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Student No	21311585
Module Title	Systematic Review of Evidence to Inform Professional Practice
Module Code	NS70163W/Z
Attempt	1st [X] 2nd [ ]
Programme	MSc Advancing Professional Practice
Branch (If Applicable)	
Intake	Sept 2022 Group
Tutor	Catherine Lynch
Word Count	**1 5 3 5 5** Due Date 2 8 0 6 2 3
Extension Agreed	Yes [ ] No [ ] (*If YES provide Reference Number below*)
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Dissertation for the Degree of MSc Advancing Professional Practice

College of Nursing, Midwifery and Healthcare

University of West London

June 2023

THE EFFECTIVENESS OF ALTERNATE ANTIPSYCHOTIC MEDICATION IN REDUCING VIOLENT AND AGGRESSIVE BEHAVIOURS IN ADULTS WITH MENTAL HEALTH DISORDERS COMPARED TO CLOZAPINE: A SYSTEMATIC REVIEW.

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ABSTRACT

Background: The majority of individuals with a diagnosed mental illness are not violent and aggressive. Nevertheless, there is an increased risk of such behaviours. Clozapine is an antipsychotic medication shown to be effective in reducing violence and aggression in adults with a mental illness; however, there are significant physical health side effects and financial implications of its use. Other antipsychotic medications are less physically detrimental and considerably cheaper. A previous systematic review recommended further research following inconclusive results.

Methods: Inclusion/exclusion criteria were developed using the PICO tool and search terms created. 160 studies were identified from a systematic search of five databases. Following screening, five studies were selected for critical appraisal and data extraction. Due to heterogeneity amongst the studies, a narrative analysis was conducted.

Findings: All five studies were included following critical appraisal and subject to the narrative analysis. Three synthesised findings were subsequently developed.

Conclusions: Clozapine is more effective than other antipsychotic medications in reducing violence and aggression in adults with diagnosed psychotic illnesses, particularly within inpatient settings, or when the individual has a history of conduct disorder or is experiencing high levels of depression. However, olanzapine is equally as effective when the individual is highly impulsive, and comparative effectiveness within in the community is inconclusive. Further research is recommended.

CHAPTER ONE: BACKGROUND

1.1 INTRODUCTION

The majority of individuals diagnosed with a mental health disorder do not display violent and aggressive behaviours; however, there is nevertheless an increased risk of such behaviours occurring within this population subgroup (Labrum et al., 2021, Whiting et al., 2021), which can lead to negative psychological and physical consequences for both the diagnosed patient and the nursing staff who are caring for them (e.g. van Leeuwen and Harte, 2017; Olashore et al., 2018; Jenkin et al., 2022). This chapter will provide a detailed background on the perception, risk, and impact of violent and aggressive behaviours displayed by individuals with diagnosed mental health disorders, and discuss the advantages and disadvantages of clozapine, an antipsychotic medication often prescribed for those exhibiting such symptomology. The rationale for the systematic review of evidence will be considered, and the aims of the review will be specified. Finally, the research question will be stated.

1.2 BACKGROUND

There is considerable misperception regarding the levels and frequency of violence and aggression perpetrated by individuals diagnosed with a mental illness, with the general public assuming that such behaviours occur at a significantly higher rate than the reality (Reavley et al., 2016; Pescosolido et al., 2019; Pescosolido et al., 2021). This can be partially attributed to high-profile, alarmist and sensationalist media reporting during the rare occasions when violent crimes have been committed by such individuals, which creates an over-association between mental illness and violent behaviour (McGinty et al., 2013; Chen and Lawrie, 2017; Gwarjanski and Parrott, 2018; Delahunt-Smoleniec and Smith-Merry, 2020). Consequently, this has contributed to increased stigmatisation and negative public perceptions of individuals

with a mental health condition, despite the majority of those with a mental disorder not committing violence or exhibiting aggressive behaviours; the population subgroup being significantly more likely to be the victims of violence and aggression than perpetrators; and the majority of violent crimes being perpetrated by persons without a mental illness (Iozzino et al., 2015; Reavley et al., 2016; Sariaslan et al., 2020; Battaglia et al., 2022; Girgis et al., 2023).

Whilst the risk of violence from individuals with a mental illness is overestimated and overreported, this does not mean, however, that there is no risk at all. Studies suggest that there is a low-to-modest risk of violence and aggression from those with a serious mental illness compared to the general population (Labrum et al., 2021, Whiting et al., 2021). Within psychiatric inpatient environments, staff are at a significantly high risk of violence and aggression from patients, causing physical and psychological injuries, increasing staff burnout, stress, and turnover, and negatively affecting their job satisfaction and quality of life (Zeng et al., 2013; Baby et al., 2014; Itzhaki et al., 2015; Ridenour et al., 2015; Choi and Lee, 2017; Llor-Esteban et al., 2017; van Leeuwen and Harte, 2017; Olashore et al., 2018; Jenkin et al., 2022). Additional negative consequences of violence within psychiatric units for patients include the use of seclusion, enforced medication and restraint, which can negatively affect the mental wellbeing of patients, lengthen admission times, and require increased staff input, which in turn can also increase the financial costs for inpatient units and reduce the quality of patient care (Volavka, 2013; Fugger et al., 2017; d'Ettorre and Pellicani, 2017; Guzmán-Parra et al., 2018; Chieze et al., 2019; Hassiotis et al., 2022). Furthermore, violent and aggressive behaviours displayed whilst in the community can lead to hospital recall, additional convictions, and reinforcement of the misperception that everyone with a mental illness is dangerous (Swanson et al., 2015;

Clarke et al., 2018; Jewell et al., 2018). In order to safely manage and mitigate violence and aggression being displayed by individuals with a mental illness, effective treatments, such as psychological and pharmacological interventions, must be employed (Ose et al., 2017). One intervention shown to be effective for such presentations is clozapine (Brown et al., 2014; Quinn and Kolla, 2017; Patchan et al., 2018; Cavaliere et al., 2022).

Clozapine is a second-generation antipsychotic medication indicated for adults with treatment-resistant schizophrenia (National Institute for Health and Care Excellence (NICE), 2015; 2022a); however, it is also an effective medication for other mental health conditions, including antisocial personality disorder, borderline personality disorder, and treatment-resistant bipolar disorder (Brown et al., 2014; Beri and Boydell, 2014; Li et al., 2014). Although clozapine is an effective pharmacological treatment for various mental illnesses, with its use reducing mortality rates, self-harm behaviours, and symptomology (Siskind et al., 2016; Wimberley et al., 2017; Cho et al., 2018), consideration must nevertheless be given to concerns associated with its use.

Whilst there is a risk of side-effects with all medications, including antipsychotic medications, the potential negative physical health consequences of clozapine are significant and serious, and can include low white blood cell count, which can increase the risk of developing infections; illnesses affecting the heart, lungs, and digestive system; low blood pressure and glucose levels; metabolic syndrome; seizures; and weight gain (Ballon et al., 2018; Yuen et al., 2018; Iqbal et al., 2020; Gürcan et al., 2021; Yuen et al., 2021). Consequently, unlike those prescribed other antipsychotic medication, individuals prescribed clozapine must be registered on a national

database and undertake frequent, mandatory physical health monitoring due to the significant physical health risks (NICE, 2021; Ninomiya et al., 2021). Moreover, NICE (2021) guidelines stipulate that if the physical health monitoring highlights any significant concerns, such a low white blood cell count, clozapine usage must be stopped immediately, even if this will have a detrimental impact on the individual's mental health (Ninomiya et al., 2021).

Compared to other common antipsychotic medications, clozapine is also significantly more expensive (see Table 1). This is presently of particular pertinence, considering a predicted increase of nearly two million new mental health referrals to the National Health Service (NHS) by 2024 (The Strategy Unit, 2020; Patel et al., 2021), the significant difference between the amount of funding estimated to be required to maintain and expand mental health services within the UK and the amount of funding announced by the British government (HM Treasury, 2020; The Strategy Unit, 2020), and the financial impact of the coronavirus pandemic on the NHS (HM Treasury, 2020; Patel et al., 2021).

Table 1. Cheapest Indicative Cost per Maximum Oral Dose of Antipsychotic Medications when Indicated for Psychotic Disorders in Adults in the United Kingdom

Medication	Maximum Oral Dose	Cheapest Indicative Cost	References
Clozapine	900mg	£6.73	NICE, 2022a; NICE, 2022b
Olanzapine	20mg	8p	NICE, 2022c; NICE, 2022d
Quetiapine (Immediate Release)	750mg	17p	NICE, 2022e; NICE, 2022f
Quetiapine (Modified Release)	800mg	£1.50	NICE, 2022e; NICE, 2022f
Risperidone	16mg	11p	NICE, 2022g; NICE, 2022h

1.3 REVIEW RATIONALE

Nursing and Midwifery Council (NMC) (2018a) guidelines state that registered nurses should use research findings to demonstrate best nursing practice, share information, and make evidence-informed decisions. Registered nurses must also contribute their knowledge within a multidisciplinary team (MDT), have an understanding of pharmacology which can be applied to patient care, and advocate on behalf of patients. Additionally, registered nurses should aim to improve safety and the quality of patient care.

Considering the unique requirement for regular physical health monitoring, the potential for inducing significant physical health side effects, and the financial implications of clozapine, it is therefore important to establish whether other, less expensive antipsychotic medications, which have lower risks of serious physical health consequences, are equally as, or more, effective as clozapine in managing violent and aggressive behaviours displayed by individuals with a mental health disorder.

A previous systematic review investigating this question found mixed evidence and recommended that further research was conducted in this area (Frogley et al., 2012). This systematic review was published over a decade ago, and more current studies within this subject area that have been published since Frogley et al.'s (2012) investigation do not appear to have been systematically reviewed, suggesting that an up-to-date systematic review within this area is required. An updated systematic review in this subject area will therefore help to advance professional nursing practice by improving the abilities of registered nurses to provide up-to-date pharmacological information to patients with a diagnosed mental health disorder who display violence and aggression. Moreover, the conclusions of this review will enable registered nurses to better advocate for patients who exhibit violent and aggressive behaviours and

contribute to MDT discussions regarding antipsychotic medications, ensuring that decisions regarding pharmacological treatment are safe, evidence-based, and in the best interests of the patient.

1.4 REVIEW AIMS AND RESEARCH QUESTION

This systematic review of effectiveness aims to establish whether alternate antipsychotic medications are an effective intervention for reducing violence and aggression in adults with mental health disorders compared to Clozapine through systematic identification and evaluation of the literature. The review also aims to update Frogley et al.'s (2012) findings, address the current gap in the research literature, and advance professional nursing practice. The aims of the systematic review will consequently be investigated through the research question *"Are other antipsychotic medications an effective intervention for reducing violence and aggression in adults with mental health disorders compared to clozapine?"*

1.5 CONCLUSION

Clozapine is an antipsychotic medication which has been shown to be an effective pharmacological treatment for violence and aggression in adults with a multitude of mental health disorders; however, there are physical health, practical, and financial concerns with its use. An up-to-date systematic review of the literature is therefore aimed to ascertain whether less expensive, and less physically detrimental, antipsychotic medication are suitable alternatives to clozapine for anti-aggressiveness in adults with mental health disorders. This research is also aimed to contribute to the advancement of professional nursing practice through increasing the abilities of registered nurses working with mental health patients displaying violent and

aggressive behaviours to provide up-to-date, evidence-based information to patients and contribute to safe multidisciplinary patient-centred care.

CHAPTER TWO: METHODS

2.1 INTRODUCTION

This chapter will discuss the research methods used to conduct the systematic review. The ethical considerations for undertaking a systematic review will be briefly highlighted, and the previous completion of a systematic review research protocol will be noted. The ontological, epistemological, and methodological perspectives of this review will then be discussed, and the structured and evidence-based decision-making process for the development of inclusion criteria and search terms will be explained. Additionally, the search strategy will be justified, and the study selection process will be described. The critical appraisal and data extraction of the screened literature will also be specified. Finally, the data synthesis process will be detailed.

2.2 ETHICAL CONSIDERATIONS

Systematic reviews are a form of secondary research. They do not require recruitment of participants or the collection of raw data, but instead utilise previously gathered data which has already been anonymised and analysed; systematic review researchers having no access to the original raw data. Subsequently, typical ethical issues regarding risks to participants, individual participant data considerations, and consent are not applicable prior to the commencement of a systematic review (Wormald and Evans, 2018; Suri, 2020). Despite the research investigating incidences of patient violence and aggression, due to the secondary nature of the data collection, there were no concerns regarding the compromise of patient and public safety as a result of the systematic review being conducting, upholding the NMC (2018b) standard of preserving safety. All data and findings were collected, treated and stored appropriately, in line with the NMC (2018b) Code of Practice.

2.3 RESEARCH PROTOCOL

Research protocols are detailed plans for prospective systematic reviews which describe the intended hypothesis, rationale, and methodology of the future study (Moher et al., 2015). Research protocols facilitate the planning and completion of systematic reviews, and can aid the reduction in bias and arbitrary decision-making by the researcher (Moher et al., 2015; Shamseer et al., 2015; Hutton et al., 2017). A research protocol was completed for this systematic review as part of a previous academic module. No changes to the research question or planned research strategy have been made since submission of this protocol.

2.4 RESEARCH DESIGN

The ontological, epistemological, and methodological perspectives of research determine the methods through which the research is conducted, and therefore must be considered in relation to the research question and the aims of the study.

Ontology is a philosophical concept that is concerned with the nature of reality (Slevitch, 2011). The ontological position of realism considers that there is an objective reality, independent of the researcher, which can be discovered (Scotland, 2012; Everest, 2014). In contrast, the ontological perspective of relativism views reality as being subjective and unique to each individual (Scotland, 2012). As the research question aims to establish the objective reality of the comparative effects of different antipsychotic medications on violent and aggressive behaviours, rather than the subjective experiences of the participants, this systematic review therefore takes a realist perspective.

Epistemology is how reality can be known by those researching it (Alharahsheh and Pius, 2020). Within healthcare research, there are three main epistemological

paradigms – positivism, interpretivism, and pragmatism (Everest, 2014). Positivism concerns researchers being objective from that which they are researching, with positivist findings being factual, value-free, and descriptive (Scotland, 2012). In contrast, interpretivism is concerned with subjective perspectives and is not value-free; interpretivism considers influences, such as social realities, culture, and circumstance, to add richness to researched insight into reality (Alharahsheh and Pius, 2020). The third paradigm often used within healthcare research, pragmatism, suggests that researchers must interact with the world in which they are researching, and that experiments cannot exist in isolation from the human experience (Everest, 2014); pragmatism can be considered a bridge between positivism and interpretivism. As the systematic review is investigating value-free facts regarding violence and aggression, rather than subjective perspectives, and the researcher is objectively approaching the data, rather than interacting directly with the research or the participants, a positivist epistemological perspective was therefore the most appropriate to adopt during this systematic review.

