-33.
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Gardner AJ, Griffiths J. Propranolol, post-traumatic stress disorder, and intensive care: incorporating new advances in psychiatry into the ICU. *Crit Care*. 2014 Dec 19;18(6):698.
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Hruska B, Cullen PK, Delahanty DL. Pharmacological modulation of acute trauma memories to prevent PTSD: considerations from a developmental perspective. *Neurobiol Learn Mem*. 2014 Jul;112:122-129.
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