Finally, the methodological position of research is developed as a consequence of its ontological and epistemological perspectives. Consequently, as objectivity is a concept at the core of positivism and realism, the methodological perspective which must be taken for this systematic review is therefore quantitative. This methodology enables reality to be objectively studied and understood through facts, in contrast to qualitative methodology, which concerns itself with exploring the subjective experience of individuals, which would be more appropriate for relativism and interpretivism (Slevitch, 2011; Everest, 2014).

2.5 INCLUSION CRITERIA

To identify appropriate studies which would enable the researcher to answer the research question, inclusion and exclusion criteria needed to be determined. The patient, intervention, comparison, outcome (PICO) tool is a well-established model recommended for use in the development of search criteria for systematic reviews, particularly those involving interventions, and is frequently used within nursing academia (Methley et al., 2014; McKenzie et al., 2019; Schiavenato and Chu, 2021). Subsequently, the PICO model was used to guide the development of the search strategy for this systematic review (see summary in Table 2).

Table 2. Summary of Eligibility Criteria

	Inclusion	Exclusion
Population	• Adults (aged 18+) • Diagnosed mental health disorder • Violent and/or aggressive behaviours	• Children (0-17) • Animal studies • No diagnosed mental health disorder • No violent and/or aggressive behaviours
Intervention	• At least one non-Clozapine antipsychotic medication	• Only Clozapine used • No antipsychotic medication
Comparison	• Clozapine	• No use of Clozapine
Outcome	• Violence and/or aggression must be measured	• No measure of violence and/or aggression
Study Design	• Primary research • English language • Published in or since April 2011 • Outpatient or inpatient studies • Any duration • Quantitative studies	• Secondary research • Non-English language • Published prior to April 2011 • Qualitative studies

Population

Relevant literature was considered to be primary research whose participants were adults, aged 18 and above of any gender and ethnicity, with a diagnosed mental health disorder. Research involving children aged 17 and below were excluded, as the frequency, types, and understanding of violence varies between adults and children (e.g. Lussier and Blokland, 2014; Sumner et al., 2015; Bushman et al., 2016). Furthermore, although there has been progress in the use of animal models to understand psychiatric illnesses in terms of structural and molecular changes to the brain, animals cannot communicate to confirm that their psychiatric symptomology exists or is accurate to the experiences of humans (Canetta and Kellendonk, 2018; Winship et al., 2018). Animal studies were consequently excluded in order to improve the validity of the systematic review.

Although antipsychotic medications are mainly prescribed for psychotic illnesses, studies were not limited to those which included only participants diagnosed with psychotic disorders, as clozapine has been shown to have anti-aggressive effects in individuals with other mental illnesses (e.g. Brown et al., 2014).

Intervention and Comparison

Studies must have involved Clozapine and at least one other antipsychotic medication, as the reviewed comparator and intervention, respectively, in order to be considered for inclusion in the systematic review. Research which did not include the use of Clozapine, or only involved Clozapine without a comparison to another antipsychotic medication, was therefore excluded.

Outcome

Participants must have displayed aggressive and/or violent behaviours prior to the commencement of the applicable primary research, in order to accurately review what, if any, effect clozapine, or other antipsychotic medications, had on such behaviours. Additionally, in order to appropriately address the research question, the studies must have included post-intervention measure of violence and aggression. There are numerous methods of measuring violence and aggression, including self-report measures, observational studies, laboratory experiments, interviews, assessment tools, and projective studies (Ravyts et al., 2021), and the selection of the most appropriate can vary depending on the nature, location, and duration of studies; the systematic review therefore did not limit the measures of violence and aggression used in order to encapsulate all relevant studies on the subject matter.

Additional Study Design Considerations

Outpatient and inpatient studies were both included, and exclusion criteria based on study duration was not applied, in line with Frogley et al.'s (2012) systematic review. As Frogley et al.'s (2012) research reviewed articles published in or before March 2011, the current systematic review only included quantitative primary research which have been conducted since April 2011. Qualitative studies were excluded, as this form of research does not contain empirical data which can be used to accurately measure effectiveness, nor does it match the methodological perspective of the research, and so was not considered appropriate for the review question (Porrit et al., 2014;

Hammarberg et al., 2016). Finally, due to the reviewer being a monolingual English speaker, articles were required to have been published in English.

2.6 SEARCH TERMS

Search terms were identified, and search strings of terms developed, in order to screen for literature that was appropriate for answering the research question (see Table 3). As research in which clozapine, as an umbrella term, had been used as a comparator needed to be identified for the systematic review, a search string of terms incorporating different brand names of clozapine was developed. Due to the vast number of alternate antipsychotic medications, both in terms of brand and generic names, it was considered that manual screening of the sourced literature for the use of alternate antipsychotics would be more appropriate to encapsulate all alternative antipsychotic medications interventions used, rather than limiting results through the use of specific search terms for this criterion.

It was not considered necessary to develop a search string for psychiatric illness terminology, as the review was not limited to any specific mental health disorder. A manual screening of the sourced literature was instead undertaken to ensure that study participants had a diagnosed mental disorder. Additionally, the identified results were also manually screened to ensure that the studies only included adult participants, as alternative words for ‘adults’ are limited and participant ages are not always explicitly detailed in abstracts, but stated later, for example when reporting participant demographics.

A search string of terms encapsulating the concept of ‘violence and aggression’ was developed based on similar examples used within other studies researching

mental illness and violence (e.g. Frogley et al., 2012; Volavka 2013). Potential alternative spellings, such as words written in American English, were also included.

Finally, as the current review aimed to investigate the effectiveness of other antipsychotic medications compared to clozapine, a search string of terms related to the phrase 'effectiveness' was created, based on terms used in other effectiveness reviews (e.g. Elbert et al., 2014; Noesgaard and Ørngreen, 2015).

Table 3. Search Terms

Umbrella Term	Search Terms
Clozapine	Clozapine; Clozaril; Denzapine; Zaponex
Violence and Aggression	Aggression; aggressive behaviour; aggressive behavior; aggressiveness; violence; violent behaviour; violent behavior; assaultive behaviour; assaultive behavior; offending; hostile; hostility
Effectiveness	Effect; impact; consequence; influence; outcome; effectiveness; efficacy

2.7 SEARCH STRATEGY

Five databases were chosen to search for studies, either published or unpublished, that were relevant to the research question. The databases selected were the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Psycinfo, Web of Science, and MEDLINE. CINAHL and MEDLINE are reliable and credible databases for nurse researchers (Oermann et al., 2021), and CENTRAL is recommended for use in conjunction with MEDLINE (Lefebvre et al., 2019). Psycinfo is a comprehensive, selective, and high-quality database for studies within the fields of behavioural science, psychology, and psychiatry (Gasparyan et al., 2016). Finally, Web of Science was chosen for being a database which contains grey literature, an important resource which can increase the impact and relevance of systematic reviews whilst also

reducing publication bias (Waddington et al., 2012; Mahood et al., 2014; Adams et al., 2017; Paez, 2017). The researcher had aimed to use the noted grey literature database Opengrey to source additional relevant grey literature; however, this database has been shut down (Greynet, 2022).

2.8 STUDY SELECTION

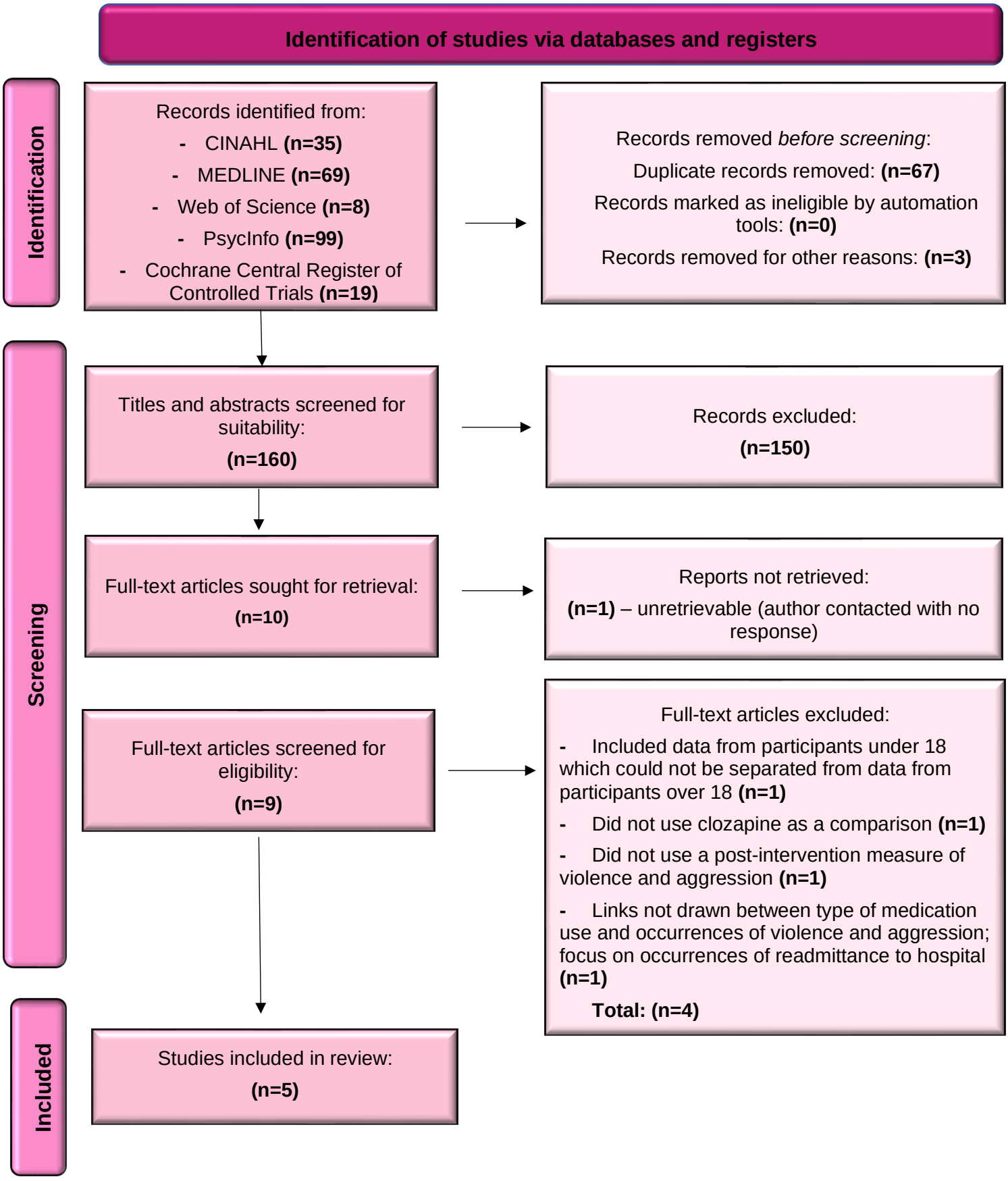

Figure 1. PRIMSA 2020 Flow Diagram (adapted from Page et al., 2021)

A search was run between January and February 2023 on each database using the identified keywords with the language and publication date limits applied. The Boolean operator ‘or’ was used to connect the search terms within each individual umbrella term search string, and the three search strings were linked together using the Boolean operator ‘and’. This initial search provided a total of 230 results across the five databases. An Excel spreadsheet was created to list all articles provided in the database searches, which was then used to screen for duplicates. Duplicate articles, of which there were 67, were then removed. Duplicate articles, of which there were 67, were then removed. Two articles were removed prior to screening for being published between January and March 2011, therefore not meeting the inclusion criteria of being published in or after April 2011; another was removed for being written in Spanish, rather than in English, as specified in the eligibility criteria. Following these exclusions, 160 articles remained for screening.

These articles were then subject to a first screening, in which titles and abstracts were screened for relevance to the review question. 150 articles which were not considered relevant to the aims of the systematic review were subsequently excluded. The remaining ten articles were then sought for retrieval to enable full text screening. Full text access for one article was unable to be obtained; the nine retrievable articles were then subject to a full text review. Four articles were not considered relevant to the research question and were consequently excluded; the rationale for these exclusions is detailed in **Appendix 1**. Five articles were considered relevant to the systematic review.

2.9 CRITICAL APPRAISAL

Critical appraisal is a vehicle through which the methodological validity of studies identified for inclusion in a systematic review can be assessed, including identifying research which may have been subject to performance, selection, or attrition biases (Porritt et al., 2014). Such biases can cause studies to either over- or underestimate the effect of an intervention, which could therefore result in incorrect conclusions being drawn (Boutron et al., 2019).

Consequently, the five studies identified for inclusion in the review were critically appraised using a tool which was appropriate to the study design of the article being appraised. Two studies were appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Randomized Control Trials (JBI, 2017a); the other three were appraised using the JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies) (JBI, 2017b).

There is not a standard metric for deciding which studies should be included in a systematic review following appraisal with these tools, and so the researcher must decide on a uniform benchmark for inclusion (Porritt et al., 2014). For the purpose of this systematic review, studies were included for scoring ≥10 on the JBI Critical Appraisal Checklist for Randomized Control Trials (JBI, 2017a) and ≥7 on the JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies) (JBI, 2017b). A score of ≥10 or ≥7 on each respective scale constitutes a rating of >75%, and was therefore considered to be an appropriate benchmark of high quality. The results of the critical appraisal are discussed in the next chapter of this review.

2.10 DATA EXTRACTION

In order to answer the research question, relevant data, such as participant demographics, study design, and outcome data, is required for analysis so that evidence-based conclusions can be drawn (Munn et al., 2014; Büchter et al., 2020). Such data was extracted from the five studies identified for inclusion in the systematic review using an adapted version of two valid, structured data extraction forms (JBI Data Extraction Form for Experimental/Observational Studies, Pearson et al., 2007, and the Cochrane Collection Data Extraction Form, Cochrane Effective Practice and Organisation of Care, 2017). The extracted data was then collated in three tables in Microsoft Word; see **Appendix 2** for a detailed summary of study characteristics and **Appendix 3** and **Appendix 4** for a detailed summary of study findings for randomised control trial (RCT) and non-RCT studies, respectively. The study findings are discussed further in the next chapter of this review.

2.11 DATA SYNTHESIS

Subsequent to the critical appraisal and data extraction of the five articles, the collected data was then synthesised. In order to do this, the PICO characteristics were summarised (see Table 4) to identify similar elements of the five studies. Superficially, there appears to be some homogeneity between the studies. However, upon closer review of the extracted data, it was evident that the five studies were heterogeneous.

Table 4. Summary of PICO Characteristics for Included Studies

Study	Population	Intervention	Comparison(s)	Outcome
Krakowski and Czobor (2014)	Adults with schizophrenia or schizoaffective disorder	Clozapine	Olanzapine Haloperidol	Violent and aggressive behaviour
Mela and Depiang (2016)	Adult offenders with mental disorders	Clozapine	Non-clozapine antipsychotics	Violent and aggressive behaviour
Ifteni et al. (2017)	Adults with schizophrenia	Clozapine	Non-clozapine antipsychotics	Violent and aggressive behaviour
Bhasvar et al. (2020)	Adults with a diagnosed psychotic disorder or schizoaffective disorder	Clozapine	Olanzapine	Violent and aggressive behaviour
Krakowski et al. (2021)	Adults with schizophrenia or schizoaffective disorder	Clozapine	Olanzapine Haloperidol	Violent and aggressive behaviour

Between the three non-RCT studies (Mela and Depiang, 2016; Ifteni et al., 2017; Bhasvar et al., 2020), there was clear clinical heterogeneity in terms of study duration (ranging between two – six years), study setting (two community, one inpatient), study population (hospitalised patients, offenders with mental disorders, the entire Swedish population), comparison characteristics (two grouped all non-clozapine medications together; one looked solely at olanzapine), and outcome measurements (use of restraint in hospital as a response to violent and aggressive behaviour versus rates of (re)offending in the community). There was also methodological heterogeneity; whilst all three studies were longitudinal, they varied in their research methods (two were retrospective cohort study, although only one was within-subjects, and the other was a matched-control follow-up study). The variation in study methodology also created statistical heterogeneity, as all three studies used different methods of statistical analysis. The risk of biases was assessed as being low in two non-RCT studies;

however, there was a slightly higher risk of attrition and selection biases in Bhasvar et al.'s (2020) study.

The two non-RCT studies (Krakowski and Czobor, 2014; Krakowski et al., 2021) were also reviewed for heterogeneity. Both were inpatient studies lasting twelve weeks; both compared the effect of same three medications on similar populations; and the risk of bias in both studies appeared low. However, both considered the effect of different variables (impulsivity and depression versus a history of conduct disorder, respectively), and used different methods of statistical analysis to investigate their findings, increasing the methodological and statistical heterogeneity. Similarly, Krakowski et al. (2021) reported odds ratios for their findings; however, Krakowski and Czobor (2014) did not. This therefore meant that statistical analysis, such as chi-squared tests and forest plots, to determine any homogeneity of intervention effects could not be conducted.

The research had aimed to statistically synthesise the data via meta-analysis; however, there was not adequate homogeneity between the five studies (Tufanaru et al., 2015; Lee, 2019). This can often occur within systematic reviews due to the differing nature of studies collected for review (Deeks et al., 2019). Additionally, due to the limited number of studies in the systematic review, further statistical investigations of heterogeneity, such as regression analyses, would have been unlikely to produce any useful findings (Deeks et al., 2019). Consequently, a narrative summary and synthesis was instead conducted (Munn et al., 2014). The findings of

the summary and the subsequent analysis of the results are discussed in the next chapter of this systematic review.

2.12 CONCLUSION

This chapter has reviewed the research design and methods used whilst undertaking the systematic review. Five articles have been identified for inclusion in the systematic review following the creation of inclusion criteria, development of a search strategy, and a clear study selection process. Using appropriate tools, these five articles have been critically appraised and had data relevant to the research question extracted for synthesis via narrative synthesis. This synthesis will allow for analysis of the data and for conclusions to be drawn.

CHAPTER THREE: FINDINGS

3.1 INTRODUCTION

This chapter will discuss the critical appraisal of the five studies selected for inclusion in the systematic review, before presenting a summary of study characteristics and conclusions. The gathered data will then be analysed, and findings identified.

3.2 CRITICAL APPRAISAL

As noted previously in Chapter Two, five studies were critically appraised in order to assess the internal validity of the studies identified for inclusion in this systematic review. Two (Krakowski and Czobor, 2014, and Krakowski et al., 2021) were randomised control trials, and so were appraised using the JBI Critical Appraisal Checklist for Randomised Control Trials (2017). The remaining three studies (Mela and Depiang, 2016; Ifteni et al., 2017; Bhavsar et al., 2020) followed a non-randomised control trial, but still quantitative, methodology, and so were appraised using the JBI Critical Appraisal Checklist for Quasi-Experimental Studies (2017). The results of the critical appraisal are summarised in Tables 5 and 6 for the RCT and quasi-experimental (non-RCT) studies, respectively; each individual appraisal for the RCT and quasi-experimental (non-RCT) studies are located in **Appendix 6** and **Appendix 7**, respectively.

Table 5. Critical Appraisal Results Summary (Randomised Control Trials)

Authors	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Total
Krakowski and Czobor (2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/13 (include)
Krakowski et al. (2021)	U	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	10/13 (include)

Krakowski and Czobor (2014) randomly assigned patients to one of three treatment groups (clozapine, olanzapine, or haloperidol) using a block randomisation scheme (Q1, 2). The allocation to treatment groups was concealed, and participants, raters, and the treating psychiatrists were all blind to group allocation (Q4, 5, 6); to maintain blindness, treating psychiatrists prescribed in 'levels', rather than doses. Additional measures were taken to ensure that all remained blind to the allocated treatment group, including all patients were given double-blind side effect medication, the entire study being conducted on a research ward, providing a uniform environment, and all participants participating in blood monitoring, which would normally only be required of patients prescribed clozapine; consequently, all treatment groups were treated identically, other than the treatment received (Q7).

There were no baseline differences (Q3) between the three groups in terms of history of community-based violence, number of aggressive episodes in the four-week period prior to study commencement, nor the antipsychotic medication received. There were also no baseline differences between the treatment groups in terms of demographics or clinical factors. All participants completed the study (Q8), and they were all analysed in the treatment groups into which they were allocated (Q9).

Outcomes were measured the same for all treatment groups (Q10), with the number and severity of aggressive events since commencement of the treatment measured using the Modified Overt Aggression Scale (MOAS) (Kay et al., 1988), a reliable and validated rating scale (Coccaro, 2020) which rates the severity of a violent incident to create a weighted score (Harris et al., 2013). The tool is one of the most extensively used for measuring violence and aggression (Harris et al., 2013). Outcomes were measured reliably (Q11); all aggressive incidents during the study period were carefully recorded, with information gathered from multiple sources

(including handovers, patient and staff interviews, camera recordings and monitoring forms) before being rated with an interrater reliability throughout the study of above 0.9, indicating excellent reliability (Koo and Li, 2016).

The trial design was appropriate to the investigation (Q13), and appropriate statistical analysis (a generalised linear model analysis, based on the Poisson distribution) was used to investigate the relationship between the independent variable (treatment group), the dependent variable (MOAS score), and the covariates of baseline depression and impulsivity (Q12); this is appropriate for analysing discrete data, such as that collected in this study, with the traditional distribution for count data, such as the number of aggressive behaviours displayed over a period of time, being the Poisson distribution (Coxe et al., 2009). Furthermore, post-hoc paired comparisons were used to compare the effects of each intervention on violence and aggression to the others (e.g. the effect of clozapine on MOAS score compared to the effect of olanzapine), which is an appropriate statistical analysis for investigating the differences between group means (Kim, 2015).

Krakowski et al. (2021) randomly assigned patients to one of three treatment groups (clozapine, olanzapine, or haloperidol); however, they did not clearly specify how they were randomly assigned, and therefore it is not clear if allocation to each treatment group was concealed (Q1, 2). The allocation to treatment groups was concealed, and participants, raters, and the treating psychiatrists were all blind to group allocation (Q4, 5, 6); to maintain blindness, treating psychiatrists prescribed in ‘levels’, rather than doses. Additional measures were taken to ensure that all remained blind to the allocated treatment group, including having all participants participate in blood monitoring and the entire study being conducted on a research ward, providing a

uniform environment; consequently, all treatment groups were treated identically, other than the treatment received (Q7). There were no baseline differences (Q3) between the three treatment groups in terms of illness characteristics, demographic factors, or baseline psychiatric symptoms. Furthermore, there were no baseline differences between the treatment groups in terms of the proportion of each group prescribed first- or second-generation antipsychotic medication before randomisation, nor the length of hospitalisation or number of assaults prior to commencement of the study.

31 participants did not complete the study (Q8); however, there was no significant difference between the three groups in terms of study completion. All participants were analysed in the treatment groups within which they were allocated (Q9). They were also additionally analysed within subgroups of each treatment group, as the researchers were also investigating the effect of having (or not having) a history of conduct disorder had on the effect of each medication on violent and aggressive behaviour.

Outcomes were measured the same for all treatment groups (Q10), with the number and severity of aggressive events since commencement of the treatment measured using the valid and reliable MOAS (Kay et al., 1988; Coccaro, 2020); however, it is unclear how reliably the outcomes were measured (Q11). The trial design was appropriate to the investigation (Q13), and appropriate statistical analysis (generalised linear model analysis, Poisson distribution) was used to investigate the relationship between the independent variable (treatment group), the dependent variable (MOAS score), and the covariate of having a history/no history of conduct disorder (Q12). This is appropriate for analysing discrete data, such as that collected in this study, with the traditional distribution for count data, for example the number of

aggressive behaviours displayed over a period of time, being the Poisson distribution (Coxe et al., 2009). Additionally, post-hoc pairwise analyses were used to compare the effects of each intervention on violence and aggression to the others (e.g. the effect of clozapine on MOAS score compared to the effect of haloperidol); as previously noted, these appropriate statistical analyses for investigating the differences between group means (Kim, 2015). Furthermore, odds ratios were calculated to determine the effect size.

Both RCT studies scored equal to or over 10 (the benchmark for inclusion, as specified in Chapter Two). Following the critical appraisal of the two RCT studies, it was therefore decided that both should be included in the systematic review.

Table 6. Critical Appraisal Results Summary (Quasi-Experimental Studies)

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Mela and Depiang (2016)	Y	Y	U	Y	U	Y	Y	Y	Y	7/9 (include)
Ifteni et al. (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9 (include)
Bhavsar et al. (2020)	Y	N	U	Y	Y	Y	Y	Y	Y	7/9 (include)

The independent and dependent variables of **Mela and Depiang's (2016)** study (clozapine and rate of reoffending behaviour, respectively) are clear (Q1). The participants in the clozapine group were matched with the non-clozapine group for gender, age, and offence severity (Q2); the latter participants formed the control group (Q4). All participants were receiving the same care in the same hospital when they were recruited for the study; however, it is unclear whether they received the same levels and types of care and treatment once released into the community, which is

acknowledged by the authors (Q3). Similarly, whilst there were multiple post-intervention measures comprehensively reported, the pre-intervention measurements were not as clearly detailed (Q5). There could, therefore, potentially be additional explanations to the conclusions of the study other than the effects of the independent variable.

Follow-up was completed for all participants who had been released into the community; the percentages of both groups who had been released were the same and clearly detailed in the reporting of the study (Q6). A small number of participants from both groups died prior to the data collection data from unspecified causes; differences between the deceased participants were not statistically significant. The follow-up outcome measures data was not created by subjective ratings from the researchers, but through objective data gathered from a national database of all charges and convictions. The stable and consistent nature of data within a national database suggests that another researcher with access to the same database would be able to gather the exact same information; the outcome measures are therefore considered to have been measured in a reliable way (Q8) (Taherdoost, 2016; de Souza et al., 2017).

The outcomes of both groups were compared in the same way (Q7) through use of survival analyses, Wilcoxon tests, mean differences and confidence intervals for the time to the first offence after release. Fisher's exact tests were also run to compare the number of convictions of the two groups in four offence categories both throughout the entire follow-up period, and also specifically within the first two years following release. Survival analysis is an appropriate statistical analysis (Q9) for analysing longitudinal 'time to event' data (that is, how long until an 'event', such as first post-release offence, occurs) (Emmert-Streib and Dehmer, 2019). Whilst survival

analysis can be complicated by issues such as fixed right censoring (for example, not all participants may experience the 'event' within the specified time frame, but could have done so after, which is therefore not reflected in the results), the researchers investigated two clear times points for convictions and drew their conclusions with reference to these, rather than making conclusions regarding of conviction rates over period of time longer than the study (Johnson, 2018; Emmert-Streib and Dehmer, 2019). Furthermore, Fisher's exact tests are appropriate for comparing independent groups, particularly when the groups are small in size (Kim, 2017).

Ifteni et al. (2017) were also clear about their independent (clozapine) and dependent (use of restraint) variables (Q1). Participants were split into two groups, clozapine and non-clozapine (the latter of which formed the control group, Q4), based on the medication they were treated with during admission. The authors acknowledged that the participants within these groups differed slightly, due to the naturalistic design of the study. However, the two groups did not statistically differ for the majority of demographic and clinical parameters, including age, gender, illness severity, and pre-intervention aggression scores, although the clozapine group included a higher proportion of patients who had been admitted to hospital due to self-destructive behaviours, and their duration of being hospitalisation-free prior to the current admission was also significantly longer than the non-clozapine group. However, on balance, the groups appear to be well-matched (Q2). All participants from both groups were inpatients within the same psychiatric hospital, and so encountered the same treatment, care, and environment (Q3).

As the study was retrospective, outcome measures are unlikely to be influenced by biases pertaining to study participation. There were also multiple post-intervention

outcome measurements (hours until first restraint post-admission; number of restraints during first 24 hours post-admission; number of restraints at any time during period of admission) (Q5), which were the same for all participants (Q7). Due to the nature of the outcome measure, this could not be measured prior to admission; however, there were other pre-intervention measurements, such as the MOAS and the PANSS, which were completed to identify if other factors would influence the outcome of the study and showed no statistical difference between the clozapine and non-clozapine group.

There was no reported incomplete or missing outcome data (Q6), and the outcome measures were reliably measured through objective data collection (number of restraints) rather than subjective researcher ratings (Q8). However, the interrater reliability of some of the pre-intervention measures, which were not directly related to measuring the outcomes, is unclear. Fisher exact test or Wilcoxon rank-sum tests were completed for group comparisons; the authors provided clear and appropriate rationale for their decision-making regarding the use of two-sided tests with alpha = 0.05 without correction. A secondary survival analysis, reviewing the first week of hospitalisation, was conducted for all patients who had not needed restraint in the first hour post-admission; this appears to consider potential right censoring by analysing whether being restraint-free in the first hour of admission was sustained within the first week. Additionally, stepwise forward regression was used to exclude other potential variables other than medication as a reason for delay of restraint (Q9).

Bhavsar et al. (2020) also clearly specified the independent (clozapine) and dependent (offending behaviour) variables of their study (Q1). The control group in the study were prescribed olanzapine (Q4). Due to the naturalistic nature of the study, which involved applying applicable inclusion/exclusion criteria to data gathered from

multiple national databases which contained data for the entire population of Sweden, the clozapine and olanzapine groups were statistically different from each other for all covariates considered in the study, including age, gender, and duration of treatment (Q2), lowering the internal validity of the study. It is unclear whether the care received by both groups is comparable, or whether participants were exposed to any other treatments, such as other medications or therapies, during the review period (Q3).

Follow-up was completed for all participants at a forward observation time which was as long as possible following the commencement of the treatment (Q6), at either the date of drug discontinuation, participant emigration from Sweden, participant death, or the end of the study. The forward observation time period was then matched for each participant to a backward observation time point of the same length. These two observation periods formed the 'before' (pre-intervention) and 'after' (post-intervention) time periods for the mirror-image study. The amount of offending behaviour which took place during the forward observation time formed the post-intervention measure, and the amount of offending by each participant in their backward observation time forming the pre-intervention measure; this was measured in the same way for all participants using data from objective national databases (Q5, 7, 8).

Zero-inflated negative binomial models were used to analysis the results of the study; the authors considered this to be the most appropriate statistical model due to the large number of zeroes within the data (caused by observation periods with no offending behaviour). Covariates were also entered into the model in order to give adjusted estimates with these factored in (Q9).

All three non-RCT studies scored over or equal to the benchmark score of seven (as specified in Chapter Two); it was therefore decided that all three should be included in the systematic review.

3.3 STUDY CHARACTERISTICS

The four studies which detailed location were conducted in the USA, Canada, Romania, and Sweden; the fifth study (Krakowski and Czobor, 2014) did not explicitly state where their research was conducted. Three studies took place within an inpatient setting, and two were community-based. Across the five studies, 3673 participants (2363, or 64.3%, of whom were male) participated in the research. Three studies explicitly detailed their participant age ranges (two were 18-60; one was 18-58). Iftani et al. (2017) provided only the median age of their participants (39), and Mela and Depiang (2016) provided only the mean age of their two groups (34.3 for the clozapine group and 37.0 for the non-clozapine group). Detailed ethnicity breakdowns were only available in two studies (Krakowski and Czobor, 2014; Krakowski et al., 2021). Samples sizes varied from 99 (Krakowski et al., 2021) to 3260 (Bhasvar et al., 2020), and the duration of the study ranged from 12 weeks (Krakowski and Czobor, 2014; Krakowski et al., 2021) to six years (Bhasvar et al., 2020).

All studies involved participants with diagnosed mental health disorders. Three studies involved participants with schizophrenia or schizoaffective disorders; one study involved participants with schizophrenia only; and one study involved patients with a psychotic or schizoaffective disorder. All studies used clozapine as the treatment intervention. One study used olanzapine for the comparison treatment (Bhasvar et al.,

2020); two used olanzapine and haloperidol (Krakowski and Czobor, 2014; Krakowski et al., 2021); and two used the umbrella term ‘non-clozapine antipsychotics’, with Ifteni et al. (2017) specifing that this was made up of haloperidol, olanzapine, amisulpride, quetiapine, aripiprazole, and risperidone, and Mela and Depiang (2016) not providing a specific breakdown.

All studies measured violence and aggression as an outcome measure; however, each study measured this differently. Krakowski and Czobor (2014), an inpatient study, measured the number and severity of aggressive events since the commencement of the intervention using the MOAS (Kay et al., 1988). Another inpatient study, Krakowski et al. (2021) also used this psychometric assessment, but only looked at certain elements (specifically, the MOAS Overall Aggression score and the Physical Assault score). The third inpatient study (Ifteni et al., 2017) did not use such assessment tools, but instead used use of restraint to measure its outcome; restraint was utilised whenever a participant appeared to be at immediate risk of violence towards others. The researchers examined the time between admission and first use of restraint against participants, the number of restraints during hospital admission, and the number of restraints during the first 24 hours of admission. Mela and Depiang (2016), one of the community-based studies, used rates of reoffending following release (using a calculated reconviction rate), and time (in mean months) between release and first post-release offence. The other community-based study (Bhasvar et al., 2020) also looked at the number of offences committed during the review period, calculating an adjusted rate ratio to determine the rate of violent and non-violent offending post-intervention.

3.4 SUMMARY OF CONCLUSIONS

Krakowski and Czobor (2014) concluded that clozapine is associated with less violence than olanzapine and haloperidol in those with schizophrenia and low impulsivity, regardless of depression level. However, the level of violence was not significantly different between clozapine and olanzapine when impulsivity was high, regardless of depression level, although both clozapine and olanzapine were significantly better than haloperidol for reducing violent and aggressive behaviours within this population. Additionally, they reported that the negative effect of high depression on violence and aggression was not modified by an improvement in positive symptoms in any of the medication groups.

Mela and Depiang (2016) found that participants treated with clozapine had a lower rate of reoffending than those treated with other antipsychotics in all reconviction categories except sexual; however, these incidences were not significantly different. Their research did, however, find that clozapine group had significantly longer duration between release and first offense than the non-clozapine group.

Ifteni et al. (2017) concluded that the length of time after admission until a patient required restraint for aggressive behaviours was significantly longer for those prescribed clozapine, and particularly those prescribed clozapine first, than those prescribed other antipsychotics. Additionally, their research found that number of restraints required due to aggressive behaviours during hospitalisation (for both the entire duration of admission and within the first 24 hours) is statistically lower for those prescribed clozapine compared to those who were not prescribed clozapine.

Bhasvar et al. (2020) suggested that treatment with clozapine is associated with a lower rate of violent offending compared to treatment with olanzapine in patients with psychotic disorders. However, they also reported that there was no significant difference in rates of non-violent offending between treatment with clozapine or olanzapine.

Krakowski et al. (2021) found that clozapine is significantly more effective than olanzapine or haloperidol at reducing assaultive behaviours in individuals with schizophrenia or schizoaffective disorder (both with and without a history of conduct disorder); however, clozapine was particularly effective in treating those with a history of conduct disorder. The authors also suggested that worsening of positive symptoms in both subgroups resulted in an increased number of assaultive behaviours, regardless of medication, particular in those without a history of conduct disorder.

3.5 DATA ANALYSIS

Synthesised finding #1: Clozapine is more effective than other antipsychotic medications for reducing violence and aggression within inpatient settings. Evidence for the effectiveness of other antipsychotic medications in reducing violence and aggression compared to clozapine in the community is inconclusive.

Four studies concluded that clozapine has a greater effect on reducing violent and aggressive behaviours than comparators; three of which were inpatient studies. For

example, participants in Krakowski and Czobor's (2014) study significantly scored lower on the MOAS when treated with clozapine compared to those treated with olanzapine or haloperidol. Similarly, participants treated with clozapine in Krakowski et al.'s (2021) study had a significantly lower average MOAS Overall score and a significantly lower average MOAS Physical Assault score than those treated with olanzapine or haloperidol. Furthermore, participants in Ifteni et al.'s (2017) study who were treated with clozapine were subject to significantly less restraints in the first 24 hours of hospitalisation and for the entire duration of their stay compared to those treated with other antipsychotic medications. The three studies all found clozapine to be more effective than other antipsychotic medications in reducing violence and aggression within inpatient settings.

Those treated with clozapine in Bhasvar et al.'s (2020) community-based study had a lower rate of reconviction for violent crimes compared to those treated with olanzapine. However, Mela and Depiang (2016) reported in their community-based study that whilst reconviction rates for violent crimes were lower for participants treated with clozapine than in those treated with other antipsychotics, this result was not significant, and so they could not conclude that clozapine was more effective. Consequently, the evidence regarding whether other antipsychotic medications are more effective than clozapine in reducing violence and aggression in the community is mixed and inconclusive. The significance of, and potential evidence-based explanations for, this finding will be discussed in subsequent chapters.

Synthesised finding #2: Clozapine is more effective than other antipsychotic medications for reducing violence and aggression when individuals with schizophrenia or schizoaffective disorder have certain comorbidities, but olanzapine is just as effective when some specific comorbidities are present.

All the studies involved participants with a diagnosed psychotic illness; however, two studies also looked into the impact of some co-morbidities on the effectiveness of clozapine. For example, Krakowski et al. (2021) found that, whilst still significantly more effective in reducing violence and aggression than other antipsychotic medications for participants who did not have a history of conduct disorder, clozapine was particularly effective when participants did have a history of conduct disorder.

Furthermore, Krakowski and Czobor (2014) suggest that clozapine is still the most effective antipsychotic medication for participants who are also experiencing high levels of depression. The results of the two studies suggest that clozapine is still the most effective antipsychotic for reducing violence and aggression when certain comorbidities are present.

However, Krakowski and Czobor (2014) also concluded that there was no significant difference between clozapine and olanzapine when impulsivity was high, suggesting that olanzapine would be as effective as clozapine in patients who are highly impulsive. The significance of, and potential evidence-based explanations for, this finding will be discussed in subsequent chapters.

Synthesised finding #3: Clozapine is more effective than other antipsychotic medications in delaying instances of violence or aggression**.**

Two studies also looked at length of time until a violent or aggressive event. Mela and Depiang (2016) noted that those treated with clozapine went, on average, 125 months before reoffending, compared to 73 months for those treated with other antipsychotics. Ifteni et al. (2017) found that patients treated with clozapine went, on average, 118 hours before being restrained due to an increased risk to others (increasing to 408 hours if they were treated with clozapine first), compared to 1.1 hours for those treated with other antipsychotic medications. The results from both studies were statistically significant. The evidence from both studies therefore suggests that clozapine is more effective at increasing the length of time before a violent and aggressive event occurs compared to other antipsychotic medications. The significance of, and potential evidence-based explanations for, this finding will be discussed in subsequent chapters.

3.6 CONCLUSION

This chapter has reviewed the critical appraisal of the five articles included in the systematic review and provided explicit evidence regarding the decision-making throughout the appraisal process. Study characteristics and conclusions have been highlighted, with the data from the five articles used to form three synthesised findings. These findings will enable the development of discussions, conclusions, and recommendations, with reference to the research question.

CHAPTER FOUR: DISCUSSION

4.1 INTRODUCTION

The effectiveness of clozapine in reducing violent and aggressive behaviours in adults with a mental health disorder appears to be well-established in the literature (e.g. Brown et al., 2014; Patchan et al., 2018; Cavaliere et al., 2022). This systematic review aimed to investigate whether other antipsychotic medications are an effective intervention for reducing violence and aggression in adults with mental health disorders compared to clozapine. To the author's knowledge, this is the first review of this topic since Frogley et al.'s (2012) systematic review found that clozapine was effective in reducing violence and aggression in individuals with a variety of mental illnesses but recommended further investigation into this area as due to mixed evidence regarding its effectiveness comparative to other antipsychotic medications.

As alluded to in previous chapters, a total of five studies were identified, appraised, and synthesised in order to draw conclusions which would enable the research question to be answered. The concept of violence and aggression was measured differently in each of these five studies, in a variety of different settings and countries with varying comparators, leading to the studies, and their subsequent results, being heterogenous from each other. Nevertheless, common themes within the studies have enabled synthesised findings to be created with reference to the research question, which appear to confirm that clozapine is more effective than other antipsychotic medications in reducing violence and aggression in adults with a diagnosed mental illness. As with Frogley et al.'s (2012) previous systematic review, there are limitations to some of the synthesised findings, as the data does not suggest that they can be generalised to all situations. This chapter will discuss the synthesised findings which

were highlighted in the previous chapter in reference to established literature in order to suggest evidence-based explanations for the synthesised findings.

4.2 DISCUSSION

Synthesised finding #1 suggests that the conclusion that clozapine is more effective than other antipsychotic medications in reducing violence and aggression in adults with mental health disorders is only applicable within inpatient settings, as the evidence from studies conducted within the community is inconclusive. There are several potential reasons why the research conducted within the community has led to an inconclusive conclusion. For example, incidences of violence and aggression are easier to monitor within inpatient settings, as such services provide 24-hour nursing care, enabling the constant support and supervision of patients (Clearly et al., 2013; Holmberg et al., 2018), and two of the three inpatient studies (Krakowski and Czobor, 2014 and Krakowski et al., 2021) explicitly stated that the nature of their studies ensured careful monitoring of assaultive behaviour. However, this is more difficult once patients are discharged into the community.

Both community-based studies which were included in the systematic review used conviction as a means of determining violence and aggression in the community, with Mela and Depiang (2016) stating that this was “to ensure the validity of the behavior (sic)” (p.88). However, whilst being convicted of a violent crime is a concrete measure of violence having occurred, it is also possible that those on clozapine (or, indeed, other antipsychotic medications) could have committed acts of violence and aggression which did not result in a criminal conviction. For example, in Canada (where Mela and Depiang’s 2016 study was conducted), it is estimated that crime is severely underreported, with 76% of violent crimes and 94% of sexual crimes not

reported to the police (Cotter, 2021). Similarly, in the UK, approximately 60% of crimes are unknown to the police (Buil-Gil et al., 2021), suggesting that this is not just an issue limited to Canada.

There are various reasons for underreporting violent crime, including the victim considering the issue to be an unimportant, minor or private issue, or that they did not feel that anyone was harmed (Cotter, 2021). This is in contrast to inpatient settings, where instances of violence and aggression, regardless of severity or outcome, would be routinely recorded (Bader et al., 2014; Eisele et al., 2021). Furthermore, reporting a crime to the police does not guarantee a conviction, with Canada having only a 61% conviction rate in 2018/19 (Statistics Canada, 2022). This may also contribute to low reporting, as over a third of Canadians do not think an offender would be adequately punished (Cotter, 2021). This is even greater in the UK, with over half of the population not confident in the criminal justice system (Hough et al., 2013), suggesting that a lack of trust in the justice system is contributing to underreporting in multiple countries. This is in contrast to in Sweden (the location of Bhavsar et al.'s 2020 study), where nearly half of the population have a high level of confidence in the justice system (Brå, 2020), which may have led to more reporting of incidences of crime, therefore further contributing to the difference in conclusions between the two studies.

Consequently, using conviction as a means of measuring violence and aggression is limited, particularly in countries with high unreported crime and low confidence in the legal system. Issues regarding the use of conviction as a measurement tool may therefore contribute to why the two community-based studies differed in their conclusions, compared to the three inpatient studies, which had greater oversight of incidences of violence and aggression and were all in agreement that clozapine was

the most effective antipsychotic medication for reducing violence and aggression in adults with mental health disorders.

Similar to incidents of violence and aggression detailed above, medication adherence can be easily monitored within inpatient settings due to the constant presence of nursing staff providing care, which could include implementing supportive measures to encourage adherence or enforcing medication (Clearly et al., 2013). However, for the majority of people within the community, medication adherence is voluntary and more difficult to accurately monitor, as adults with mental illnesses will often not fully engage with mental health community services (Corrigan et al., 2014). Whilst clozapine entails more regular physical health monitoring (e.g., regular blood tests, NICE, 2021) than other antipsychotics, suggesting more frequent engagement with community mental health teams (Sarpal et al., 2023), and consequently more routine monitoring of their mental wellbeing (Coates et al., 2017), this does not necessarily guarantee long-term adherence to treatment.

Adherence to antipsychotic medication is considered to be a significant clinical issue in the treatment of psychotic disorders (Taub et al., 2022), with non-adherence estimated to have a prevalence of around 50% of those diagnosed with schizophrenia (Haddad et al., 2014; Semahegn et al., 2020), and can lead to relapse and subsequent violent and aggressive episodes (Witt et al., 2013; Keers et al., 2014; Rababa'h et al., 2017; Buchanan et al., 2019). Medication non-adherence within the community could therefore be suggested as one explanation for the inconclusive element of synthesised finding #1.

There are factors which can increase engagement with treatment, such as adopting a person-centred approach, a good therapeutic alliance, and accessibility of care (Dixon et al., 2016); however, the quality and consistence of the community care participants were receiving in the included studies is unclear. This may have therefore impacted their engagement with services and, subsequently, on their medication adherence. Participants could have chosen to be nonadherent with their antipsychotic medication and disengage with mental health services (Corrigan et al., 2014), which would mean that services (and, later, the researchers) would have had limited scope to accurately monitor their concordance.

In countries such as the UK, USA, and Australia, if an individual is subject to a Community Treatment Order (CTO) in which medication concordance is a stipulated condition, non-adherence would consequently lead to recall to hospital, where medication can be enforced (Kisely et al., 2013; Burns et al., 2013; Kisely et al., 2017). Both Sweden and Canada, the locations of the two community-based studies included in this systematic review, also have the ability to utilise CTOs (Kjellin and Pelto-Piri, 2014; Gray et al., 2016); however, neither study specified how many, if any, participants were subject to a CTO. As the use of CTOs in both studies are unclear, it could be argued that differing levels of monitoring through the use of CTOs between the community-based studies may have impacted on medication adherence and, subsequently, the results of the studies. However, a systematic review has previously found no significant difference in medication concordance between individuals who are subject to a CTO and those who are under voluntary care (Kinsley et al., 2017), suggesting that the potential application of more CTOs in one study would not explain the difference in results.

Whilst CTOs may not improve medication adherence (Kinsley et al., 2017), their use would enable more accurate recording of medication non-concordance. Without knowing whether participants were subject to, and subsequently met/breached the conditions of, a CTO, participants of the community-based studies included in the systematic review could have potentially stopped taking their medication at any time following their release from hospital without the researchers having accurate data on this. Mela and Depiang (2016) only used the first 45 days of prescription as evidence of compliance, as they considered that this time frame was sufficient to confirm participant commitment to their prescribed medication – however, their study went on for several years, providing ample opportunity for unmonitored disengagement from pharmaceutical treatment, which may have therefore impacted on their results.

Good medication adherence is often at its highest in the first six-month period before decreasing after a year, due to the influence of various sociodemographic and clinical factors (Andre et al., 2013), suggesting that Mela and Depiang's (2016) compliance monitoring period was not long enough. The lack of long-term monitoring in Mela and Depiang's (2016) study could have potentially had an influence on their non-significant conclusion if large numbers of participants from either the clozapine or non-clozapine group became non-concordant with their medication beyond the 45th day, or if one group became, on average, non-concordant sooner than the other, as the researchers have drawn their conclusions on the assumption that their participants remained concordant, despite evidence suggesting a high prevalence of non-adherence within such population groups (Haddad et al., 2014; Semahegn et al., 2020).

Bhavsar et al. (2020) utilised a different approach to monitoring medication adherence by basing their conclusions on the assumption that dispensed prescriptions

for the medications was equivalent with full medication adherence, the monitoring of which continued throughout the duration of the time period studied. Whilst this method of monitoring can only provide an indirect approximation of concordance (Lehman et al., 2013), more evidence over a longer period of time may explain why Bhavsar et al.'s (2020) results showed a significant difference between the effectiveness of clozapine and olanzapine as an intervention for reducing violence and aggression in adults with mental health disorders, whereas Mela and Depiang (2016) did not. High medication concordance was explicitly acknowledged in two of the three inpatient studies (Krakowski and Czobor, 2014 and Krakowski et al., 2021), giving further weight to the suggestion that medication concordance may have had an impact on the results and subsequent conclusions.

Similar to synthesised finding #1, **synthesised finding #2** also contains a caveat. Synthesised finding #2 suggests that, whilst clozapine is more effective than other antipsychotic medications for reducing violence and aggression when individuals with schizophrenia or schizoaffective disorder have high levels of depression or a history of conduct disorder, olanzapine is just as effective when high impulsivity is present. Olanzapine has previously been shown to have a reductive effect on violent behaviour in adults with mental health disorders (Baruch et al., 2014; Gobbi et al., 2014; Kasinathan et al., 2016), and so this current systematic review finding that olanzapine has these effects in general is therefore potentially unsurprising. However, that the effects are equal to those of clozapine when high impulsivity is present is interesting, especially as other comorbidities have not had similar results, suggesting there is something specific about impulsivity that olanzapine is particularly adept at targeting.

Research suggests that olanzapine is a strong antagonist of 5-HT_{2a} and 5-HT_6 receptors within the brain (Jayarajan et al., 2013). Antagonism of 5-HT_{2a} receptors have been shown to decrease impulsivity (Homberg, 2012), and antagonism of 5-HT_6 receptors have been shown to decrease compulsivity and impulsivity (Homberg, 2012). Olanzapine has high affinity for these receptors, which has been shown to reverse the effects by scopolamine, a muscarinic receptor in the brain which has various effects on the central nervous system, including causing impulsivity (Jayarajan et al., 2013). The metabolism of the thalamus, an area of the brain that is part of the central nervous system linked with impulsivity (Wang et al., 2017), has been shown to decrease when individuals take olanzapine (Camchong et al., 2018). Additionally, whilst clozapine is also a 5-HT antagonist, olanzapine has been shown to be more effective than clozapine in reducing impulsivity in patients with schizophrenia (Witten et al., 2012). Clozapine is also a strong antagonist of 5-HT_{2a} (Aringhieri et al., 2017; Nasrallah et al., 2019); however, it only has intermediate effects on 5-HT_6 receptors (de Bruin et al., 2013).

Whilst clozapine was generally shown in results of the current systematic review to be the more effective antipsychotic medication for adults with mental health disorders who have displayed violence and aggression behaviours, the strong effects of olanzapine on impulsivity may have therefore improved its anti-aggressive effects on individuals who were highly impulsive, as impulsivity is linked to violence in individuals with mental health disorders (Ouzir, 2013; Bousardt et al., 2015; Hoptman, 2015). This may therefore explain why both olanzapine and clozapine were equally as effective when high impulsivity was present. Haloperidol has been found to have no effect on impulsivity in patients with schizophrenia (Jayarajan et al., 2013), potentially

explaining why haloperidol was not as effective as olanzapine and clozapine, and also suggesting that impulsivity mediation is not a common effect of all antipsychotics.

With regard to the other comorbidities, clozapine was shown to be more effective than other antipsychotics in managing violent and aggressive behaviours in adults with psychotic disorders when participants had a history of conduct disorder. Conduct disorder is a childhood disorder which is characterised by aggressive and antisocial behaviour (Fairchild et al., 2019). Clozapine has been shown to have a strong effect on the symptoms of conduct disorder in children, including those diagnosed with severe conduct disorder (Teixeira et al., 2013; Juárez-Treviño et al., 2019). Clozapine has also been shown to be more effective than risperidone, which is otherwise the most effective antipsychotic medication for managing aggression in children with conduct disorder (Gorman et al., 2015; Balia et al., 2018; Juárez-Treviño et al., 2019), suggesting that clozapine is the most effective antipsychotic medication for managing aggressive behaviours in children with conduct disorders. It could therefore be proposed that clozapine was particularly effective when participants had a history of conduct disorder due to its effectiveness in managing related symptoms of aggression in children with conduct disorder.

Another explanation could be that the effectiveness of clozapine at managing violence and aggression in participants with a history of conduct disorder is related to the effectiveness of clozapine at managing aggression in adults with antisocial personality disorders (ASPD) (Brown et al., 2014), as up to 50% of children with a conduct disorder will develop an ASPD in adulthood (NICE, 2017). Participants may have had an ASPD which was not diagnosed, or made aware to the researchers,

which may have increased the effectiveness of clozapine compared to other antipsychotic medication.

One further explanation is regarding the neurological effects of clozapine. Men with schizophrenia and a history of conduct disorder have been shown to have an increased volume of grey matter in the brain compared to those without a history of conduct disorder (Schiffer et al., 2012), and increased grey matter volumes are positively correlated with aggressive behaviour (Schiffer et al., 2012; Leutgeb et al., 2016). Conversely, clozapine has been shown to extensively reduce grey matter volume (Anderson et al., 2015). It could therefore be suggested that clozapine is particularly effective in reducing violence and aggression in individuals with schizophrenia and a history of conduct disorder due to its reductive effects on the volume of grey matter within the brain.

Regarding other antipsychotic medications and conduct disorder, one study suggests that olanzapine, one of the comparator medication used in the two studies which considered co-morbidities, has a good effect on treating conduct disorder, especially related to impulsive aggression (Balia et al., 2018), which also fits in with previous finding regarding impulsivity; however, its effects were shown to be less prevalent on callous-unemotional aggression (Balia et al., 2018), and overall research for the effects of olanzapine on conduct disorder, and antisocial personality disorder, is limited (Loy et al., 2017; Sagar et al., 2019; Stoffers-Winterling et al., 2021), making it difficult to draw accurate conclusions. Haloperidol, the other comparator medication used in two studies which considered co-morbidities, is one of several psychiatric medications not recommended for the treatment of conduct disorder due to limited evidence of its effectiveness (Pringsheim et al., 2014; Gorman et al., 2015), potentially giving further credence to the suggestion that clozapine was especially effective in

participants with a history of conduct disorder due to its high effectiveness in treating conduct disorder in children, compared to the partial effectiveness of olanzapine and low-to-non-effectiveness of haloperidol.

The conclusion that clozapine Is m”re e’fective than other antipsychotic medications when participants had high levels of depression may be attributable to clozapine also being an effective treatment for depressive disorders and symptoms, especially suicidality (Li et al., 2014; Wilkowska et al., 2019). Depression and depressive symptoms are a risk factor for violence and aggression (Dutton and Karakanta, 2013; Fazel et al., 2015), suggesting that effectiveness in managing depressive symptoms should also have a positive impact on reducing violent and aggressive behaviours. Research has suggested that clozapine and olanzapine have equal effectiveness in treating general depressive symptoms (Nakajima et al., 2015); however, clozapine is the only antipsychotic medication which has been found to effectively reduce suicidality in patients with schizophrenia (Forte et al., 2021). It could therefore be suggested that clozapine is more effective at treating high levels of depression than olanzapine, thus explaining why clozapine was more effective than olanzapine in reducing violent and aggressive behaviours in the participants, as lowering the level of depression is suggested to lower the risk of violence (Dutton and Karakanta, 2013; Fazel et al., 2015).

Animal studies have suggested that haloperidol, the other comparative medications used in the trial which considered comorbidities, actually exacerbates, rather than reduces, negative symptoms (Ulak et al., 2016; Morais et al., 2017). This may therefore explain why haloperidol was less effective in managing violence and aggression in patients with high depression compared to clozapine, as the medication

was potentially increasing depressive symptoms and, consequently, the violence and aggression.

Synthesised finding #3 suggests that clozapine is more effective than other antipsychotic medication in delaying instances of violence and aggression; that is, those who were treated with clozapine went longer before committing an act of violence and aggression than those who were treated with other antipsychotic medication, with results from both the community (Mela and Depiang, 2016) and inpatient settings (Ifteni et al., 2017) supporting this. One potential explanation of this finding is that clozapine may lead to an uptake in non-pharmacological interventions, such as psychological therapy, which may contribute to a delay in violent incidents.

Engagement with psychological therapies can decrease violence in adults with a mental health disorder in both inpatient and community settings (Witt et al., 2013; Ross et al., 2013; Pardede and Laia, 2020; Rampling et al., 2020), but participation in such therapies can often fail when psychotic symptoms are severe (Doyle et al., 2014; Korsavva and Dhadesugar, 2019). Clozapine has been shown to be more effective than other antipsychotic medications in reducing positive symptoms, particularly in those with treatment-resistant schizophrenia (Siskind et al., 2018). Consequently, by reducing psychotic symptoms, clozapine may have a better mediating effect on engagement in psychological therapies than other antipsychotic medications, leading to more uptake in such therapies amongst those being treated with clozapine compared to those on other antipsychotic medication, which may in turn contribute to increased delays to violent episodes. Engagement in psychological therapies was not specified in either study which investigated time delays to violent episodes, so it is unclear whether this is a contributing factor within these studies; however, the

literature suggests that this should be considered as a potential influence on the results.

Another potential non-pharmacological influence on synthesised finding #3 is substance misuse. Clozapine has been shown to both delay the initiation and reduce the misuse of illicit substances (Kelly et al., 2012; Khokhar et al., 2018; Krause et al., 2019), with clozapine more effective than other antipsychotics, including olanzapine and haloperidol, in reducing substance misuse (Krause et al., 2019). Clozapine is effective in reducing suicidality in individuals with schizoaffective disorder or schizophrenia (Masdrakis and Baldwin, 2023), and the ability of clozapine to reduce substance misuse amongst such individuals has been suggested as a potential explanation for this (Khokhar et al., 2018). It could therefore be suggested that the same principles may apply to the link between clozapine, substance misuse, and violence and aggression. Amongst individuals with psychotic disorders, substance misuse can increase violence and aggression (Witt et al., 2013), including recidivism (Igoumenou et al., 2015), and decrease medication compliance (Higashi et al., 2013). Subsequently, clozapine may therefore be more effective than other antipsychotic medication in delaying violent and aggressive incidences through reduction, or delay, of substance misuse.

Another explanation for synthesised finding #3 is the treatment of psychotic symptomology. It has been suggested that the presence of active psychotic symptoms is related to faster rates of violent reoffending (Igoumenou et al., 2015), and, consequently, continual adherence with pharmacological treatment following release

into the community to manage such symptomology significantly reduces violent reoffending (Keers et al., 2014). Clozapine has been shown to be more effective than other antipsychotic medications, including olanzapine and haloperidol, in the management of both positive and negative symptoms of schizophrenia (Souza et al., 2013; Stroup et al., 2016; Siskind et al., 2018). The effectiveness of clozapine in managing these symptoms compared to other antipsychotic medication may therefore provide an explanation to its superiority in delaying instances of violence and aggression through reduction in experienced symptomology.

4.3 CONCLUSION

This chapter has discussed some of the potential reasons for the three synthesised findings of this systematic review using the current literature base to explain these conclusions. Synthesised finding #1 is likely to be a consequence of the ability to maintain high levels of medication concordance and careful monitoring of violence and aggression within inpatient settings, which was not able to be achieved within the community-based studies. Synthesised finding #2 is a probable consequence of the strong mediating effects of olanzapine on impulsivity, the effectiveness of clozapine on treating conduct disorder and antisocial personality disorder compared to olanzapine or haloperidol, and the effectiveness of clozapine in reducing high levels of depression compared to olanzapine and particularly haloperidol, which arguably worsens, rather than treats, such symptomology. Synthesised finding #3 is potentially due to a combination of factors, including the influence of non-pharmacological factors, such as uptake in psychological treatment and reducing/delaying the misuse of illicit substances, the presence of psychotic symptoms, and medication adherence. From these synthesised findings, recommendations for advancing professional nursing

practice and areas of future research can be suggested and will be discussed in the next chapter of this systematic review.

CHAPTER FIVE: RECOMMENDATIONS AND CONCLUSION

5.1 INTRODUCTION

The synthesised findings of this systematic review and the subsequent evidenced-based explanations and considerations for these suggest that there are numerous clinical implications of the results. This chapter will discuss recommendations for the advancement of professional nursing practice, both in clinical practice and in education, and suggestions for future research based on these synthesised findings before drawing conclusions for this systematic review into the effectiveness of alternate antipsychotic medication in reducing violent and aggressive behaviours in adults with mental health disorders compared to clozapine.

5.2 RECOMMENDATIONS FOR ADVANCING PROFESSIONAL PRACTICE

Synthesised finding #1 highlighted that clozapine is superior to other antipsychotic medications in inpatient settings for reducing violence and aggression in adults with diagnosed mental illnesses, but that the evidence within the community was inconclusive. One of the evidence-based explanations for the inconclusive nature of this finding was due to potential non-adherence of antipsychotic medications, including clozapine, whilst in the community. This has important clinical implications for advancing professional practice, as it suggests that registered mental health nurses (RMNs) need to find and use innovative ways to improve antipsychotic medication adherence in the community, as non-adherence can lead to relapses in mental wellbeing (Haddad et al., 2014), and subsequently an increase in violent and aggressive behaviours (Buchanan et al., 2019). This is additionally pertinent given that synthesised finding (#3) highlighted that clozapine can delay instances of violence, including in the community where the general public would be at risk.

One potential way in which RMNs could improve community medication adherence is through technology. For example, SMS text message reminders for antipsychotic medications are an accessible, minimally invasive, and low-cost intervention (Bogart et al., 2014; Kannisto et al., 2015; D'Arcey et al., 2020), which can be tailored to individual preferences, including date, time, content, and volume of messages (Kauppi et al., 2015). SMS message reminders have been shown to increase engagement in community treatment of psychotic illnesses, including improving adherence to antipsychotic medication (Montes et al., 2012; Bogart et al., 2014; Drake et al., 2015; Kannisto et al., 2015; Xu et al., 2019; D'Arcey et al., 2020). Similarly, mobile apps are another convenient method of improving antipsychotic medication adherence within the community through the provision of educational messages and medication reminders (Zhu et al., 2020).

Based on the findings of this current systematic review, which suggests that adherence to antipsychotic medication may be worse in the community than in inpatient settings, which can have serious negative consequences on both mental wellbeing and on increased risks of violence and aggression (Haddad et al., 2014; Buchanan et al., 2019), innovative methods of improving concordance within the community, such as utilising SMS messages and mobile apps, should therefore be adopted by community RMNs for both the mental wellbeing of patients and the safety of the general public.

The findings of this systematic review should also be used as evidence to inform national policy and guidelines regarding the indications for antipsychotic medication for the treatment of violence and aggression in adults with diagnosed mental health disorder. NICE develop national guidelines, advice, and recommendations which

informs health and social care practice within the UK using the best evidence that is available, including findings developed from research (NICE, 2022i). This can take the form of recommending the most suitable care and treatment for a group of people with specific needs or conditions or who are within certain settings (NICE, 2022i). Guidelines should therefore be developed from the findings of this review, which could include recommending the use of clozapine to manage violence and aggression in adults with diagnoses mental health disorders within inpatient settings, based on synthesised finding #1; recommending olanzapine to manage such behaviours if members of this population are highly impulsive, based on synthesised finding #2; or recommending clozapine for those at risk of recidivism, based on synthesised finding #3. Evidence gathered in this review would therefore be used to advance professional nursing practice through the creation, publication and implementation of evidence-based national guidelines which would enhance and improve the quality of care provided to adults with diagnosed mental illnesses who display violent and aggressive behaviours.

The findings of this review and any developed policies as a consequence should be also disseminated to mental healthcare service providers, particularly those which commission and oversee secure psychiatric inpatient settings and forensic community teams, who care for patients with histories of violence and aggression (Coffey, 2012; Ramesh et al., 2018; Oates et al., 2020). Dissemination of the findings and subsequent policies to these clinical areas would help to advance professional practice through psychiatric service providers demonstrating a commitment to quality improvement, one of NICE's (2023) principles for putting evidence-based guidance into practice. This would be achieved by developing the understanding of RMNs regarding the comparative benefits of different antipsychotic medications in reducing violent and

aggressive behaviours by adults with mental health disorders, particularly when setting or comorbidities are considered. This would empower them to advocate on behalf of their patients regarding the best antipsychotic medication for their treatment needs, as well as demonstrate best nursing practice, improve the quality of patient care and making evidence-based decisions, in line with the NMC (2018a) code.

For example, the findings from this systematic review would enable RMNs to make the evidence-based suggestion of utilising clozapine as the pharmaceutical treatment of choice for their patients who display high levels of violence and aggression, particularly if they have a history of conduct disorder or have high levels of comorbid depression, as highlighted by synthesised finding #2. Similarly, it would enable RMNs to advocate for the prescription of olanzapine, rather than clozapine, for violent and aggressive patients who are highly impulsive, following the evidence highlighted by synthesised finding #2 that olanzapine was just as effective as clozapine for this patient population. Successful evidence-based advocacy would subsequently mean that their patients would be subject to less invasive physical health monitoring (NICE, 2021) and would be less likely to develop significant physical health concerns, such as the reduction of white blood cells to a dangerously low level, which can put patients at increased risk of potentially fatal infections (Ng et al., 2021). Furthermore, utilising olanzapine instead of clozapine for such populations, when the evidence suggests that they are equally as effective as each other, would also be cheaper for service providers (NICE, 2022b; 2022d).

RMNs could also use the findings of this systematic review to provide evidence-based psychoeducation to their patients regarding their medication, including on the importance and benefits of concordance with clozapine. Moreover, dissemination of the results of this systematic review will empower forensic RMNs to implement more

evidence-based practice, rather than the current tendency to utilise experiential or social sources of information to inform their practice (Newman et al., 2020).

As well as mental healthcare service providers, the findings of this systematic review should also be shared with nursing education providers, such as universities which run undergraduate nursing courses. This will enable the findings to be taught to students as part of their mental health nursing education, and will be of particular relevance and interest to those who are undertaking placements within forensic mental health settings or are studying a forensic mental health module. Research suggests that teaching related to forensic mental health nursing is limited in both undergraduate and postgraduate training courses (Kalayci et al., 2014; Simmons et al., 2014), despite this being an established mental health nursing specialism (Oates et al., 2021), which can often mean that graduate nurses can enter the forensic mental health nursing workforce with limited experience or knowledge in this area (Maguire et al., 2023).

Furthermore, even outside of forensic psychiatric environments, RMNs are still exposed to violence and aggression from patients (Baby et al., 2014; Llor-Esteban et al., 2017). This suggests that improved education on violence and aggression within mental health nursing is required in order to prepare nursing students for the future workplace, including through greater understanding of effective pharmacological treatments of violence and aggression in adults with mental health disorders. Disseminating the results of this systematic review will therefore facilitate the advancement of professional nursing practice by enhancing the knowledge of trainee mental health nurses within this area, enabling them to apply their learning and understanding of antipsychotic medications which effectively reduce violent and

aggressive behaviours in adults with diagnosed mental illnesses to their assignments, placements, and future nursing careers.

5.3 RECOMMENDATIONS FOR AREAS OF FUTURE RESEARCH

The synthesised findings have highlighted a number of areas for potential future research which would help further advance professional nursing practice. For example, all five studies included in the systematic review focused on psychotic illnesses, which is likely to be due to antipsychotics being most commonly prescribed to treat such disorders (Marston et al., 2014). Research has previously shown that clozapine can effectively reduce violent and aggressive behaviours in adults with other mental illnesses, such as personality disorders, dementia, and mood disorders (Brown et al., 2014; Teodorescu et al., 2018; Teodorescu et al., 2021); however, there appears to be limited research into the effectiveness of other antipsychotics, both in absolute terms and in comparison to clozapine. It is therefore recommended that research is conducted to investigate the effectiveness of other antipsychotics in comparison to clozapine on reducing violent and aggressive behaviours in adults with mental health disorders other than psychotic illnesses.

Furthermore, this systematic review of effectiveness focused solely on adults with diagnosed mental illnesses. Literature suggests that antipsychotic medication, including clozapine, can also be effectively utilised to manage violence and aggression in children and adolescents with mental health disorders (Argent and Hill, 2014; Masi et al., 2015; Kumar et al., 2016; McInnis and Kasinathan, 2018; Juárez-Treviño et al., 2019; Pattnaik et al., 2023). Frogley et al.'s (2012) previous systematic review also noted that clozapine is effective within this population; however, their findings were not

in comparison to other antipsychotic medications. Research should therefore be conducted into whether similar results to this systematic review would be found in children and adolescents with mental health disorders who display violent and aggressive behaviours.

Additionally, synthesised finding #2 highlighted the influence that certain comorbidities can have on the effectiveness of particular antipsychotic medications on reducing violent and aggressive behaviours in adults with diagnoses mental health disorders (Krakowski and Czobor, 2014; Krakowski et al., 2021). However, more research should be conducted to confirm this conclusion, as the two studies which provided evidence for this finding investigated the impact of two different comorbidities. Further research regarding the impact of these two comorbidities on the effectiveness of antipsychotic medications in treating these behaviours within this population group, for example in other countries or different contexts, would therefore provide additional evidence to support or challenge this finding and increase the rigor of this research (Coiera et al., 2018; Franklin and Thomas, 2022).

Similarly, conclusions regarding the effectiveness of antipsychotic medications when factoring in comorbidities should not be generalised beyond the presence of depression, impulsivity, or a history of conduct disorder, as these are the only comorbidities which were considered by studies included in this systematic review (Murad et al., 2018; Varpio et al., 2020). Additional research should therefore be conducted to investigate the impact of additional comorbidities, for example traumatic brain injuries (Luukkainen et al., 2012; Sariaslan et al., 2016), on the effectiveness of antipsychotic medications of treating violence and aggression in adults with diagnosed

mental health disorders in order to widen the generalisability of this synthesised finding.

Synthesised finding #1 suggested the effectiveness of other antipsychotic medications on violence and aggression in adults with mental illnesses in the community compared to clozapine is inconclusive, suggesting that additional research is required within this area to clarify whether other antipsychotic medications are equally as, or more, effective than clozapine in managing this presentation within the community, or whether the inconclusiveness is due to methodological issues (Coiera et al., 2018; Franklin and Thomas, 2022). For example, one evidence-based reason previously suggested for this finding is non-concordance with medication in the community. Future research should therefore consider investigating the use of long-acting injectable antipsychotics (LAIs). LAIs have been shown to significantly reduce violence, aggression, hostility and recidivism (Fazel et al., 2014; Mohr et al., 2017), potentially due to improved treatment adherence as a consequence of using LAIs rather than oral antipsychotics (Tiihonen et al., 2017), as covert nonadherence is not possible with LAIs (Haddad et al., 2014).

Currently, clozapine is limited in its alternate forms, with it mostly commonly being prescribed as an oral medication, with nasogastric administration the most easily available alternative means of administration (Till et al., 2018). Intramuscular (IM) clozapine can also be used to improve the mental wellbeing of patients with serious mental illnesses (Gee et al., 2021), and it could be suggested that its use would increase adherence, particularly within the community. However, IM clozapine is uncommon (Casetta et al., 2020), and has only been available for use as an unlicensed medicine within the UK since 2018 (Gee et al., 2021). Additionally, IM

clozapine is not long acting; it requires daily administration, similar to oral medication (Henry et al., 2020). It is therefore suggested that in order to advance professional practice, research should be conducted into the development of a LAI version of clozapine.

Following the development of a LAI for clozapine, research should then be conducted into the comparative effectiveness of a clozapine LAI compared to the more traditional antipsychotic LAIs. Similarly, research should also be conducted into whether the use of LAIs impacts on effectiveness, as arguably a community prescription of a LAI would also ensure more regular contact with community mental health teams (Tiihonen et al., 2017). Such research involving improved monitoring of medication adherence is also recommended in order to confirm or challenge synthesised finding #1.

Finally, this systematic review only investigated the comparative effectiveness of different antipsychotic medications on reducing violence and aggression in adults with diagnosed mental health disorders, as systematic reviews typically involve the inclusion of only one comparative intervention (Hartling et al., 2014). The current research did not study the effectiveness, relative to clozapine, of other interventions which may reducing violent and aggressive behaviours in adults with a diagnosed mental illness, such as pharmacological interventions, for example antidepressant or mood stabilising medication (Fazel et al., 2014), other possible treatments, such as electroconvulsive therapy (Kristensen et al., 2012; Isakov et al., 2013), or psychological interventions such as cognitive-behavioural therapy (Kim et al., 2014), dance therapy (Lee et al., 2015) or animal-assisted therapy (Nurenberg et al., 2015). Subsequently, it is recommended that additional research be conducted to investigate

whether other potential interventions which were not included in the current systematic review are equally as, or more, effective than clozapine in reducing violent and aggressive behaviours in adults with diagnosed mental illnesses.

5.4 CONCLUSION

This systematic review aimed to answer the question of whether other antipsychotic medications are an effective intervention for reducing violence and aggression in adults with mental health disorders compared to clozapine and, in doing so, update the findings from Frogley et al.'s (2012) review and address the current gap in the research literature. Through use of a systematic methodology to develop an appropriate inclusion/exclusion criterion, search strategy, and study selection, five studies were selected for critical appraisal and inclusion in the review. Following data extraction, synthesis, and analysis, three synthesised findings were developed.

The review findings suggest that clozapine is more effective than other antipsychotic medications in reducing such behaviours in most circumstances in adults with diagnosed psychotic illnesses, particularly within inpatient settings, when the individual has a history of conduct disorder, or if they are also experiencing high levels of depression. However, the findings also highlighted that olanzapine is equally as effective as clozapine when the individual is highly impulsive, and that clozapine's comparative effectiveness in the community is currently inconclusive.

Evidence-based explanations for these findings have been discussed and have led to the development of a number of recommendations for the advancement of professional nursing practice, including the provision of evidence for the development of national guidelines and the dissemination of the findings to service and education providers. Areas for future research based on the limitations of the current review have also been suggested to continue expanding the literature base.

In conclusion, this systematic review has contributed to, and updated, the current literature base regarding the effectiveness of other antipsychotic medications in comparison to clozapine in reducing violence and aggression in adults with psychotic illnesses; however, there is still a need for further research to add additional evidence and to expand the generalisability to other populations, mental illnesses, interventions, and comorbidities.

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Zeng, J-Y., An, F-R., Xiang, Y-T., Qi, Y-K., Ungvari, G., Newhouse, R., Yu, D., Lai, K., Yu, L-Y., Ding, Y-M., Tang, W-K., Wu, P-P., Hou, Z-J. and Chiu, H. (2013). Frequency and risk factors of workplace violence on psychiatric nurses and its impact on their quality of life in China. *Psychiatry Research,* 210(2), 510-514.

Zhu, X., Li, M., Liu, P., Chang, R., Wang, Q., and Liu, J. (2020). A mobile health application-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. *Archives of Psychiatric Nursing,* 34(6), 472-480.

Appendix 1. Studies excluded from the systematic review following full text screening.

Citation	Reason for Exclusion
Sariaslan, A., Leucht, S., Zetterqvist, J., Lichtenstein, P. and Fazel, S. (2021). Associations between individual antipsychotics and the risk of arrests and convictions of violent and other crime: a nationwide within-individual study of 74 925 persons. *Psychological Medicine,* 52(16), 1-9.	Included data from participants under 18 which could not be separated from data from participants over 18
Mauri, M., Cirnigliaro, G., Piccoli, E., Vismara, M., De Carlo, V., Girone, N., and Dell'Osso, B. (2022). 'Substance abuse associated with aggressive/violent behaviors in psychiatric outpatients and related psychotropic prescription'. To be published in *International Journal of Mental Health and Addiction.* Available at: https://doi.org/10.1007/s11469-022-00842-w [Accessed: 06 March 2023].	Did not use a post-intervention measure of violence and aggression.

Hariman, K., Cheng, K., Lam, J., Leung, S., Lui, S. (2020). Clinical risk model to predict 28-day unplanned readmission via the accident and emergency department after discharge from acute psychiatric units for patients with psychotic spectrum disorders. *BJPSych Open*, 6(1), e13.	Whilst denoted number of patients on Clozapine and number of violent incidences, this data was listed independent of each other; the focus of the research was on whether these independent factors impacted on recall to hospital, rather than their impact on each other.
Bogers, J., Schulte, P., Broekman, T., Moleman, P. and de Haan, L. (2018). Dose reduction of high-dose first-generation antipsychotics or switch to ziprasidone in long-stay patients with schizophrenia: A 1-year double-blind randomized clinical trial. *European Neuropsychopharmacology,* 28(9), 1024-1034.	Did not use clozapine as a comparison.

Appendix 2. Summary of Data Extraction of Study Characteristics (Adapted from Pearson, Field and Jordan, 2007, and Cochrane Effective Practice and Organisation of Care, 2017).

Authors (Year)	Study Design	Setting	Aim	Duration	Demographics	Intervention (Sample Size)	Risk of Bias	Outcome Description	Method of Analysis
Krakowski and Czobor (2014)	RCT	**Setting:** Inpatient **Location:** Unclear	To establish whether baseline impulsivity and depression predicts aggression and response to anti-aggressive treatments.	**Study Duration:** 12 weeks	**Sample Population:** 101 patients with schizophrenia or schizoaffective disorder with a confirmed episode of physical aggression during the present hospitalization and additional aggression (physical, verbal, or against property) over a 2-week period following the initial incident. **Gender:** 19 females; 82 males **Age:** 18-60. **Ethnicity:** 16 White; 66 African American; 17 Hispanic; 2 Other	**Intervention 1:** Clozapine (31) **Intervention 2:** Olanzapine (36) **Intervention 3:** Haloperidol (34)	**Selection Bias – Low Risk:** Patients randomly allocated to groups using a block randomisation scheme. No baseline differences in demographic or clinical factors, including baseline depression and impulsivity, between the three intervention groups. No baseline differences between the three intervention groups in terms of antipsychotic medication received before randomisation. No difference between three groups in terms of number of aggressive incidents in the 4-week period pre-study, nor number of participants with a history of violence in the community. **Performance Bias – Low Risk:** All study procedures were identical for all three groups to preserve blind assessment, including blood monitoring. Treating psychiatrists were blind to treatment group assignment; they prescribed via 'levels' rather than dosages. Side effect medication, or a placebo, or both, was given to all patients (double-blind). No baseline differences between the three intervention groups in terms participants receiving non-antipsychotic psychotropic medication received before randomisation, reducing risk of cointervention bias. High treatment compliance reported. Study took place on a research ward; thus, the environment was uniform for all participants. **Detection Bias – Low Risk:** Raters were blind to treatment group.	**Outcome 1:** Number and severity of aggressive events since start of intervention **Outcome 2:** Effect of depression on response to antiaggressive treatment **Outcome 3:** Effect of impulsivity on response to antiaggressive treatment	Generalised linear model analysis.

							Outcomes were measured at the same time across all intervention groups. **Attrition Bias – Low Risk:** All participants completed the study. **Other Bias – Low Risk:** Study received some funding from pharmaceutical companies; however, these companies had no role in experimental design, data acquisition, statistical analysis, or interpretation of results. Medication dosages were restricted in range, which did not allow for comparisons of clozapine and olanzapine with lower dosages of haloperidol. Authors acknowledge concern that their findings may not be generalisable to other dosages of haloperidol.		
Mela and Depiang (2016)	Longitudinal (Matched-control follow-up study)	**Setting:** Community **Location:** Saskatoon, Canada	To establish the effect of clozapine on reoffending in released offenders with mental disorders.	**Retrospective Data Period*:** 21 years (1984-2005). **Current Study Duration:** Follow-up period of two years (until November 17th 2012); however, exact start date unclear.	**Sample Population:** 98 offenders with mental disorders treated within the Regional Psychiatric Center with sentences of more than two years for serious offences. **Gender*:** 94 males; 4 females **Age*:** Mean for Intervention Group: 34.3 (SD ± 9.03). Mean for Control Group: 37.0 (SD ± 10.3). Range and Median: Unknown. **Ethnicity*:** 53 Aboriginal; 45 Non-aboriginal. No more detailed breakdown of this demographic available.	**Intervention:** Clozapine (65) **Control:** Non-clozapine antipsychotics (33)	**Selection Bias – Low Risk:** Patients were not randomly allocated to intervention group. However, non-clozapine group was matched with the clozapine group for gender, age, and offense severity. Additionally, due to the nature of the study, the outcome measures are unlikely to be influenced by the lack of concealment of the treatment received at the time of intervention provision. **Performance Bias – High Risk:** Study is not a double-blind control study. Compliance was estimated using the initial 45 days of participants prescription; however, they acknowledge that some patients may have stopped taking their medication in the community. Whilst not monitored, researchers assumed clozapine group had more contact with health professionals and therefore any deterioration/non-compliance may have been better managed. **Detection Bias – Low Risk:** Outcome measures did not require subjective rating; knowledge of allocated intervention therefore not likely to influence outcome. Outcomes were	**Outcome 1:** Rates of reoffending following release. **Outcome 2:** Time between release and first post-release offence.	**Outcome 1:** Incident relative risk calculated. Rates of reconviction compared using Fisher's exact test. **Outcome 2:** Survival analysis. Mean survival times compared. Wilcoxon test used for overall comparison. Mean differences between release and first reconviction calculated.

							measured at the same time across all intervention groups. **Attrition Bias – Low Risk:** 24 participants from Intervention 1 (36.9%) and 12 participants from Intervention 2 (36.4%) did not have follow-up data available at the end of data collection, as they had not been released into the community by the data collection date (November 12th 2022); however, the percentages of released persons were the same (63.1% and 63.6%, respectively). **Other Bias – Low Risk:** No conflicts of interest declared. All participants were reportedly on a therapeutic dose of medication.		
Ifteni et al. (2017)	Longitudinal (Retrospective cohort study)	**Setting:** Inpatient **Location:** Brasov, Romania	To establish the anti-aggressive effects of clozapine, compared to other anti-psychotic treatments, during hospital admission.	**Retrospective Data Period:** Four years (January 1st 2011 – December 31st 2014)	**Sample Population:** 115 consecutive patients with schizophrenia who were involuntarily admitted to the Psychiatry and Neurology Hospital between January 1st 2011 and December 2014. **Gender:** 56 females; 59 males **Age:** Range unknown. Mean: 39 years old (SD ± 11.05). Median: Unknown. **Ethnicity:** Unknown	**Intervention:** Clozapine (24) **Subgroup:** Clozapine-first (13) **Control:** Non-clozapine antipsychotics (91)	**Selection Bias – Low Risk:** Due to the retrospective nature of the study, patients were not randomly allocated into treatment groups; patients were divided by the medication they were receiving. However, the majority of clinical and demographic parameters were not significantly different between the treatment groups. Furthermore, due to the nature of the study, the outcome measures are unlikely to be influenced by the lack of concealment of the treatment received at the time of intervention provision. **Performance Bias – Low Risk:** Due to the retrospective nature of the study, outcome measures are highly unlikely to be influenced by a lack of blinding of participants or care providers at the time of the treatment provision, as the data is being retrospectively reviewed. Unclear if participants were receiving any other interventions during their periods of hospitalisation. No reported issues with compliance in either group; researchers noted that the medications (including clozapine) could be given involuntarily if necessary, suggesting a low compliance bias.	**Outcome 1:** Time between admission and first use of restraint against patient **Outcome 2:** Restraints during admission to hospital. **Outcome 3:** Restraints during first 24 hours of admission	Fisher exact test or Wilcoxon rank-sum tests for group comparisons, a Kaplan–Meier survival analysis, and nominal logistic fits. Two-sided tests with alpha = 0.05 were used without correction for multiple comparisons due to the descriptive nature of the study. Secondary survival analysis one week after hospitalisation for all patients who had not needed restraint in first hour post-admission. Stepwise forward regression used to exclude other

							Detection Bias – Low Risk: Outcome measures did not require subjective rating; knowledge of allocated intervention therefore not likely to influence outcome. Outcomes were measured at the same time across all intervention groups. **Attrition Bias – Low Risk:** No reported incomplete or missing outcome data. **Other Bias – Low Risk:** No conflicts of interest declared. Effect of medication dosage on outcome measures unclear.		potential variables other than medication as a reason for delay of restraint.
Bhasvar et al. (2020)	Longitudinal (Within-subjects retrospective cohort study)	**Setting:** Community **Location:** Sweden	To establish the effect of clozapine on the rate of nonviolent and violent offending.	**Retrospective Data Period:** Six years (January 1st 2006 – December 31st 2011)	**Sample Population:** 3260 individuals with a diagnosed psychotic disorder or schizoaffective disorder first prescribed either clozapine or olanzapine for at least 8 weeks between Jan 1st 2006 and Dec 31st 2011. **Gender:** 1214 females; 2048 males **Age:** 18 – 58 years old. Mean and Median: Unknown. **Ethnicity:** 2518 participants born in Sweden; no more detailed breakdown of this demographic available. No additional information available about the background of the remaining participants.	**Intervention:** Clozapine (1004) **Control:** Olanzapine (2258)	**Selection Bias – Medium Risk:** Due to the retrospective nature of the study, patients were not randomly allocated into treatment groups; patients were divided by the medication they were receiving. There were statistical differences between the two treatment groups for all covariates included in the study. However, due to the nature of the study, the outcome measures are unlikely to be influenced by the lack of concealment of the treatment received at the time of intervention provision. **Performance Bias – Low Risk:** Due to the retrospective nature of the study, outcome measures are highly unlikely to be influenced by a lack of blinding of participants or care providers at the time of the treatment provision, as the data is being retrospectively reviewed. Unclear if participants were receiving any other interventions. No reported issues with compliance in either group. **Detection Bias – Low Risk:** Outcome measures did not require subjective rating; knowledge of allocated intervention therefore not likely to influence outcome. Outcomes were measured at the same time across all intervention groups. **Attrition Bias – Medium Risk:** Outcome data was available for 96.4% of all identified individuals who had been prescribed clozapine during the	**Outcome 1:** Rate of violent offences committed after treatment initiation compared to before. **Outcome 2:** Rate of non-violent offences committed after treatment initiation compared to before. **Outcome 3:** Overall rate of offences committed after treatment initiation compared to before.	Zero-inflated negative binomial models.

							study period, compared to 81.6% of those who had been prescribed olanzapine. Those who did not have available outcome data were not included in the study. There is therefore a higher proportion of individuals prescribed olanzapine who were not included in the study. **Other Bias – Medium Risk:** No conflicts of interest declared. Effect of medication dosage on outcome measures unclear.		
Krakowski et al. (2021).	RCT	**Setting:** Inpatient **Location:** New York, USA	To establish the effect of conduct disorder on the anti-aggressive effects of three anti-psychotic medications.	**Study Duration:** 12 weeks	**Sample Population:** 99 patients with a diagnosis of schizophrenia or schizoaffective disorder with a confirmed episode of physical assault directed at another person and a separate occurrence of aggression (either physical, verbal, or against property) over a 4-week period following the physical assault. **Gender:** 19 females; 80 males **Age:** 18-60. Mean and Median: Unknown. **Ethnicity:** 16 White; 61 African Americans; 20 Hispanic; 2 Other	**Intervention 1:** Clozapine (33) **Subgroup 1:** No conduct disorder (12) **Subgroup 2:** Conduct disorder (21) **Intervention 2:** Olanzapine (34) **Subgroup 1:** No conduct disorder (15) **Subgroup 2:** Conduct disorder (19) **Intervention 3:** Haloperidol (32) **Subgroup 1:** No conduct disorder (19) **Subgroup 2:** Conduct disorder (13)	**Selection Bias – Unclear Risk:** Patients randomly allocated to groups; however, process of this unclear. Also unclear whether those assigning participants to the intervention groups knew the allocation sequence. No baseline differences between treatment groups in demographic factors or baseline psychiatric symptoms. No baseline differences between the three intervention groups in terms of illness characteristics, nor in the proportion of each group prescribed first- or second-generation antipsychotic medication before randomisation. No difference between three groups in terms of length of hospitalisation or number of assaults prior to commencement of the study. **Performance Bias – Low Risk:** All study procedures were identical for all three groups to preserve blind assessment, including blood monitoring. Treating psychiatrists were blind to treatment group assignment; they prescribed via 'levels' rather than dosages. Study took place on a research ward; thus, the environment was uniform for all participants. **Detection Bias – Low Risk:** Raters were blind to treatment group. **Attrition Bias – High Risk:** 31 patients (31.31%) did not complete the 12-week study. **Other Bias – Low Risk:** No conflicts of interest declared. Authors acknowledge	**Outcome 1:** Violent and aggressive behaviour since start of treatment **Outcome 2:** Schizophrenia symptoms since start of treatment	Generalized linear model analysis (Poisson distribution) used to investigate differences between treatment groups, in terms of categorical efficacy, and comparing age distribution for age at first arrest for violent crime. Post hoc pairwise analyses used when main effects or interaction effects reached significance. Odds ratios used to determine effect size. Least squares mean estimates used to investigate interactions between PANSS positive score changes and MOAS scores.

							that, due to the need to titrate clozapine slower than olanzapine or haloperidol, there was less time to fully assess the antiaggressive efficacy of clozapine, and therefore the results may not reflect the true efficacy of clozapine.		

*Information not directly reported in text; gathered from a previous study referenced in-text (Balbuena et al., 2010).

Appendix 3. Summary of Data Extraction of Findings (RCT Studies) (Adapted from Pearson, Field and Jordan, 2007, and Cochrane Effective Practice and Organisation of Care, 2017).

Authors (Year)	Measure(s) of Violence and Aggression and Variable(s)	Study Results		Authors' conclusions
		Outcome 1	Interactions	

Krakowski and Czobor (2014)	**Outcome 1:** Modified Overt Aggression Scale (MOAS) score **Variable 1:** Positive and Negative Syndrome Scale (PANSS) Depression factor score **Variable 2:** Barratt Impulsiveness Scale score	**Mean values (±SD):** Clozapine 24.8 (±30.5) Olanzapine 33.3 (±32.2) Haloperidol 38.2 (±50.7) **Difference between interventions:** *F* = 12.4, *df* = 2,99, *p* < .001. **Post-hoc paired comparisons:** CLO-OLZ *p* <.01 CLO-HAL *p* <.01 OLZ-HAL *p* <.01	**Least Square (LS) Means for Outcome 1 with Low Depression and Low Impulsivity (SE):** Clozapine: 10.6 (0.7) Olanzapine: 16.6 (0.9) Haloperidol: 14.1 (1.0) **Pairwise comparisons, *t (p)*:** CLO-OLZ -5.6 (<.001) CLO-HAL -3.2 (<.01) OLZ-HAL 1.9 (<.06) **LS Means for Outcome 1 with Low Depression and High Impulsivity (SE):** Clozapine: 10.0 (0.8)	Clozapine is associated with less violence than olanzapine and haloperidol in those with schizophrenia and low impulsivity, regardless of depression level. However, the level of violence was not significantly different between clozapine and olanzapine when impulsivity was high, regardless of depression level, although both clozapine and olanzapine were significantly better than haloperidol for this population.

	Variable 3: PANSS Positive Symptom factor score		Olanzapine: 12.1 (0.9) Haloperidol: 16.9 (1.0) **Pairwise comparisons, *t (p)*:** CLO-OLZ -1.9 (<.06) CLO-HAL -5.6 (<.001) OLZ-HAL -3.6 (<.001) **LS Means for Outcome 1 with High Depression and Low Impulsivity (SE):** Clozapine: 25.9 (3.5) Olanzapine: 52.1 (2.7) Haloperidol: 66.0 (5.2) **Pairwise comparisons, *t (p)*:**	The negative effect of high depression on violence and aggression was not modified by an improvement in positive symptoms in any of the medication groups.

			CLO-OLZ -4.9 (<.001) CLO-HAL -6.1 (<.001) OLZ-HAL -2.5 (<.01) **LS Means for Outcome 1 with High Depression and High Impulsivity (SE):** Clozapine: 47.2 (3.5) Olanzapine: 48.1 (3.4) Haloperidol: 85.9 (4.8) **Pairwise comparisons, *t (p)*:** CLO-OLZ -0.2 (<.8) CLO-HAL -6.7 (<.001) OLZ-HAL -6.4 (<.001)	

			LS Means for Outcome 1 with Low Baseline Variable 1 and Improved Variable 3 (SE): Clozapine: 20.9 (2.9) Olanzapine: 10.2 (1.3) Haloperidol: 13.6 (1.4) **LS Means for Outcome 1 with High Baseline Variable 1 and Improved Variable 3 (SE):** Clozapine: 30.9 (4.5) Olanzapine: 59.9 (7.3) Haloperidol: 72.3 (9.1)	

			Interaction between Intervention, baseline Variable 1, and Variable 2 in determining Outcome 1: *F* = 13.4, *df* = 2, 99, *p* < .001.	
Krakowski et al. (2021).	**Outcome Measure 1:** MOAS Overall Aggression score **Outcome Measure 2:** MOAS Physical Assault score **Variable:** PANSS Positive	**Outcome Measure 1 Subgroup 1:** CLO-HAL *t*=7.75, *p* = <0.001 CLO-OLZ *t*=5.86, *p* = <0.001 OLZ-HAL *t*=2.21, *p* = 0.03 **Odds Ratio (95% CI):** CLO-HAL 1.92 (1.61–2.27) CLO-OLZ 1.66 (1.41–1.96) OLZ-HAL 1.15 (1.02-1.30) **Subgroup 2:** CLO-HAL *t*=17.38, *p* = <0.001 CLO-OLZ *t*=7.66, *p* = <0.001 OLZ-HAL *t*=10.90, *p* = <0.001	**Main Effect of Variable Measure on Outcome Measure 1:** *F*=250.0, *df*=1, 98, *p* = <0.001 **Main Effect of Variable on Outcome Measure 2:** *F*=137.0, *df*=1, 98, *p* = <0.001 **Main Effect of Interaction between Subgroup and Variable on Outcome Measure 1:** *F*=44.8, *df*=1, 98, *p* = <0.001	**Outcome 1:** Clozapine is significantly more effective than olanzapine or haloperidol at reducing assaultive behaviours in individuals with schizophrenia or schizoaffective disorder (both with and without a history of conduct disorder); however, clozapine was particularly effect in treating those with a history of conduct disorder.

	Symptom factor score	**Odds Ratio (95% CI):** CLO-HAL 2.70 (2.38-3.03) CLO-OLZ 1.54 (1.34–1.69) OLZ-HAL 1.76 (1.59-1.95) **Main Effect of Subgroup on Outcome Measure 1:** *F*=223.2, *df*=1, 98, *p* = <0.001 **Outcome Measure 2 Subgroup 1:** CLO-HAL *t*=7.32, *p* = <0.001 CLO-OLZ *t*=6.02, *p* = <0.001 OLZ-HAL *t*=1.83, *p* = 0.07 **Odds Ratio (95% CI):** CLO-HAL 3.09 (2.27-3.13) CLO-OLZ 2.56 (1.89–3.57) OLZ-HAL 1.20 (0.99-1.45)	**Main Effect of Interaction between Subgroup and Variable on Outcome Measure 2:** *F*=18.1, *df*=1, 98, *p* = <0.001	**Effect of Variable:** Worsening of positive symptoms in both subgroups resulted in an increased amount of assaultive behaviours, regardless of medication, particular in those without a history of conduct disorder.

		Subgroup 2: CLO-HAL *t*=16.94, *p* = <0.001 CLO-OLZ *t*=6.11, *p* = <0.001 OLZ-HAL *t*=12.16, *p* = <0.001 **Odds Ratio (95% CI):** CLO-HAL 4.12 (3.45-4.76) CLO-OLZ 1.66 (1.43–2.00) OLZ-HAL 2.44 (2.12-2.82) **Main Effect of Subgroup on Outcome Measure 2:** *F*=230.2, *df*=1, 98, *p* = <0.001		

Appendix 4. Summary of Data Extraction of Findings (Non-RCT Studies) (Adapted from Pearson, Field and Jordan, 2007, and Cochrane Effective Practice and Organisation of Care, 2017).

Authors (Year)	Measure(s) of Violence and Aggression	Study Results			Authors' conclusions
		Outcome 1	Outcome 2	Outcome 3	
Mela and Depiang (2016)	**Outcome 1:** Reconviction rate (n) **Outcome 2:** Reconviction rate (n) **Outcome 3:** Time (mean months)	**Intervention (% of group):** Any/all offences: 21 (51.2) Nonviolent: 19 (46.3) Violent: 13 (31.7) Sexual: 8 (19.5) **Control (% of group):** Any/all offences: 11 (52.4) Nonviolent: 9 (42.9) Violent: 7 (33.3) Sexual: 2 (9.5)	**Intervention (% of group):** Any/all offences: 10 (24.4) Nonviolent: 10 (24.4) Violent: 5 (12.2) Sexual: 4 (9.8) **Control (% of group):** Any/all offences: 9 (42.9) Nonviolent: 6 (28.6) Violent: 6 (28.6) Sexual: 1 (4.8)	**Intervention:** 125 **Control:** 73 **Statistical Analysis:** independent *t* test = 4.834, *df* = 60; *p* < .000	**Outcome 1 and 2:** The clozapine group had a lower number of reoffending than the non-clozapine group in all reconviction categories except sexual; however, these incidences were not significantly different. **Outcome 3:** The clozapine group had significantly longer duration between release and first offense than the non-clozapine group.

		Statistical Analysis: Fisher's Exact Test *p* = Any/all offences: 0.572 Nonviolent: 0.505 Violent: 0.558 Sexual: 0.265	**Statistical Analysis:** Fisher's Exact Test *p* = Any/all offences: 0.115 Nonviolent: 0.474 Violent: 0.108 Sexual: 0.444		
Ifteni et al. (2017)	**Outcome 1:** Time (hours) **Outcome 2**: Number of restraints (n) **Outcome 3:**	**Intervention:** 118 **Subgroup:** 408 **Control:** 1.1 **Statistical Analysis:** Intervention vs Control *p* = <0.0001 Subgroup vs remainder of intervention group *p* = <0.0001	**Intervention (% of group):** 16 (66.6) **Subgroup (% of group):** 3 (23.0) **Control (% of group):** 87 (95.6) **Statistical Analysis:** Intervention vs Control *p* = 0.0003	**Intervention (% of group):** 5 (20.8) **Subgroup (% of group):** 1 (7.6) **Control (% of group):** 66 (72.5) **Statistical Analysis:** Intervention vs Control *p* = <0.0001	**Outcome 1:** The length of time after admission until a patient required restraint for aggressive behaviours was significantly longer for those prescribed clozapine, and particularly those prescribed clozapine first, than those prescribed other antipsychotics.

	Number of restraints (n)		Subgroup vs remainder of intervention group *p* = <0.0001	Subgroup vs remainder of intervention group *p* = <0.0001	**Outcomes 2 and 3:** The number of restraints required due to aggressive behaviours during hospitalisation (for both the entire duration of admission and within the first 24 hours) is statistically lower for those prescribed clozapine compared to those who were not prescribed clozapine.
Bhasvar et al. (2020)	**Outcome 1:** Adjusted rate ratio **Outcome 2:** Adjusted rate ratio	**Intervention (95% CI):** 0.13 (0.03, 0.18) **Control (95% CI):** 0.82 (0.47, 1.43) **Statistical Analysis:** *p* =.002	**Intervention (95% CI):** 0.37 (0.17, 0.80) **Control (95% CI):** 0.61 (0.44, 0.86) **Statistical Analysis:** *p* = .263	**Intervention (95% CI):** 0.24 (0.12, 0.48) **Control (95% CI):** 0.62 (0.45, 0.85) **Statistical Analysis:** *p* = 0.15	**Outcomes 1, 2 and 3:** Treatment with clozapine is associated with a lower rate of violent offending compared to treatment with olanzapine in patients with psychotic disorders. No significant

	Outcome 3: Adjusted rate ratio				difference in rates of non-violent offending between treatment with clozapine or olanzapine.

Appendix 5. Critical Appraisal Checklist for Randomized Control Trials (Joanna Briggs Institute, 2017a).

JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer 21311585 Date 15.02.23

Author Krakowski and Czobor Year 2014

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	X	☐	☐	☐
2. Was allocation to treatment groups concealed?	X	☐	☐	☐
3. Were treatment groups similar at the baseline?	X	☐	☐	☐
4. Were participants blind to treatment assignment?	X	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	X	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	X	☐	☐	☐
7. Were treatments groups treated identically other than the intervention of interest?	X	☐	☐	☐
8. Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?	X	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	X	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	X	☐	☐	☐
11. Were outcomes measured in a reliable way?	X	☐	☐	☐
12. Was appropriate statistical analysis used?	X	☐	☐	☐
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	X	☐	☐	☐

Overall appraisal: Include X Exclude ☐ Seek further info ☐

JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer 21311585 Date 15.02.23

Author Krakowski, Tural and Czobor Year 2021

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	☐	☐	X	☐
2. Was allocation to treatment groups concealed?	☐	☐	X	☐
3. Were treatment groups similar at the baseline?	X	☐	☐	☐
4. Were participants blind to treatment assignment?	X	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	X	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	X	☐	☐	☐
7. Were treatments groups treated identically other than the intervention of interest?	X	☐	☐	☐
8. Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?	X	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	X	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	X	☐	☐	☐
11. Were outcomes measured in a reliable way?	☐	☐	X	☐
12. Was appropriate statistical analysis used?	X	☐	☐	☐
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	X	☐	☐	☐

Overall appraisal: Include X Exclude ☐ Seek further info ☐

Appendix 6. Critical Appraisal Checklist for Quasi-Experimental Studies (Non-Randomized Experimental Studies) (Joanna Briggs Institute, 2017b).

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer 21311585 Date 15.02.23

Author Mela and Depiang Year 2016

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	X	☐	☐	☐
2. Were the participants included in any comparisons similar?	X	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	X	☐
4. Was there a control group?	X	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☐	X	☐
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?	X	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	X	☐	☐	☐
8. Were outcomes measured in a reliable way?	X	☐	☐	☐
9. Was appropriate statistical analysis used?	X	☐	☐	☐

Overall appraisal: Include X Exclude ☐ Seek further info ☐

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer 21311585 Date 15.02.23

Author Ifteni, Szalontay and Teodorescu Year 2017

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	X	☐	☐	☐
2. Were the participants included in any comparisons similar?	X	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	X	☐	☐	☐
4. Was there a control group?	X	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	X	☐	☐	☐
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?	X	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	X	☐	☐	☐
8. Were outcomes measured in a reliable way?	X	☐	☐	☐
9. Was appropriate statistical analysis used?	X	☐	☐	☐

Overall appraisal: Include X Exclude ☐ Seek further info ☐

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer_ _ _ _ _ _ 21311585_ _ _ _ _ _ _ _ _ _ _ Date_ _ _ _ _ _ _ _ _ 15.02.23 _ _ _ _ _ _ _ _ _ _ _

Author _ _ _ _ _ _ Bhavsar, Kosidou, Widman, Orsini, Hodsoll, Dalman and MacCabe _ _ Year_ _ _2020_ _ _

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	X	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	X	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	X	☐
4. Was there a control group?	X	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	X	☐	☐	☐
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?	X	☐	☐	☐
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Overall appraisal: Include X Exclude ☐ Seek further info ☐